Optimizing the precipitation of organic compounds

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Optimizing the precipitation of organic compounds

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Abstract

Crystallization and precipitation processes are used in the chemical and pharmaceutical industry to produce crystals with desired product properties, such as flowability, filterability, drying time and bioavailability. These properties are greatly affected by the particle size distribution and control of it is one of the major goals in process design. Model-based design approaches require accurate kinetics and thermodynamic data.

Therefore, the focus of this thesis is on the development of protocols for the measurement of nucleation, growth, agglomeration and polymorph transformation kinetics as well as on the development of suitable models for process design and optimization. Three different crystallization and precipitation processes are investigated: pH-shift precipitation of L-glutamic acid, combined cooling/antisolvent crystallization of acetylsalicylic acid and antisolvent precipitation of L-asparagine.

Depending on the intrinsic kinetics of the substance and on the operating conditions different experimental methods for the determination of the kinetics have to be applied. If the kinetics are relatively slow the experiments can be carried out in a stirred tank reactor. FBRM, ATR-FTIR and Raman spectroscopy are used for process monitoring. Kinetics are determined based on crystallization experiments by a combination of a population balance model and an integral parameter estimation technique. The process models are used for process design and optimization.

If the characteristic time scale of precipitation is similar to or shorter than the one of mixing in a stirred tank, alternative equipment is required to avoid transport limitations and the associated effect on the particle size distribution. This problem can be overcome using efficient mixing devices, such as static micro-mixers. The mixing efficiencies of two static mixers with different geometries are characterized using competitive-parallel chemical reactions and computational fluid dynamics (CFD). Finally, the mixer setup is used to determine nucleation and growth kinetics at high supersaturations and to conduct continuous precipitation experiments.
Zusammenfassung


Unterschiedliche experimentelle Methoden werden abhängig von den intrinsischen Kinetiken und Betriebsbedingungen verwendet, um die Kinetiken zu bestimmen. Im Falle relativ langsamer Kinetiken können die Experimente in einem Rührreaktor durchgeführt werden. FBRM, ATR-FTIR und Raman Spektroskopie werden zur Prozessbeobachtung eingesetzt. Die Kinetiken werden auf Basis von Kristallisationsexperimenten und mittels einer Kombination von Populationsbilanzmodellen und integraler Parameterschätzung bestimmt. Das Model wird dann zum Design und zur Optimierung von Prozessen verwendet.

Sind die charakteristische Zeit für die Fällung im gleichen Bereich wie die Mischzeiten im Rührreaktor (oder kürzer), so wird alternatives Equipment benötigt, um Transportbeschränkungen und den damit verbundenen Einfluss auf die Partikelgrößenverteilung zu vermeiden. Dieses Problem kann durch den Einsatz effizienter Mischer, z.B. statischer Mikromischer, bewältigt werden. Die Mischeffizienz zweier Mikromischer mit unterschiedlicher Geometrie wird mit Hilfe eines parallelen chemischen Reaktionssystems und numerischer Strömungssimulation (CFD) untersucht. Der experimentelle Aufbau mit den
statischen Mischern wird schliesslich verwendet, um Keimbildungs- und Wachstumskinetiken bei hohen Übersättigungen zu bestimmen und um kontinuierliche Fällungsexperimente durchzuführen.
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1 Introduction

1.1 Background
Crystallization is a widely used process for the purification and production of solid particles. In most industrial processes seeded cooling crystallization is applied, in which seed crystals of the specific compound are added to the reactor and the supersaturation is generated by cooling. Cooling crystallization is employed if the solubility changes significantly with temperature and if the compound is thermally stable. Alternatively, the supersaturation can be created by adding an antisolvent, i.e. a solvent with a significantly lower solubility, or by a chemical reaction, e.g. due to a pH-shift. One goal in production is the control of the product properties, e.g. particle size and particle size distribution, purity, residual solvent content, crystallinity, and polymorphic, hydrate or solvate form. To a certain extent the product properties can be manipulated by changing the process parameters. A crystal size distribution fulfilling assigned specifications, e.g. maximum average particle size, minimum coefficient of variation, etc., can be obtained by growing given seed crystals and for instance by minimizing nucleation, i.e. by keeping the system in the metastable zone, provided agglomeration and breakage can also be avoided. The operating conditions to obtain the desired product properties can be selected by a trial and error approach or through a model-based process optimization.

In precipitation processes carried out at high supersaturations, i.e. at conditions where the kinetics of particle formation are very fast and small particles are typically produced, the course of the process as well as the properties of the final crystalline product can depend on the mixing conditions. If the timescales of mixing are comparable to or larger than those of precipitation the resulting spatial inhomogeneity of the concentration can lead to undesired product properties, e.g. large crystal size and broad crystal size distribution. Moreover, if the process is scaled-up the mixing conditions can change and the product properties might be different.

Model-based design and optimization of crystallization processes requires the knowledge of the key mechanisms of particle formation and growth. Therefore,
the goal of this thesis is to devise protocols for the determination of all relevant kinetics and to develop tools to simulate precipitation and crystallization processes. If the precipitation kinetics are slow compared to the mixing, experiments can be conducted in a stirred tank. The experimental protocols for this case are presented in the first part of this thesis (chapters 2 and 3). If on the other hand precipitation kinetics are fast, experiments should be carried out in a micro-mixer. This topic is covered in the second part of the thesis (chapters 4 and 5).

1.2 Thesis outline

Chapter 2 describes the pH shift precipitation of L-glutamic acid. Protocols for the determination of nucleation, growth, agglomeration and polymorph transformation kinetics are presented. The methods are based on seeded and unseeded batch desupersaturation experiments and adopt different in-situ process analytical techniques, namely ATR-FTIR, Raman spectroscopy and FBRM. Moreover, a process model based on the population balance equation is introduced.

Chapter 3 is dedicated to the design and optimization of the combined cooling/antisolvent crystallization of acetylsalicylic acid. Nucleation and growth kinetics are determined based on crystallization experiments by combination of a population balance model and an integral parameter estimation technique. The model is finally used to calculate optimal cooling and antisolvent addition profiles of the combined cooling/antisolvent crystallization process using a multiobjective optimization approach which optimizes the process with respect to product properties, i.e. particle size distribution, and performance, i.e. process time.

Mixing in static mixers is studied in chapter 4 using a set of competitive-parallel chemical reactions and computational fluid dynamics (CFD). Two kinds of mixers, a wide angle Y-mixer and a two jet vortex mixer are compared in terms of reaction yields and mixing times and their performance is studied in a wide range of operating conditions.

In chapter 5, an experimental setup based on a static mixer is used to determine nucleation and growth kinetics of L-asparagine precipitated via antisolvent addition. The method is based on measuring the PSD obtained at different resi-
1.2 Thesis outline

dence times using a Coulter Multisizer. The effect of additives on the precipitation is presented in the second part of chapter 5.
Chapter 6 presents the main findings of this thesis and provides an outlook for future research in this area.
2 L-glutamic acid pH-shift precipitation

Precipitation from solution involves several fundamental mechanisms, namely nucleation, growth, agglomeration and breakage, that determine the particle size distribution, shape and polymorphic form of the final product. The ability to measure the kinetics of these mechanisms is of crucial importance for process design and development, e.g. in the pharmaceutical or chemical industry. This chapter is dedicated to the development of protocols for the determination of the kinetics of the key mechanism in precipitation processes, i.e. growth (section 2.2), nucleation (section 2.3), agglomeration (section 2.4), and polymorph transformation (section 2.5). During the precipitation of L-glutamic acid all these different phenomena can be observed, thus making it an ideal compound to be studied. The materials, setup, as well as in-situ and offline characterization techniques are the same for all sections in this chapter and are presented in the following section.

2.1 Materials and methods

The supersaturated solution is generated by mixing equimolar solutions of monosodium glutamate and hydrochloric acid. Upon addition of the acid the glutamate ion gets protonated in aqueous solutions, thus forming the free acid, which has a much lower solubility and precipitates. Monosodium glutamate monohydrate (≥ 98%, Sigma-Aldrich, Buchs, Switzerland), fuming hydrochloric acid solution (37–38%, L.T.Baker, Deventer, The Netherlands) and deionized water were used in all experiments.

L-glutamic acid has two monotropically related polymorphs, the metastable α and the stable β form (Bernal, 1931; Hirokawa, 1955). The solubilities of the α and the β polymorph have been measured previously (Schöll et al., 2006a) and are plotted as a function of temperature in Figure 2.1. In this work, the polymorphic purity of the solid fraction was characterized by X-ray powder diffraction, Raman spectroscopy and scanning electron microscopy, as reported elsewhere (Schöll et al., 2006a; Schöll et al., 2006b).
2. L-glutamic acid pH-shift precipitation

Figure 2.1: Solubility of the α and the β polymorph of L-glutamic acid. The solubilities have been determined previously (Schöll et al., 2006a) using ATR-FTIR spectroscopy.

2.1.1.1 Batch crystallizer set-up
A jacketed 500 mL borosilicate glass reactor with an inner diameter of 100 mm from LTS (Basel, Switzerland) was used in all experiments. The 4-blade glass stirrer from LTS (Basel, Switzerland) with 45° inclined blades had a diameter of 50 mm, was positioned 10 mm above the reactor bottom, and was operated at 250 rpm to ensure a homogeneous dispersion of the crystals in the reactor. The conveying direction was towards the bottom. The temperature in the crystallizer was controlled using a Pt 100 together with a CC230 thermostat from Huber (Offenburg, Germany). The position of the immersion probes (ATR-FTIR, FBRM and Raman, see section 2.1.1.2) was chosen in the zone of high fluid velocities, i.e. close to the impeller tips, to minimize clogging of the probe windows, thus optimizing the quality of the measured data (Schöll et al., 2006b). The experimental setup is shown in Figure 2.2.
2.1 Materials and methods

Figure 2.2: Schematic of the 0.5 L batch reactor used for the induction time experiments. The setup allows for employing several in-situ probes at the same time, e.g. FBRM and ATR-FTIR.

2.1.1.2 In-situ characterization techniques

Combined Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectroscopy and Focused Beam Reflectance Measurement (FBRM) have been recently applied successfully to monitor the liquid and solid phase during crystallization processes (O'Sullivan and Glennon, 2005; Schöll et al., 2006b). ATR-FTIR allows for the acquisition of liquid phase IR spectra in the presence of solid material due to the low penetration depth of the IR beam into the liquid phase (Dunuwila et al., 1994). An ATR-FTIR ReactIR 4000 system from Mettler-Toledo (Greifensee, Switzerland), equipped with a 11.75” Di-Comp immersion probe and a diamond ATR crystal, has been used. Spectra were collected with a resolution of 2 cm$^{-1}$ and were averaged over 128 scans. The calibration of the ATR-FTIR has been presented elsewhere (Cornel et al., 2008b).
The Focused Beam Reflectance Measurement (FBRM) allows for in-situ measurement of the chord length distribution (CLD). From the obtained CLD, the actual particle size distribution can in principle be restored (Kempkes et al., 2008; Worlitschek et al., 2005). In this work, a FBRM 600L from Lasentec (Redmond, USA) is applied in a non-quantitative manner only to detect the onset of particle formation in induction time experiments and to verify that no significant nucleation occurred during growth experiments. The latter point would in fact be evident as it would yield a sudden increase in the small chord lengths, i.e. 1-10 μm, which has never been observed in the experiments reported in this work.

Raman spectroscopy was employed to monitor the solid phase composition in the polymorph transformation experiments. However, since the Raman scattering effect results from both the solid and the liquid phase, Raman spectroscopy can also be applied for solute concentration monitoring (Cornel et al., 2008b). In this work, a RA 400 Raman spectrometer from Mettler-Toledo (Greifensee, Switzerland) equipped with a 250 mW frequency stabilized laser diode at 785 nm and a thermoelectrically cooled CCD detector was used. In-situ measurements were recorded using a 5/8" ball type immersion probe purchased from Inphotonics (Norwood, USA) connected via a fiber optic (thickness of collection and excitation fibers were 100 μm and 200 μm, respectively). Solid powder mixtures were analyzed using a flat immersion probe with identical characteristics as the probe used for suspension monitoring. Raman spectra were collected at a laser intensity of 150 mW in the -50 – 3600 cm\(^{-1}\) range with a resolution of 0.5 cm\(^{-1}\) and averaged over 10 scans using an exposure time of 5 seconds.

2.1.1.3 Off-line characterization techniques, Beckman Multisizer

Particle size distributions were measured using a Multisizer 3 from Beckman Coulter (Nyon, Switzerland). This device applies the electrical sensing zone or coulter method to measure the number and volume particle size distribution with a high resolution in the overall range of 0.4 to 1200 μm. The measurement principle of electrical sensing zone particle analyzers have been discussed in detail elsewhere (Schuhmann and Muller, 1998). The present study employs the Multisizer 3 since this device both counts the measured particles and measures
very accurately their volume with an unchallenged resolution; this information is then used to calculate the particle size of volume equivalent spheres (Xu and Di Guida, 2003).

Every measurement consisted of at least 40,000 particles and PSDs were smoothed using a moving average filter. Measurements were performed by adding approximately 100 mg of crystals to 200 ml of a saturated aqueous solution of L-glutamic acid at room temperature. This saturated solution was prepared by mixing equimolar solutions of monosodium glutamate and hydrochloric acid; therefore the free ions required for this measurement technique were already present and no additional salt needed to be added.
2.2 Growth kinetics*

In this section, the growth kinetics of α L-glutamic acid are determined based on seeded batch desuperaturation experiments. The growth rate correlation accurately describes the growth process in a temperature range of 25 to 45 °C and in a supersaturation range of 1 to 3. The newly developed approach for the growth rate characterization has the advantage of a high robustness especially with respect to the influence of competing particle formation mechanisms as nucleation or agglomeration. The efficient technique employs in-situ process analytical technologies, e.g. Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (ATR-FTIR) and Focused Beam Reflectance Measurement (FBRM), different ex situ analytical tools and population balance modeling combined with a non-linear least squares optimization algorithm to determine the growth kinetics. The growth mechanism is identified to be integration controlled and of birth and spread (B+S) type. The quality of the determined growth rate correlation is assessed by comparison with the experimental data and with literature data.

2.2.1 Introduction

Various methods can be found in literature to determine growth rate kinetics for crystallization processes. Besides single crystal methods, where the growth mechanism and kinetics of different crystal faces are usually determined by optical or atomic force microscopy (AFM) under different flow and supersaturation conditions (Kitamura and Ishizu, 2000), seeded batch multiparticle experiments are employed for process design purposes (Garside and Mersmann, 2002).

Recently, the use of in-situ process analytical technologies (PAT) has become more and more frequent for the characterization of crystallization and precipitation processes: growth kinetics of monosodium glutamate were determined combining several PATs (Grön et al., 2003), a method for the direct measurement of crystal growth kinetics of sodium carbonate using the Focused Beam Reflectance Measurement (FBRM) was proposed (Shaikh et al., 2005), and the combination of an in-situ concentration measurements and FBRM with popula-

tion balance modeling was employed to determine the growth kinetics of paracetamol (Worlitschek and Mazzotti, 2004). This work focuses on a PAT based characterization of the growth kinetics of L-glutamic acid precipitated from monosodium glutamate solutions upon addition of hydrochloric acid. We consider seeded growth experiments under different conditions and estimate the parameters of the growth rate correlation by combining the offline measurement of the particle size distribution of seeds and the time resolved measurement of the concentration in solution through ATR-FTIR with population balance modeling and an optimization routine. The chord length distribution of particles in suspension is monitored during the experiments using FBRM, to make sure that no new particles are formed and thus to confirm that the desupersaturation process is dominated by particle growth and not by nucleation. In order to assess the role of agglomeration, simulation results for the final particle size distributions are compared with experimental data and scanning electron micrographs (SEM) of the product particles are analyzed.

### 2.2.2 Measurement of concentration

In this work, ATR-FTIR was used to monitor the concentration of L-glutamic acid using the two bands in the IR spectra at 1224 cm\(^{-1}\) and 1408 cm\(^{-1}\), which correspond to the protonated and dissociated forms of the carboxylic groups of the molecule, respectively (Bergin et al., 1990). Independent calibrations were performed for these two bands at 25, 35 and 45 °C using a set of solutions with known L-glutamic acid concentrations (always at its isoelectric point) and applying the law of Beer-Lambert (Schöll et al., 2006b). Figure 2.3 shows both calibrations at 25 °C, which achieve values of the regression coefficient \(R^2\) of 0.9997.

The differences in concentrations determined based on these two calibrations were in the order of less than 4 %, which was considered to be acceptable. The supersaturation was calculated in this work by averaging the concentration values calculated with the two calibrations and by dividing the result by the solubility of the metastable \(\alpha\) form:

\[
S = \frac{c_{1224} + c_{1408}}{2c^*(T)};
\]  
(2.1)
here \( c_{1224} \) and \( c_{1408} \) denote the concentration values calculated with the IR bands at 1224 cm\(^{-1}\) and 1408 cm\(^{-1}\), respectively, and \( c^* \) is the solubility, which is a function of temperature.

Figure 2.3: Calibration data at 25 °C for the absorbance values at 1224 and 1408 cm\(^{-1}\), that correspond to the protonated and dissociated carboxylate group of the L-glutamic acid molecule.

The solubilities of \( \alpha \) L-glutamic acid, \( c^*(T) \), are 73.9 mol/m\(^3\) (10.9 g/kg solvent) at 25 °C, 104.0 mol/m\(^3\) (15.4 g/kg solvent) at 35 °C and 146.0 mol/m\(^3\) (21.7 g/kg solvent) at 45 °C; they were measured using ATR-FTIR spectroscopy as reported and discussed earlier (Schöll et al., 2006a). Contrary to a previous work (Schöll et al., 2006a), the solvent mediated polymorphic transformation from the metastable \( \alpha \) to the stable \( \beta \) form was not observed here due to the relatively low temperature (less than 45 °C) and rather short duration (less than one hour) of the experiments.

With reference to Eq. (2.1) a remark is worth making. As discussed in section 2.2.3.1, all experiments reported in this work have been carried out at the pH level corresponding to the isoelectric point of L-glutamic acid. During growth the pH value does not change. L-glutamic acid in aqueous solution is present as neutral form, also called free acid, together with its protonated, dissociated and twice dissociated species. At the isoelectric point the concentration of the free
2.2 Growth kinetics

acid is higher than that of the other species (Schöll et al., 2006b). The concentration of the free acid, \([Glu]\), is linearly related to the nominal L-glutamic acid concentration, \(c\), i.e. the total concentration of all species of L-glutamic acid in solution, by the following equation:

\[
[Glu] \left(1 + \frac{[H^+]}{K_a} + \frac{K_J}{[H^+] + \left[H^+\right]^2} \right) = c,
\]

where \(K_a\), \(K_J\) and \(K_b\) are the equilibrium constants of the dissociation and protonation reactions (the values at 25 °C are \(K_a = 6.46 \times 10^{-3}\), \(K_J = 5.62 \times 10^{-5}\) and \(K_b = 2.14 \times 10^{-10}\)) (Lide, 2004; Schöll et al., 2006b). At constant pH value and assuming an ideal solution the proportionality constant is independent of the total concentration: at the isoelectric point and 25 °C about 84% of the L-glutamic acid in solution is present as free acid according to Eq. (2.2). In Eq. (2.1) and in the calibration illustrated in Figure 2.3 the nominal concentration \(c\) is used. However, thanks to the linear relationship given by Eq. (2.2) and the fact that the pH value is constant during growth at the isoelectric point, the supersaturation ratio in Eq. (2.1) is the same whether it is calculated with the nominal concentration \(c\) or with the free L-glutamic acid concentration \([Glu]\).

2.2.3 Desupersaturation experiments

Desupersaturation experiments have been carried out by various authors to determine overall growth kinetics (Glade et al., 2004; Qiu and Rasmuson, 1991). In this work a similar but improved approach is proposed, that is based on the accurate measurement of the PSD of the seed particles and of the solute concentration time profile, which are combined with population balance modeling and an optimization routine to determine the growth kinetics. The experimental technique as well as the limitations of this method are described and discussed in detail in section 2.2.3.1. An important prerequisite of the experimental technique is the production, preparation, and characterization of seed crystals, as highlighted in section 2.2.3.2. Finally, the measurement results of the desupersaturation experiments are presented in section 2.2.3.3.
2.2.3.1 Experimental procedure

All desupersaturation experiments were conducted in the following way: first, a supersaturated solution was created by mixing equimolar solutions of monosodium glutamate and hydrochloric acid in the temperature-controlled reactor. It is worth noting that the mixture is at the isoelectric point of L-glutamic acid under these conditions, i.e. pH = 3.22 at 25 °C. Second, the in-situ monitoring with ATR-FTIR and FBRM was started and afterwards a certain amount of dry seeds was introduced in the reactor. Figure 2.4 shows measured solute concentration profiles, in short desupersaturation curves, for two repeated runs of experiments with different initial conditions. It can be observed that the repeatability is satisfactory. Nevertheless, the experiments being used for the parameter estimation were performed twice. The repeatability of the PSD at the end of the desupersaturation experiments was similar but is not explicitly shown here, since the PSDs were not used for parameter estimation. This aspect will be discussed in detail in section 2.2.4.3.

![Figure 2.4: Repeatability of two sets of desupersaturation experiments presented in this work.](image)

Figure 2.4: Repeatability of two sets of desupersaturation experiments presented in this work. ●, ○, ▲, and △ represent run 5, 6, 11, and 12 of the set of experiments given in Table 2, respectively. The different initial conditions are highlighted in the graph.
The method requires that experimental conditions are chosen in such a way that particle growth is dominating the desupersaturation process and other competing mechanisms, e.g. nucleation, agglomeration and breakage, are of negligible influence. To confirm that no nucleation occurred the CLD was monitored during the process using the FBRM and the SEM microphotographs of the final particles were analyzed. A typical time evolution of the CLD of the particle population during a growth experiment is shown in Figure 2.5. It can be observed that the number of particle counts in the small size range is virtually constant during the experiment, thus indicating that no nucleation occurred during the process. Similar behavior was observed in all experiments carried out in this work. Breakage could be avoided by using a glass impeller with rounded stirrer blade tips. The occurrence of agglomeration could not be prevented, but it will be shown in section 2.2.4.3 that agglomeration does not affect the results in this study.

Figure 2.5: FBRM data of run 9. It can be observed that no significant nucleation occurred over the course of the experiment since the counts of small chords remain at a constant low level.

Furthermore, it is assumed that the speciation of L-glutamic proceeds instantaneously upon mixing of monosodium glutamate and hydrochloric acid solutions. The mixing time in this reactor is in the range of a few seconds, as moni-
2. L-glutamic acid pH-shift precipitation

stored using ATR-FTIR (Schöll et al., 2006b). Thus, mixing and reaction are much faster than growth and do not influence the course of the growth process. The final dried crystals are analyzed using Raman spectroscopy and no polymorph transformation from the metastable α to the stable β polymorph (Schöll et al., 2006a) has been observed due to the short experimental times.

2.2.3.2 Preparation and characterization of seed crystals

The main objective of seed preparation was to obtain strain free, undamaged, and non agglomerated crystals of the metastable α form of L-glutamic acid in three different size fractions. Consequently, the seeds were produced by precipitation at low initial supersaturation, and the different size fractions were obtained by wet-sieving the grown crystals. Monosodium glutamate and hydrochloric acid solutions of 0.5 mol/l concentration were prepared and purified by filtration with a 0.22 μm filter. Both solutions were mixed in a 2 L stirred batch reactor, where particle formation occurred. The precipitated crystals were wet-sieved using four sieves with nominal mesh sizes of 64, 125, 250, and 355 μm, respectively. Three seed fractions, labeled S, M, and L, were obtained by collecting crystals triple sieved in the size ranges of 64 – 125 μm (S), 125 – 250 μm (M), and 250 – 355 μm (L), respectively. Crystals coarser than 355 μm or finer than 64 μm were discarded. Finally, the crystals of all three fractions were washed, filtered, and dried. The α polymorphic form of the seeds was confirmed using X-ray powder diffraction, SEM, and Raman spectroscopy as described elsewhere (Schöll et al., 2006b). The PSDs of the three seed fractions were characterized using a Coulter Multisizer 3 (see Figure 2.6). Additionally, scanning electron micrographs were taken of the three seed fractions, which are shown as inset in Figure 2.6; it can be observed that all fractions consist mostly of single crystals and only a few agglomerates.

2.2.3.3 Experimental results

A series of experiments was conducted at 25, 35 and 45 °C using different seed fractions, seed masses, and initial supersaturation values. The operating conditions of all experiments are listed in Table 2.1. The mass of the solution was 400 g in each experiment.
Table 2.1: Experimental conditions of the desupersaturation experiments and corresponding mean residual values $R_m$ (Eq. (2.8)) of the two optimized growth correlations given in section 2.2.4.2. The fractions S, M, and L, correspond to small, medium and large seeds and the corresponding experimental PSDs and SEM microphotographs are shown in Figure 2.6, respectively.

The influence of changing either seed fraction, seed mass or initial supersaturation on the measured desupersaturation curves is illustrated for 25 °C in Figure 2.7, Figure 2.8, and Figure 2.9, respectively. In these figures the experimental data are shown together with simulation results which will be discussed in section 2.2.4. Experimental data are represented by symbols, whereas simulation
results are plotted as lines. It can be observed, that an increase of the total surface area of the seed crystals, either by reducing seed size as shown in Figure 2.7 or by increasing seed mass as shown in Figure 2.8, leads as expected to a faster decrease in supersaturation. Yet, the experimental desupersaturation curves exhibit only small differences for a change in seed mass, whereas an increase in crystal surface by seeding with smaller crystals results in a faster decrease of supersaturation. This can be related to the difference in available seed surface, which is more significant in the experiments with different seed fractions. Moreover, it can be seen that during run 21, i.e., the experiment with an initial supersaturation of $S_0 = 3.86$ illustrated in Figure 2.9, significant clogging of the probe window occurred which induced corruption of the in-situ liquid phase data.

![Figure 2.6: Particle size distributions of the three seed fractions S, M, and L. The inset shows the corresponding scanning electron micrographs.](image)

The desupersaturation profiles for 35 °C and 45 °C are shown in Figure 2.10 and Figure 2.11, respectively. The comparison of the desupersaturation profiles for different temperatures as given by Figure 2.9, Figure 2.10 and Figure 2.11 shows a faster depletion of the supersaturation at elevated temperatures and hence a higher growth rate, as expected.
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Figure 2.7: Effect of seed size for two experiments at 25 °C. Symbols: experimental data; lines: simulation results.

Figure 2.8: Effect of seed mass for two experiments at 25 °C. Symbols: experimental data; lines: simulation results.
Figure 2.9: Effect of initial supersaturation for two experiments at 25 °C. Symbols: experimental data; lines: simulation results.

Figure 2.10: Effect of initial supersaturation for two experiments at 35 °C. Symbols: experimental data; lines: simulation results.
2.2 Growth kinetics

Figure 2.11: Effect of initial supersaturation for two experiments at 45 °C. Symbols: experimental data; lines: simulation results.

Figure 2.12: Final particle size distributions of three experiments at 25 °C with different seed fractions S, M, and L. Symbols: experimental data; lines: simulation results. The inset shows a SEM picture of agglomerates in the final particles of run 1 consisting of several single particles.
At the end of each experiment the mass of the grown crystals was determined after filtration, washing and drying. The yield of all experiments was within 92 and 97% of the calculated masses. The PSD of the grown particles was measured after drying using the Coulter Multisizer 3. The measured PSDs corresponding to the experiments shown in Figure 2.7 are shown in Figure 2.12. These PSDs will be used to verify the assumptions made and thus to validate the growth rate parameters estimated and discussed in the next section.

2.2.4 Growth kinetics of α L-glutamic acid

In the following the experimental results presented in the previous section are analyzed using a population balance equation (PBE) model to determine a growth rate correlation for α L-glutamic acid. Section 2.2.4.1 presents the model equations and the parameter estimation procedure. The chosen growth mechanism and the estimated parameters are presented in section 2.2.4.2. Then, in section 2.2.4.3 the quality of the model is discussed in terms of description capability of the experiments. Finally, the results reported in this study are discussed and compared with available data in the literature in section 2.2.4.4.

2.2.4.1 PBE model and parameter estimation procedure

The model used in this work consists of a population balance equation and a material balance equation. The population balance equation for the particles can be written as follows:

\[
\frac{\partial n}{\partial t} + G \frac{\partial n}{\partial L} = 0,
\]

where \(L\) is a characteristic dimension of the crystal, \(t\) is the time, and \(n(L,t)\) is the particle size distribution, i.e. \(n(L,t)dL\) is the number concentration of crystals of size between \(L\) and \(L + dL\) (Randolph and Larson, 1988). It is worth noting that \(L\) is the diameter of a volume equivalent sphere. The crystal growth rate \(G\) is assumed to be size independent. This assumption could be validated by carefully designed experiments in this work, as discussed in section 2.2.4.3. The material balance equation for the solute can be written as follows:

\[
\frac{dc}{dt} = -\frac{3}{M}k_v \rho_c G \int_0^\infty nL^2 dL,
\]
2.2 Growth kinetics

where \( c \) is the molar concentration of the solute, \( M \) is the molar mass of the solute, \( \rho_c \) and \( k_v \) are the solid density and the volume shape factor of the \( \alpha \) crystals, respectively. In this work, we have used the values of \( \rho_c = 1540 \text{ kg/m}^3 \) for the solid density and \( k_v = \pi/6 \) for the surface shape factor. The following initial and boundary conditions apply for the two equations above:

\[
c(0) = c_0 \tag{2.5}
\]

\[
n(L,0) = n_0(L) \tag{2.6}
\]

\[
n(0,t) = 0 \tag{2.7}
\]

with \( c_0 \) and \( n_0(L) \) being the initial solute concentration and PSD, respectively. The growth rate \( G \) depends on supersaturation, i.e. on the solute concentration \( c \), as discussed below. It is worth noting that neither nucleation nor agglomeration nor breakage are accounted for in the model, since experiments are run under conditions where these phenomena are absent or negligible.

The model equations above were solved using the discretization method proposed by Kumar and Ramkrishna (Kumar and Ramkrishna, 1997). This technique combines the discretization of the PBE with the method of characteristics and allows for the control of grid resolution and for computational efficiency, while greatly reducing numerical diffusion and instability.

The optimization procedure used in this work for the parameter estimation is based on a weighted non-linear least squares algorithm, which is described by

\[
\min \sum_{m=1}^{N_e} R_m^2 = \min \sum_{m=1}^{N_e} \left[ \frac{1}{t_{m}^{\text{end}}} \int_{0}^{t_{m}^{\text{end}}} \left[ S_m^{\text{exp}}(t) - S_m^{\text{mod}}(t) \right]^2 dt \right], \tag{2.8}
\]

where \( N_e \) is the number of experiments, \( R_m \) the mean residual, \( S_m^{\text{exp}} \) and \( S_m^{\text{mod}} \) are the experimental and calculated supersaturation values, respectively, and \( t_{m}^{\text{end}} \) is the duration, all referred to the \( m \)-th experiment. The optimization problem was solved using the \textit{lsqnonlin} algorithm of the MATLAB optimization toolbox.

The calculation of approximate confidence intervals of the model parameters is presented in section 2.4.4.4.
2.2.4.2 Growth mechanism and growth rate parameters

Different crystal growth mechanisms have been proposed in the literature to characterize the growth kinetics of α-L-glutamic acid during cooling crystallization. Tai et al. compared an integration-controlled BCF screw dislocation mechanism with the empirical two-step model and found a better description of the experiments using the BCF correlation (Tai et al., 1992). Kitamura compared two integration-controlled mechanisms, the BCF and the surface nucleation based birth and spread (B+S) mechanism, and found that the B+S correlation only yielded meaningful results (Kitamura and Ishizu, 2000). Since the growth mechanism is not unambiguously reported in the literature, the optimization algorithm was used together with the desupersaturation data to estimate the parameters for both surface integration-controlled growth mechanisms, B+S and BCF. It is worth noting that run 21 could not be used for the parameter estimation due to the partly corrupted desupersaturation data. The growth parameters were estimated simultaneously for the three temperatures by using run 1 to run 20. The equations used to describe the B+S and BCF mechanism can be cast as follows (Mersmann, 2001):

$$ G_{B+S} = AT \exp \left( \frac{-B}{T} \right) (S-1)^{2/3} (\ln S)^{1/6} \exp \left( \frac{-C}{T^2 \ln S} \right) $$  \hspace{1cm} (2.9)

$$ G_{BCF} = DT \exp \left( \frac{-E}{T} \right) (S-1) (\ln S) \tanh \left( \frac{-F}{T \ln S} \right), $$ \hspace{1cm} (2.10)

where $A$, $B$, $C$, $D$, $E$ and $F$ are parameters (three for each model) that are estimated from experiments. The optimization of the growth rate parameters yielded the following values for the B+S mechanism:

$$ A = (3.63 \pm 0.12) \times 10^{-4} \text{ m s}^{-1} \text{ K}^{-1} $$  \hspace{1cm} (2.11)

$$ B = (3.72 \pm 0.10) \times 10^{3} \text{ K} $$ \hspace{1cm} (2.12)

$$ C = (5.42 \pm 0.09) \times 10^{4} \text{ K}^{2}, $$ \hspace{1cm} (2.13)

and for the BCF correlation:

$$ D = (1.57 \pm 0.06) \times 10^{-3} \text{ m s}^{-1} \text{ K}^{-1} $$  \hspace{1cm} (2.14)

$$ E = (4.34 \pm 0.12) \times 10^{3} \text{ K} $$ \hspace{1cm} (2.15)
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\[ F = (4.15 \pm 0.39) \times 10^2 \text{ K}. \]  \hspace{1cm} (2.16)

Changing the initial values of the parameters in the optimization procedure over several orders of magnitude always produced the same final results, thus indicating that the values in Eqs. (2.9) to (2.16) correspond to a global optimum. The confidence intervals of the parameters are calculated for 95% probability using Eq. (2.85).

In contrast to findings reported in the literature (Kitamura and Ishizu, 2000), the parameter estimations for both growth mechanisms yield physically meaningful results. The overall mean residuals describing the deviation between measured and simulated desupersaturation curves for the entire set of experiments, as calculated using Eq. (2.8), are 6.0 \times 10^{-1} and 8.1 \times 10^{-1} for the B+S and BCF mechanisms, respectively. This indicates that the B+S growth mechanism describes the observed growth behavior of the experimental set more accurately, which is in agreement with atomic force microscopy (AFM) studies, where screw dislocation growth sites typical for the BCF mechanism could not be observed, whereas patterns characteristic for the B+S mechanism could be identified (Kitamura and Onuma, 2000). Consequently, the kinetics described by the B+S mechanism will be used in the following sections.

We have also checked whether the growth kinetics was influenced by diffusional limitations. To this aim, the mass transfer coefficient \( k_d \) was predicted using the Sherwood correlation (Mersmann, 2001):

\[
k_d = \frac{D_{AB}}{L} \left( 2 + 0.8 \left( \frac{\bar{\varepsilon} L^4}{v^3} \right)^{1/5} Sc^{1/3} \right), \hspace{1cm} (2.17)
\]

where \( D_{AB} \) is the diffusivity, \( L \) the crystal size, \( \bar{\varepsilon} \) the average power input, \( \nu \) the kinematic viscosity and \( Sc \) the Schmidt number, i.e. \( Sc = \frac{\nu}{D_{AB}} \). With typical values for water of \( D_{AB} = 2 \times 10^{-9} \text{ m}^2/\text{s} \) and \( \nu = 1 \times 10^{-6} \text{ m}^2/\text{s} \), average particle size of \( L = 2 \times 10^{-4} \text{ m} \), and characteristic average power input for our crystallizer of \( \bar{\varepsilon} = 5.9 \times 10^{-2} \text{ W/kg} \), the mass transfer coefficient \( k_d \) from Eq. (2.17) is \( 2.2 \times 10^{-4} \text{ m}^2/\text{s} \). Diffusion-controlled crystal growth rates can be calculated using the following equation (Mersmann, 2001):

\[
G = k_d \frac{k_a}{3k_c \rho_c} \left( c - c^* \right), \hspace{1cm} (2.18)
\]
where \( \rho_c \) is the crystal density, \( k_a \) and \( k_v \) denote the surface and volume shape factors, respectively. The experimental growth rates were found to be at least one order of magnitude smaller than the diffusion limited growth rates computed with the mass transfer coefficient predicted by the Sherwood correlation. Therefore, it was concluded that under the conditions studied in this work the growth of \( \alpha \) L-glutamic acid is controlled by the surface integration of new molecules in the crystal lattice.

### 2.2.4.3 Accuracy of the growth rate model

The accuracy of the model predictions and the validity of the initial assumptions can be evaluated by comparison of the computed model results with the experimental data, e.g., the desupersaturation curve and the final PSD. It is worth noting that the desupersaturation curve is a time-resolved experimental information yielding several measurement information over the course of an experiment while the final PSD is an integral one. However, the desupersaturation data does not describe which particle formation mechanisms are responsible for the solute consumption over time. Consequently, one needs, besides the accurate information about the crystal surface at the beginning of the experiment, additional information about the mechanisms being involved. This information can be obtained by comparison of simulated and experimental final PSD for each experiment. The final PSD contains valuable information whether and to what extent undesired phenomena like nucleation or agglomeration occurred during the experiment.

First, let us consider the experimental and simulation results obtained at 25 °C by using the different seed fractions, shown in Figure 2.6, but otherwise identical operating conditions. The desupersaturation curves and final PSDs corresponding to the different seed fractions are shown in Figure 2.7 and Figure 2.12, respectively. It can be observed in Figure 2.7 that the computed desupersaturation curves are in good agreement with the experimental data, which is also reflected by the low values of the mean residuals given in Table 2. If we compare the final PSDs for the three experiments with different seed fractions shown in Figure 2.12, it can be observed that all PSDs computed for run 1, 4, and 5 agree reasonably well with the experimental results. However, simulated PSDs are shifted towards smaller particle sizes compared to the experimental ones, and the deviation is larger for smaller seeds. Such behavior can be attrib-
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uted to agglomeration of particles during growth, i.e. a phenomenon that is not accounted for by the model used in this work. The existence of agglomeration is supported by SEM micrographs of grown crystals at the end of run 1 as shown in the inset of Figure 2.12.

A model describing the agglomeration of L-glutamic acid is presented in section 2.4. This model accounts for a size-dependent agglomeration kernel and for the shear rate distribution in the stirred tank. It is used here to show the influence of agglomeration on the final PSD and on the desupersaturation curve. In Figure 2.13 the experimental and computed final PSDs of run 4 are shown. The experimental PSD (symbols) is compared with three simulated PSDs, namely the PSD accounting for sole growth and computed with the model presented in this work (solid line), the PSD calculated accounting for agglomeration as reported in section 2.4 (dashed line) and the PSD calculated assuming that the agglomeration rate is five times larger than determined in section 2.4 (dotted line). It can be seen that the difference in the final PSDs between model and experiment is mainly caused by agglomeration. For the agglomeration rate given in section 2.4 the inclusion of agglomeration in the model improves the prediction of the final PSD quite significantly. When simulating the process with a five times higher agglomeration rate the final PSD is broadened and shifted towards larger particle sizes.

Let us now consider the effect of agglomeration on the desupersaturation profile, which is shown in Figure 2.14. It can be seen that even at high agglomeration rates the desupersaturation curve is not significantly affected by agglomeration. Therefore, it is concluded that in this case the growth rate can be estimated from solute concentration data with significant less error than from solid phase data.

When comparing the model prediction quality for the solid and liquid phase properties, i.e., the supersaturation in Figure 2.7 and the PSDs in Figure 2.12, it can be clearly observed that supersaturation data can be predicted with higher accuracy than the PSDs. Consequently, the use of desupersaturation data as reported here represents a robust method to determine growth kinetics parameters. However, it is necessary to check the final PSDs to verify whether and to what extent the basic conditions of minimizing concurrent phenomena were respected during the experiments. Finally, in combination with the experiments using different seed fractions it can be concluded, that size dependent crystal
growth, a phenomena observed for other systems (Garside and Jancic, 1978), cannot be observed in the size range of the three seed fractions used.

![Graph showing particle size distributions](image)

Figure 2.13: Effect of agglomeration on final particle size distributions (PSDs) of run 4. Symbols: experimental data; lines: simulation results.

The final PSD of run 1 is most affected by agglomeration compared to all other experiments. Therefore, the final PSDs of these experiments are not displayed and it is assumed that the influence of agglomeration on growth rate estimation can be neglected too. Furthermore, no indication of nucleation was given by the final PSDs since there was neither an increased number of particles in the small size range of the Coulter Multisizer 3 nor a bimodal PSD, as in the case of significant nucleation.

The experimental and modeling results obtained using different seed masses of fraction M of either 2, 3, or 4 g, are illustrated in Figure 2.8. Similar to the desupersaturation curves with different seed fractions, also the computed profiles for different seed masses are in good agreement with the experimental values, although the differences between the three runs are rather small.
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Figure 2.14: Effect of agglomeration on desupersaturation curves of run 4. Circles: experimental desupersaturation curve; continuous line: computed desupersaturation curve accounting for sole growth; dashed line: computed desupersaturation curve for the agglomeration rate given in section 2.4; dotted line: computed desupersaturation curve for a five times larger agglomeration rate.

The computed and experimental desupersaturation curves obtained at different initial supersaturations are shown in Figure 2.9. In the case of run 21, whose data were not used for the parameter optimization procedure, the corresponding model results can be considered as predictive. Similar to the experiments with varying crystal surface presented above, the model results for different initial supersaturation are in good agreement with the experimental desupersaturation curves. It is worth noting that this holds true also for run 21 for the data points where the experimental values are not corrupted by probe clogging. An interesting feature of the system can be observed by closely comparing the course of the different experiments shown in Figure 2.9. It can be observed, that the measured supersaturation values of run 21 drop below the values of both other experiments. This crossover is also predicted by the simulation results. The computed desupersaturation curves exhibit also a crossover between runs 10 and 12, which is yet too small to be verified experimentally. The reason for the crossing over of the desupersaturation curves is related to the significant change
of available crystal surface over the course of the experiment. The initial crystal
surface is the same in all three cases since the same seed fraction and seed mass
were used. Yet, due to the higher crystal growth rates at higher supersaturation
the available crystal surface area increases faster in runs 12 and 21 when com-
pared to run 10. This results in a higher mass deposition rate and leads ulti-
mately to the crossover behavior observed experimentally.
Unlike cooling crystallization, where the driving force of the process is induced
by a change in temperature the supersaturation was created in this work by a
chemical reaction. Thus, the growth kinetics of α L-glutamic acid were studied
at constant temperature. The temperature dependence of the growth rate was
determined by conducting the experiments at different temperatures, as can be
seen in Table 2.1. Experimental and simulated desupersaturation profiles are
shown in Figure 2.10 and Figure 2.11 for 35 and 45 °C, respectively. For both
temperatures the experiments were carried out at two different initial supersatu-
rations. It can be observed that also at elevated temperatures experimental and
simulation results are in good agreement.

2.2.4.4 Comparison with literature data
In this section, we aim at comparing the overall growth kinetics determined in
this work with the overall growth rate of α L-glutamic acid measured at 15 °C
(Tai and Shei, 1993) and with the growth rate of individual faces of α L-
glutamic acid measured at 25 °C (Kitamura and Ishizu, 2000).
To our knowledge, the overall growth kinetics of α L-glutamic acid has been
determined from batch experiments at 15 °C (Tai and Shei, 1993) and 45 °C
(Schöll et al., 2006a) only. The growth rate at 15 °C is plotted together with
that calculated using Eq. (2.9) for the temperatures 15, 25, 35 and 45 °C as a
function of supersaturation in Figure 2.15.
Although the application of Eq. (2.9) to 15 °C is an extrapolation, the predicted
growth rate is in excellent agreement with the empirical growth rate expression
proposed by Tai et al (Tai and Shei, 1993). The growth rate of α L-glutamic
acid was determined at 45 °C based on unseeded batch experiments by Schöll
et al (Schöll et al., 2006a). The comparison of this growth rate with that being
presented here shows some discrepancy. We believe this is due to the fact that
in that work nucleation and growth rates had been determined together (Schöll
et al., 2006a). Based on the new results we should conclude that nucleation and
growth rate are highly correlated. Hence, the accuracy of each individual rate was lower than that of the overall model, which in that paper was used to describe the formation of metastable α crystals and their transformation to stable β crystals (Schöll et al., 2006a). Therefore, the overall growth kinetics should be measured independently in order to improve the accuracy and prediction quality of a model, as it is done here.

Figure 2.15: Comparison of the growth kinetics of α L-glutamic acid determined in this work for different temperatures with kinetics found in literature (Tai and Shei, 1993).

To allow for the direct comparison of our correlation for the overall growth rate given by Eq. (2.9) with measured growth rates of the single faces of α L-glutamic acid published in literature for 25 °C (Kitamura and Ishizu, 2000), these face growth rates have to be used to calculate a corresponding overall growth rate of a volume equivalent sphere. This conversion is presented in the following. The volumetric change of a crystal by growth can be written as:

\[
\frac{dV}{dt} = \sum_{i=1}^{N_{\text{faces}}} G_i A_i = \sum_{i=1}^{N_{\text{faces}}} s_i k_a L^2 G_i ,
\]

(2.19)
where \( G_i \) is the growth rate, \( A_i \) the surface area and \( s_i \) the surface fraction of \( i \)-th face, \( L \) is a characteristic dimension of the particle and \( k_a \) the corresponding surface shape factor. The number of faces \( N_{\text{faces}} \) with distinctly different growth rates is 3 for \( \alpha \) L-glutamic acid and these have the Miller indices (001), (111) and (011) (Kitamura and Ishizu, 2000).

The volumetric change of a crystal can also be described by

\[
\frac{dV}{dt} = 3k_v L^2 \frac{dL}{dt} = 3k_v L^2 G_L, \tag{2.20}
\]

where \( k_v \) is the volume shape factor of the particle and \( G_L \) is the growth rate of the characteristic dimension \( L \). By combining Eqs. (2.19) and (2.20) the growth rate \( G_L \) can be expressed in terms of the growth rate of individual faces as well as of their surface fraction:

\[
G_L = \frac{k_a}{3k_v} \sum_{i=1}^{3} s_i G_i. \tag{2.21}
\]

To allow for the comparison with the growth rate given by Eq. (2.9), the growth rate of a volume equivalent sphere has do be determined from Eq. (2.21) using

\[
G = G_L \left( \frac{6k_v}{\pi} \right)^{1/3}, \tag{2.22}
\]

with \( G \) being the growth rate of the volume equivalent sphere. Based on the growth rate correlations for the different faces of \( \alpha \) L-glutamic acid published in literature (Kitamura and Ishizu, 2000) and data for the surface fractions \( s_i \) of the corresponding faces determined from a geometric particle model the growth rate \( G \) can be determined using Eqs. (2.21) and (2.22). The calculated growth rates for two specific crystal shapes are shown in Figure 2.16 together with the growth rate given by Eq. (2.9) at 25 °C.

All crystal geometries observed in the seeded batch experiments are somewhere within the range of the thick and compact crystals represented by shape (1) and the thin platelets represented by shape (2) in Figure 2.16. Thus, the corresponding growth rate curves can be understood as the lower and upper bounds for the growth rates that different crystals would experience during the desupersaturation experiments. The overall growth rate determined in this work and given by Eq. (2.9) is quite close to those obtained using growth rates of individual faces,
although there is a deviation. Considering the quite different nature of the two measurement approaches, with one being a bulk crystallization involving a large number of particles and the other being essentially a single particle characterization method, the agreement can still be considered satisfactory especially for larger supersaturations.

Figure 2.16: Comparison of the growth kinetics of α-L-glutamic acid determined in this work for 25 °C with kinetics calculated with Eqs. (2.21) and (2.22) from face growth rates from literature (Kitamura and Ishizu, 2000). Shape 1: \( s_1 = A_{(001)}/A_{\text{crystal}} = 0.14; \ s_2 = A_{(111)}/A_{\text{crystal}} = 0.80; \ s_3 = A_{(011)}/A_{\text{crystal}} = 0.06. \) Shape 2: \( s_1 = 0.67; \ s_2 = 0.31; \ s_3 = 0.02. \)

### 2.2.5 Conclusions

A method for the fast and robust measurement of growth rate kinetics is presented, and it is based on two in-situ process analytical technologies, namely ATR-FTIR spectroscopy and FBRM to monitor the liquid and the solid phase during seeded batch desupersaturation experiments. Additionally, a Coulter particle analyzer employing the electric zone sensing method is used to characterize the initial PSD of the different seed fractions. The experimental requirements for an independent growth kinetics determination, i.e., the absence of
other mechanisms such as nucleation, agglomeration and breakage, are checked using the Coulter Multisizer and scanning electron microscopy. It could be shown, that the presented characterization method was robust also in case of occurring agglomeration. For the first time, the overall growth kinetics of α L-glutamic acid were determined independently at 25, 35 and 45 °C when the supersaturation is created by pH-shift. The growth mechanism considered was birth and spread in agreement with other authors. The comparison of the determined growth kinetics to correlations proposed in literature at different temperatures has shown satisfactory agreement.
2.3 Nucleation kinetics

In this section, the nucleation kinetics of α L-glutamic acid is determined on the basis of induction time measurements. The induction times are measured at different supersaturations using ATR-FTIR spectroscopy and focused beam reflectance measurement (FBRM), and applying a previously developed method (Schöll et al., 2006b). Moreover, the effect of temperature on the induction time is studied. Together with independently measured growth kinetics the nucleation rates are determined. Finally, the nucleation kinetics is used to calculate the interfacial energies. The analysis of the estimated kinetics parameters and of the calculated interfacial energies indicates a heterogeneous nucleation mechanism.

2.3.1 Introduction

In precipitation processes, the determination of nucleation rates is of key importance for the development of process models that can be used for process design and optimization. A number of different methods to determine nucleation rates have been reported in literature, e.g. methods based on particle counting (Mahajan and Kirwan, 1994; Roelands et al., 2004), mixed-suspension mixed-product removal (MSMPR) experiments (Mersmann, 2001), combination of population balance modeling and particle size distribution measurement (Aoun et al., 1999; Blandin et al., 2001), and induction time experiments (Kashchiev et al., 1991; Schöll et al., 2006b). An overview about the different techniques can be found elsewhere (Garside and Mersmann, 2002). In this work, we apply a previously developed method (Schöll et al., 2006b), which is based on induction time measurements, to determine the nucleation kinetics of α L-glutamic acid. This method allows for a robust and reliable estimation of nucleation rates based on in-situ measurements in batch precipitation processes, which are not limited by mixing. The mixing time is determined simultaneously, thus it can be assessed whether the measurement technique is applicable. As an extension of an earlier work (Schöll et al., 2006b), the effect of temperature is studied and the interfacial energies are calculated and compared to theoretical values.

2.3.2 Experimental procedure

In each experiment, first, the monosodium glutamate solution is loaded into the reactor. Then the solution is heated to the desired temperature. A preheated hydrochloric acid solution is added to the monosodium glutamate solution via a funnel. The funnel is always at the same position and the outlet of the funnel is placed close to the stirrer to allow for fast mixing. The temperature is monitored and never deviates from the set point by more than 1 °C. The final dried crystals are analyzed using Raman spectroscopy and no polymorph transformation from the metastable \( D \) to the stable \( E \) polymorph (Cornel et al., 2008a; Schöll et al., 2006a) has been observed due to the short experimental times.

2.3.3 Background

2.3.3.1 Nucleation kinetics

Classical nucleation theory predicts that the nucleation rate depends on the difference in the chemical potential of the compound as a crystal and in solution. The homogeneous nucleation rate is then given by (Kashchiev, 2000)

\[
J = A_{\text{hom}} S \exp\left( -\frac{B_{\text{hom}}}{\ln^2 S} \right),
\]

(2.23)

where \( A_{\text{hom}} \) is a kinetic parameter, \( B_{\text{hom}} \) is a thermodynamic parameter, and the supersaturation \( S \) is defined as follows:

\[
S = \frac{c}{c^*(T)},
\]

(2.24)

where \( c \) is the concentration of the solute and \( c^* \) is the solubility of the \( \alpha \) polymorph, which is a function of temperature \( T \). The solubility has been determined previously (Schöll et al., 2006a) and is plotted in Figure 2.1. The thermodynamic parameter \( B_{\text{hom}} \) is defined as

\[
B_{\text{hom}} = \frac{16\pi^2 \gamma^3}{3(kT)^3},
\]

(2.25)
where \( v_0 \) is the molecular volume of the crystalline phase, \( \gamma \) is the interfacial energy of the crystal, and \( k \) is the Boltzmann constant. The molecular volume is defined as

\[
v_0 = \frac{M}{\rho c N_A}, \tag{2.26}
\]

where \( M \) is the molar mass, \( \rho_c \) is the crystal density, and \( N_A \) is the Avogadro number. The functional form of \( A_{\text{hom}} \) depends on the attachment mechanism; for interface-transfer control it is given by (Kashchiev, 2000)

\[
A_{\text{hom},I} = \left( \frac{4\pi}{3v_0} \right)^{1/3} \left( \frac{\gamma}{kT} \right)^{1/2} D_{AB} c^* N_A, \tag{2.27}
\]

with \( D_{AB} \) being the diffusivity of the solute in the solvent, whereas for volume-diffusion control it is given by (Kashchiev, 2000)

\[
A_{\text{hom},D} = \left( \frac{kT}{v_0^2 \gamma} \right)^{1/2} D_{AB} c^* N_A \ln S. \tag{2.28}
\]

Also for heterogeneous nucleation, i.e. the nucleation in the presence of foreign particles or surfaces, different mechanisms exist (Kashchiev, 2000). The same functional form of the nucleation rate expression, i.e. Eq. (2.23), applies also to 3D heterogeneous nucleation, whereas the nucleation work is reduced as compared to homogeneous nucleation and the following expression for \( B_{\text{het}} \) is obtained (Mersmann, 2001):

\[
B_{\text{het}} = \frac{16\pi v_0^2 \gamma_{\text{eff}}^3}{3(kT)^3}, \tag{2.29}
\]

where \( \gamma_{\text{eff}} \) is the effective interfacial energy which can be substantially smaller than the interfacial energy \( \gamma \) in homogeneous nucleation. Moreover, the kinetic parameter \( A_{\text{het}} \) for heterogeneous nucleation is of different form than Eq. (2.27) or (2.28); it is proportional to the nucleation-active centers in the system and is typically many orders of magnitude lower than that for homogeneous nucleation (Kashchiev and van Rosmalen, 2003).
2.3.3.2 Prediction of physical properties

In principle, the nucleation kinetics can be predicted using Eq. (2.23) since all unknown parameters can be determined (Mersmann et al., 2002) as described in the following.

The Stokes-Einstein equation can be used to estimate the diffusion coefficient:

\[ D_{AB} = \frac{kT}{6\pi r_0 \eta}, \]

(2.30)

with \( r_0 \) being the radius of the molecule and \( \eta \) being the dynamic viscosity.

The viscosity can be estimated using the following equation (Laliberte, 2007):

\[ \eta = \frac{0.001\theta + 0.246}{(0.05594\theta + 5.2842)\theta + 137.37}, \]

(2.31)

where \( \eta \) is given in Pa·s and \( \theta \) is the temperature in °C.

Nielsen and Söhnel observed a linear relationship between the interfacial energy and the logarithm of the bulk solubility for 58 electrolyte crystals on the basis of experimentally determined nucleation rates (Nielsen and Sohnel, 1971; Sohnel, 1982). Mersmann derived the following equation, which relates the interfacial energy to the solubility of the compound (Mersmann, 1990):

\[ \gamma = \beta kT (c_c N_A)^{2/3} \ln \left( \frac{c_c}{c^*} \right), \]

(2.32)

where \( \beta = 0.514 \) for spherical nuclei (Kasheiev and van Rosmalen, 2003), \( c_c \) is \( \rho_c/M \) and \( \gamma \) is given in J/m².

Substituting Eqs. (2.30) and (2.32) into Eqs. (2.29) and (2.27) in the case of interface-transfer control and then into Eq. (2.23) yields:

\[ J = a_I \frac{T}{\eta} \left( \ln \frac{c_c}{c^*} \right)^{0.5} c^* S \exp \left[ -b_I \frac{\ln^3 c_c}{\ln^2 S} \right], \]

(2.33)

where the parameters \( a_I \) and \( b_I \) are given by

\[ a_I = \left( \frac{4\pi}{3V_0} \right)^{1/3} \left( \beta \left( c_c N_A \right)^{2/3} \right)^{1/2} \frac{kN_A}{6\pi r_0}, \]

(2.34)
Substituting Eqs. (2.30) and (2.32) into Eq. (2.28) in the case of volume-diffusion control and then into Eq. (2.23) yields:

\[
J = a_D \frac{T}{\eta} \left( \ln \frac{c_c}{c} \right)^{0.5} c^* S \ln(S) \exp \left( -b_D \frac{\ln^3 \frac{c_c}{c}}{\ln^2 S} \right),
\]

(2.36)

where \(a_D\) is given by

\[
a_D = \left( \frac{1}{\nu_0^2 \beta (c_c N_A)^{2/3}} \right)^{1/2} \frac{k_N A}{6 \pi r_0},
\]

(2.37)

and \(b_D = b_J\). It must be noted that the parameters \(a_I, a_D, b_I\) and \(b_D\) depend only on the physical properties of the compound and are independent of supersaturation and temperature.

### 2.3.3.3 Induction time

The induction time, i.e. the time period between the attainment of the initial supersaturation and the detection of the onset of particle formation, depends on the monitoring instrument and is related to the nucleation rate. Assuming constant supersaturation during the induction time, stationary nucleation and growth kinetics, and a polynuclear mechanism, i.e. nucleation and growth of many nuclei to a detectable size, the following equation relating the induction time to nucleation and growth can be derived (Kashchiev et al., 1991; Schöll et al., 2007a; Schöll et al., 2006b):

\[
t_i = \left( \frac{4 \alpha_v}{k_v J G^3} \right)^{1/4},
\]

(2.38)

where \(t_i\) is the induction time, \(\alpha_v\) is the detectable volume fraction of the newly formed solid phase, \(G\) is the overall growth rate in terms of diameter of a volume equivalent sphere and \(k_v\) is the corresponding volume shape factor, i.e. \(k_v = \pi/6\). The value of \(\alpha_v\) depends on the measurement device and on the substance; for the Lasentec FBRM and \(\alpha\) L-glutamic acid, \(\alpha_v\) was estimated to be
4×10^{-3} assuming it is temperature independent (Schöll et al., 2006b). Eq. (2.38) is valid for 3D growth of spheres, when the growth kinetics is controlled by surface integration (Kashchiev et al., 1991). The last assumption about the growth controlling mechanism is consistent with a previous work where it was shown to be based on the “birth and spread” mechanism, as given by in section 2.2:

\[ G = 3.63 \times 10^{-4} T \exp\left(\frac{-3.72 \times 10^3}{T}\right) (S - 1)^{2/3} (\ln S)^{1/6} \exp\left(\frac{-5.42 \times 10^4}{T^2 \ln S}\right). \]  

(2.39)

Moreover, volume diffusion control, i.e. the alternative mechanism, never applies to new nuclei in the early phase of growth, as growth due to diffusion is infinitely fast for crystals of size approaching zero. It must be noted that the growth kinetics were determined in a supersaturation range of 1 to 3 and that the application of Eq. (2.39) to larger supersaturation values represents an extrapolation. At high supersaturation the mechanism might change from integration-controlled (Eq. (2.39)) to diffusion-controlled growth (Mersmann, 2001). However, it was shown in section 2.2 that the measured growth rates of L-glutamic acid are at least one order of magnitude smaller than predicted diffusion-controlled growth rates.

### 2.3.4 Results

#### 2.3.4.1 Induction time

The nucleation kinetics was determined based on induction time data, which is measured using ATR-FTIR and FBRM, as reported elsewhere (Schöll et al., 2006b). The experimental procedure for the induction time measurements is shown schematically in Figure 2.17. ATR-FTIR is used to determine the starting time of the precipitation process, namely when mixing is completed and the initial supersaturation is established. To determine this point the band in the IR spectra at 1408 cm\(^{-1}\), which corresponds to the dissociated carboxylic groups in the L-glutamic acid molecule (see section 2.2), is used. Phase 1 in Figure 2.17 is the time period before adding the hydrochloric acid solution to the glutamate solution and is characterized by a constant IR signal and zero counts from the FBRM. In phase 2, the HCl solution is added and a drop in the IR signal, owing to protonation of the carboxylic group and dilution, is observed. Phase 3 begins
2.3 Nucleation kinetics

when the IR signal is stable again. At that point mixing is complete and the nominal supersaturation is assumed to be attained everywhere in the reactor. In phase 4, a rapid increase of the FBRM counts, owing to the formation of particles, can be observed. In the following period the IR signal decreases gradually due to the consumption of supersaturation by growth. Phase 3, i.e. the time period between attainment of the initial supersaturation and the detection of the onset of particle formation is called induction time.

Figure 2.17: Experimental procedure for the measurement of the induction times. The four phases are discussed in detail in the text. The plot shows the experimental results for an initial supersaturation of 2.5 and a temperature of 45 °C.

If the induction time is measured for various initial supersaturations, then its dependence on supersaturation is obtained. The induction times have been measured at 25, 35 and 45 °C. Each run has been carried out at least three times. The experimental conditions are given in Table 2.2 and the results are shown in Figure 2.18. Each point represents the mean of at least three measurements. It can be observed that with increasing supersaturation the induction time decreases for all three temperatures. Moreover, for the same supersaturation level the induction time decreases with increasing temperature.
2. L-glutamic acid pH-shift precipitation

<table>
<thead>
<tr>
<th>Run</th>
<th>Temperature [°C]</th>
<th>Supersaturation [-]</th>
<th>Induction time [s]</th>
<th>Stdv. [s]</th>
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</thead>
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<td>1026</td>
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<tr>
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<td>57</td>
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<tr>
<td>3</td>
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<tr>
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<td>65</td>
</tr>
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<td>3.50</td>
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<td>4.00</td>
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<td>45</td>
<td>4.75</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 2.2: Experimental conditions of the induction time experiments and corresponding measured induction times and standard deviations of the induction times. Each run was carried out at least three times and the reported induction times represent the corresponding average values.
2.3 Nucleation kinetics

The average induction times and the corresponding standard deviations are also given in Table 2.2. It can be observed that the standard deviation decreases with increasing supersaturation, but its relative value compared to the average induction time is not decreasing and can reach up to 50 % of it. The relatively poor repeatability might be attributed to different amounts of microscopic dust, which is very difficult to control and might promote heterogeneous nucleation.

![Figure 2.18: Measured induction times as a function of supersaturation and for three different temperatures.](image)

The effect of different reactor configurations on the induction time at 25 °C is shown in Figure 2.19 where the closed circles represent the experimental data measured in this study in a 0.5 L reactor and the open circles represent the data previously measured in a 2 L reactor (Schöll et al., 2006b). It can be seen that the agreement between the 0.5 L and the 2 L reactor is satisfactory, especially if one considers that the induction times have been measured in different reactors at different times and that the impurity profile of the substance used might have changed. The main differences are that the induction time measured in the 0.5 L reactor are slightly longer for low supersaturations, and that the induction times in the 0.5 L reactor do not exhibit the shoulder in the supersaturation range of 5 to 7 that is observed in the 2 L reactor. However, the differences are not signifi-
cant and the nucleation rate can be considered independent of the reactor volume.

![Figure 2.19: Induction times measured at 25 °C in the 0.5 L reactor (filled circles) and in the 2 L reactor (open circles) by Schöll and coworkers (Schöll et al., 2006b).](image)

2.3.4.2 Nucleation rates

The experimental nucleation rates for the different temperatures are calculated from the induction time data using Eq. (2.38), with $G$ given by Eq. (2.39), and $k_v = \pi/6$ and $\alpha_v = 4 \times 10^{-3}$ as discussed above. Their natural logarithm is plotted in Figure 2.20 as a function of $\ln^2 S$. The nucleation rate increases with increasing supersaturation, i.e. decreasing $\ln^2 S$, and increasing temperature. It is readily observed that for each temperature two regimes can be identified, I at high and II at low supersaturation, respectively, and that in each of them the corresponding experimental points follow different curves. Such curves can be obtained first by linearizing either Eq. (2.33) writing $\ln(J/S)$ in terms of $\ln^2 S$, or Eq. (2.36) writing $\ln(J/S \ln S)$ in terms of $\ln^2 S$, then by least-square regressing the experimental data using these linearized expressions, and finally by plotting the obtained functions in the coordinate system of Figure 2.20 (only the regressed curves for interface-transfer control are shown,
being those for volume-diffusion control very similar). A good agreement with the experimental nucleation data can be observed. It must be noted that the experimental data do not allow for a discrimination between the different mechanisms of homogeneous nucleation, e.g. interface-transfer and volume-diffusion control.

Figure 2.20: Nucleation rates of L-glutamic acid as a function of supersaturation and for three different temperatures. The experimental data are given as symbols. The solid lines correspond to the estimated nucleation rates in regime I and the dashed lines to the estimated nucleation rates in regime II.

During the regression procedure, for each temperature, the supersaturation threshold separating regimes I and II was obtained by minimizing the sum of the squared residuals between experimental and estimated nucleation rate for both regimes. The values of the parameters \( a_I, a_D, b_I \) and \( b_D \) were also obtained and are reported in Table 2.3, where the subscript \( \text{exp} \) highlights their being obtained by regressing experimental data. The corresponding experimental estimates of the value of the kinetic parameter \( A \) in Eq. (2.23) can be obtained by substituting the parameters \( a_I \) and \( a_D \) into the pre-exponential term of Eqs. (2.33) and (2.36), respectively; such estimates for interface-transfer control, \( A_{\text{exp}} \) (those for volume-diffusion control are very similar), are reported in Table 2.4, together with the corresponding predicted values of the kinetic parameter.
2. L-glutamic acid pH-shift precipitation

\[ A_{\text{hom}} \] as calculated using Eq. (2.27). Likewise, the experimental estimates of the value of the thermodynamic parameter \( B \) in Eq. (2.23), \( B_{\text{exp}} \), are calculated as

\[ B_{\text{exp}} = b_{\text{exp}} \ln^{-3} \left( \frac{c}{c^*} \right). \tag{2.40} \]

<table>
<thead>
<tr>
<th>Regime</th>
<th>( a_{t,\exp} ) [J mol(^{-1}) K(^{-1}) m(^3)]</th>
<th>( b_{t,\exp} ) [-]</th>
<th>( a_{D,\exp} ) [J mol(^{-1}) K(^{-1}) m(^3)]</th>
<th>( b_{D,\exp} ) [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.0 \times 10^6</td>
<td>2.5 \times 10^1</td>
<td>3.6 \times 10^6</td>
<td>2.3 \times 10^1</td>
</tr>
<tr>
<td>II</td>
<td>1.0 \times 10^1</td>
<td>5.7 \times 10^2</td>
<td>2.7 \times 10^1</td>
<td>5.2 \times 10^2</td>
</tr>
</tbody>
</table>

Table 2.3: Estimated parameters of the nucleation rate for volume-diffusion and interface-transfer control and for the two different observed regimes.

### 2.3.4.3 Interfacial energy

Experimental values of the interfacial energies (or effective interfacial energies in the case of heterogeneous nucleation) at the different temperatures and for the different regimes were estimated using Eq. (2.25) from the values of \( B_{\text{exp}} \), and are given in Table 2.4. The experimental interfacial energies scale with temperature according to Eq. (2.32) and the values for regime I are larger than those for regime II. Moreover, the experimental interfacial energies are of the same order of magnitude as those for other organic compounds (Roelands et al., 2006).

<table>
<thead>
<tr>
<th>Regime</th>
<th>( \theta ) [°C]</th>
<th>( A_{\exp} ) [m(^3) s(^{-1})]</th>
<th>( A_{\text{hom}} ) [m(^3) s(^{-1})]</th>
<th>( \gamma_{\exp} ) [mJ/m(^2)]</th>
<th>( \gamma_{\text{hom}} ) [mJ/m(^2)]</th>
<th>( n^* ) [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>25</td>
<td>1.6 \times 10^{13}</td>
<td>3.9 \times 10^{35}</td>
<td>17.1</td>
<td>35.7</td>
<td>7-13</td>
</tr>
<tr>
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<td>5.4 \times 10^{35}</td>
<td>16.4</td>
<td>34.3</td>
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</tr>
<tr>
<td>I</td>
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<tr>
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<td>9.57</td>
<td>32.7</td>
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</tr>
</tbody>
</table>

Table 2.4: Comparison of experimentally and theoretically obtained kinetic parameter \( A \), interfacial energy \( \gamma \), and critical nucleus size \( n^* \).
Besides the experimental interfacial energies, the values predicted using Eq. (2.32) are reported in Table 2.4 as well. Monte Carlo simulations of homogeneous nucleation of L-glutamic acid at 300 K gave very similar values of the interfacial energy as compared to the predicted ones, namely 26.5 mJ/m$^2$ (Deij et al., 2007).

Based on the experimental interfacial energies the number of molecules forming the critical nucleus, $n^*$, can be calculated using the Gibbs-Thomson equation (Kashchiev and van Rosmalen, 2003). The results are given in Table 2.4 for each nucleation regime and the corresponding supersaturation range. The values of $n^*$ are in the 4 to 18 range, i.e. relatively far from the $n^* \rightarrow 1$ limit. Thus, the density and the interfacial energy can be assumed to be equal to the values for macroscopic crystals and the application of the classical nucleation theory is physically meaningful (Kashchiev and van Rosmalen, 2003; Roelands et al., 2006).

### 2.3.4.4 Discussion

The experimental kinetic parameters $A_{exp}$ presented in Table 2.4 are about 22 to 27 orders of magnitude smaller than the theoretical values for homogeneous nucleation $A_{hom}$. Thus, it can be concluded that although two different nucleation regimes are observed most likely they both correspond to the heterogeneous nucleation mechanism. Moreover, the deviations of the experimental interfacial energies with respect to those predicted using Eq. (2.32) are about 50 to 70 % for regimes I and II, respectively. Recently it was reported that for a number of different molecular compounds the experimentally determined interfacial energies were much lower than the theoretical ones calculated using Eq. (2.32) (Roelands et al., 2006). Thus, it was concluded that the nucleation mechanism was heterogeneous despite the fact that two different regimes in the diagram of $\ln(J)$ over $\ln^2(S)$ were observed, and the different regimes were attributed to a change in experimental setup. In the nucleation rate data presented here two different regimes are also observed though all experiments were conducted in the same apparatus and all nucleation rates were determined using the same method.

Since the different nucleation regimes in Figure 2.20 cannot be explained by a transition from heterogeneous to homogeneous nucleation, they might occur due to the presence of nucleation-active sites for heterogeneous nucleation with
two different activities, whereas the more and less active sites control the nucleation at lower and higher supersaturations, respectively. It might also be possible that a change in the mode of heterogeneous nucleation occurs, i.e. a change from 3D nucleation at lower supersaturations to 2D nucleation at higher supersaturations (Kashchiev, 2000). Exploring this last possibility was however beyond the scope of this work.

To further evaluate the nucleation mechanism, experiments at higher supersaturation should be carried out. However, this cannot be done in the setup used here because of mixing limitations. Nucleation rates at higher supersaturations should rather be determined using a fast static mixer, e.g. the one presented in chapter 4, and applying the method proposed in chapter 5.1.

2.3.5 Conclusions

Induction times of α L-glutamic acid precipitated from aqueous solution via pH-shift have been measured as a function of supersaturation and temperature. It was shown that the induction times decrease with increasing supersaturation and temperature. A scale effect has also been investigated by comparing induction times measured in a 0.5 and a 2 L reactor, respectively. The induction times measured in the two reactors agree relatively well and no significant difference was observed. Combined with independently measured growth kinetics the nucleation rates were determined at 25, 35 and 45 °C and in a supersaturation range between 1 and 8. The estimated kinetic parameters and calculated interfacial energies were much lower than predicted theoretical values for homogeneous nucleation, thus indicating a heterogeneous nucleation mechanism. To the best of our knowledge, for the first time, the effect of temperature on the nucleation rates and the interfacial energies of α L-glutamic acid has been studied.
2.4 Agglomeration effects*

The effect of agglomeration on the final particle size distribution is investigated for batch precipitation processes carried out in stirred tank reactors. Agglomeration kinetics of α L-glutamic acid is determined based on seeded batch experiments by combination with a population balance model and an integral parameter estimation technique. Different modeling approaches for the description of agglomeration are applied and assessed. The empirical model only takes into account the influence of supersaturation and stirring rate on the agglomeration process, while it neglects size-dependencies. In the more rigorous modeling approaches the agglomeration kernel is decomposed into a size-dependent collision frequency and an agglomeration probability. Computational fluid dynamics (CFD) is used to model the turbulent flow in the stirred reactor and to extract information about the shear rate distribution, which in turn can be used to incorporate the dependence of the agglomeration kernel on the local shear rate. The population balance model accounting for nucleation, growth and agglomeration is used to predict the particle size distribution in precipitation experiments.

2.4.1 Introduction

The determination of agglomeration models and of the corresponding agglomeration rates continues to be a major challenge. A number of authors have reported that a size-independent agglomeration rate can be used to describe their experimental data (Collier and Hounslow, 1999; Li et al., 2001; Tavare et al., 1985; Wojcik and Jones, 1997). Based on a more rigorous approach David and co-workers have concluded that the agglomeration process can not be considered as a size-independent phenomenon (David et al., 1991). Mumtaz and co-workers have combined a deposition model and a hydrodynamic model to describe the agglomeration rate and have found out that the agglomeration rate is relatively insensitive to crystal size but highly sensitive to supersaturation (Mumtaz et al., 1997). Hounslow and coworkers have reported that the size ratio of the particles is of limited importance, but that the average particle size has to be accounted for (Hounslow et al., 2001). Ilievski and Livk have devel-

2. L-glutamic acid pH-shift precipitation

Ilievski and Livk (2006) developed an agglomeration model for gibbsite precipitation based on a theoretical analysis of the agglomeration process and a large number of experimental data. The model has shown to give a good fit to the experimental data, yet the authors conclude that the limitations of the model primarily arise from the use of volume-averaged quantities in the model formulation. The implementation of agglomeration kinetics in a CFD model, which was presented by Baldyga and coworkers to simulate the agglomeration of barium sulphate in a pipe, can be used to account for the effect of mixing and shear rate distribution, but is very computational intensive (Baldyga et al., 2003).

In this work, we want to characterize the influence of particle size, stirring rate and supersaturation on the agglomeration rate and we want to avoid the shortcomings of using volume-averaged quantities for the calculation of the agglomeration rate. Moreover, the computational demands should be small enough to allow for estimating the agglomeration kinetics by means of an iterative parameter estimation technique. Our approach for characterizing agglomeration kinetics is based on seeded batch experiments. By FBRM monitoring of these experiments it was confirmed that nucleation effects are negligible. The particle size distribution (PSD) was measured using the Beckman Coulter Multisizer and the desupersaturation profile was determined by employing ATR-FTIR. The experiments show the influence of different process parameters, i.e. initial supersaturation, seed crystal mass and stirring rate, on the final PSD. Based on these results, the parameters in the agglomeration kernel are determined using an integral parameter estimation technique. A population balance model accounting for nucleation, growth and agglomeration has been developed to simulate the precipitation of L-glutamic acid in stirred vessels. Finally, the accuracy of the kinetics correlations is assessed by comparison of simulation results and experimental data.

2.4.2 Experimental procedure

In this study the α-polymorph of L-glutamic acid was precipitated by pH shift of a monosodium glutamate solution using hydrochloric acid as described in section 2.2.

For the determination of agglomeration kinetics a seeded batch procedure was applied. First, the initial supersaturation was created by mixing equimolar aqueous solutions of monosodium glutamate and hydrochloric acid. Secondly,
the seeds were added to the reactor. All experiments were repeated at least once. The repeatability was highly satisfactory, as can be seen in Figure 2.21 for runs 7 and 10. The operating conditions of all experiments are listed in Table 2.5.

<table>
<thead>
<tr>
<th>Run</th>
<th>$S_0$</th>
<th>Seed fraction</th>
<th>Seed mass [g]</th>
<th>Stirring rate [rpm]</th>
<th>$d_{43,seed}$ [μm]</th>
<th>$d_{43,final}$ [μm]</th>
<th>$X$ [-]</th>
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<tr>
<td>1</td>
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</tbody>
</table>

Table 2.5: Experimental conditions, average size $d_{43}$ for seed and final PSD, degree of agglomeration $X$ of the batch experiments. Each run was repeated once. Runs 14 to 16 are unseeded precipitation experiments.

The polymorphic form of the crystals obtained in each experiment was characterized with Raman spectroscopy. The Raman spectra of the two polymorphs of L-glutamic acid exhibit characteristic differences that can be used for polymorph identification (Schöll et al., 2006a). Furthermore the $\alpha$-polymorph has a prismatic, while the $\beta$-polymorph has a needle-like morphology, as can be seen on SEM micrographs (Schöll et al., 2006b). A polymorph transformation, as
reported in a previous work (Schöll et al., 2006a), could not be observed here due to the relatively low temperature of 25 °C.

Figure 2.21: Repeatability of two experiments with different initial seed PSD. Circles: run 7; Squares: run 10.

ATR-FTIR spectroscopy was employed to measure the concentration of L-glutamic acid in the liquid phase by using two characteristic bands in the IR spectra at 1224 cm\(^{-1}\) and 1408 cm\(^{-1}\), which correspond to the protonated and dissociated forms of the carboxylic groups of the L-glutamic acid molecule, respectively. Details about the calibration and the concentration measurements can be found in section 2.2.

The FBRM was employed to confirm that no significant nucleation occurred during the seeded batch experiments. Nucleation can be detected by an increased number of particle counts in the small size range. In none of these experiments nucleation was observed, neither by FBRM monitoring nor by analysis of SEM pictures of the final particles.

The initial and final particle size distributions in each experiment were measured with the Multisizer 3 from Beckman Coulter. Every measurement consists of at least 100,000 particles. The PSD data were smoothed with a moving average filter. In order to minimize breakage in the orifice the differential pressure was reduced from 6 inHg (20318 Pa), which is the default value, to 2 inHg (6773 Pa), thus reducing the shear in the orifice. Furthermore, the crystals to be
measured were directly taken from the wet samples, because filtering and drying might cause breakage of the agglomerates.

The seed crystals were precipitated in a 2 L glass reactor by mixing equimolar aqueous solutions of monosodium glutamate and hydrochloric acid each with a concentration of 0.4 mol/kg. The crystals were wet-sieved with mesh sizes of 64, 125 and 250 μm, respectively. The procedure was repeated until a sufficient amount of seed crystals had been produced. The particle size distributions of the four seed fractions produced are shown in Figure 2.22.

![Particle size distribution of the four seed fractions](image)

Figure 2.22: Particle size distribution of the four seed fractions which were obtained by collecting particles sieved in the size ranges of 64-125 μm (F1), 64-250 μm (F2), 125-250 μm (F3) and >250 μm (F4).

### 2.4.3 Theory of particle agglomeration

The agglomeration of particles can often be observed in precipitation processes, especially at high supersaturations. Agglomeration consists of the cementation of individual particles by chemical forces, i.e. the build-up of a crystalline bridge, while aggregation represents the loose collection of particles by van-der-Waals or electrostatic forces (Braun, 2003). In a supersaturated solution agglomeration usually prevails owing to the higher strength of the crystalline bridge compared to the van-der-Waals forces.

The expression for the rate of agglomeration in a population balance framework accounting for only two-particle collisions was derived by Hulburt and Katz
L-glutamic acid pH-shift precipitation (Hulburt and Katz, 1964). The following equation gives the rate of formation of particles of mass $M$ due to agglomeration:

$$B(M) = \frac{1}{2} \int_{0}^{M} \beta n(M - M') n(M') dM',$$  \hfill (2.41)

where $n$ is the number density, and $\beta$ is the agglomeration kernel. Simultaneously to the formation of a particle by agglomeration, two particles disappear. The following equation defines the rate of disappearance of particles of mass $M$ due to agglomeration:

$$D(M) = \beta n(M) \int_{0}^{\infty} n(M') dM'.$$  \hfill (2.42)

The birth term $B$ and death term $D$ can also be expressed in terms of characteristic particle length with the volume as internal coordinate (Mersmann, 2001):

$$B(L) = \frac{L^2}{2L} \int_{0}^{\lambda} \frac{\beta \left((L^3 - \lambda^3)^{1/3}, \lambda\right)}{(L^3 - \lambda^3)^{2/3}} n\left((L^3 - \lambda^3)^{1/3}\right) n(\lambda) d\lambda$$  \hfill (2.43)

$$D(L) = n(L) \int_{0}^{\lambda} \beta(L, \lambda) n(\lambda) d\lambda ,$$  \hfill (2.44)

where $L$ is the size of the larger and $\lambda$ of the smaller particle. In Eqs. (2.41) and (2.42) the mass is preserved during agglomeration, while in Eqs. (2.43) and (2.44) the volume is preserved and it is assumed that the agglomerate can be described by a characteristic length. However, most expressions for the agglomeration kernel are given in terms of size, and the results of the simulations can be directly compared to the output of the Coulter Multisizer 3 measurements of the PSD.

The challenge in agglomeration modeling is to find a suitable expression for the agglomeration kernel $\beta$. In principle $\beta$ can be expressed as the product of a size-dependent collision kernel $\beta_{col}$, accounting for the collisions of particles in the turbulent flow, and an efficiency factor $\psi$, to take into account only the collisions that lead to a stable agglomerate (Mersmann, 2001):

$$\beta = \psi \beta_{col} .$$  \hfill (2.45)
In the following different approaches for the agglomeration efficiency and the collision kernel are introduced. Then, based on the experimental data, all combinations of these expressions are tested and lastly the most suitable combination is presented.

### 2.4.3.1 Collision kernel

Depending on the particle size and shape as well as on the flow regime different expressions for the collision kernel $\beta_{col}$ can be applied. An overview of the different kernels is presented elsewhere (Braun, 2003). Basically, a distinction can be made between collisions due to the Brownian motion of particles in the submicron range (perikinetic agglomeration) and collisions due to the fluid motion for larger particles (orthokinetic agglomeration).

The collision kernel developed by Saffman and Turner (Saffman and Turner, 1956) can be applied in turbulent flows for isotropic turbulence and if the particles follow the streamlines of the fluid completely (Braun, 2003):

$$\beta_{col}^{I} = 1.3\gamma \left( (L + \lambda) / 2 \right)^{3}.$$  \hspace{1cm} (2.46)

Assuming simple shear flow within the smallest eddies the local shear rate $\gamma$ can be estimated as (Mersmann, 2001):

$$\gamma = \left( \varepsilon / \nu \right)^{0.5},$$  \hspace{1cm} (2.47)

where $\varepsilon$ is the rate of kinetic energy dissipation and $\nu$ is the kinematic viscosity. Shamlou and Tichener-Hooker state that the collision kernel is applicable for particle sizes less than ten times the Kolmogorov microscale $\lambda_{K}$ (Shamlou, 1993), where

$$\lambda_{K} = \left( \nu^{3} / \varepsilon \right)^{0.25}.$$  \hspace{1cm} (2.48)

For the setup and operating conditions used in this study $\lambda_{K}$ is in the range from 40 to 130 μm, hence Eqs. (2.46) and (2.47) can be applied for the entire range of particle sizes used in this study.

For particles larger than the Kolmogorov microscale another equation for the collision kernel was proposed by Kuboi (Kuboi et al., 1972):
Several studies have described the agglomeration efficiency in crystallization processes based on first principle models (Baldyga et al., 2003; David et al., 1991; Ilievski and Livk, 2006). Baldyga and coworkers suggest two expressions for the agglomeration efficiency (Baldyga et al., 2003):

\[
\psi' = \exp \left( -\frac{t_c}{t_r} \right) \tag{2.50}
\]

\[
\psi'' = \left( 1 + k \frac{t_c}{t_r} \right)^{-1} \tag{2.51}
\]

where \( t_c \) is the critical cementation time or time necessary to build a strong bridge between the particles, \( t_r \) is the average interaction time or the time between two rupture events, and \( k \psi \) is an empirical parameter. Eq. (2.50) is based on a formalism used for drop coalescence (Chesters, 1991). Nevertheless, we observed in our experiments that the agglomeration rate is proportional to the growth rate, which can be described better by Eq. (2.51).

The critical cementation time \( t_c \) can be estimated from a force balance of the particle doublet in the turbulent flow (Ilievski and Livk, 2006):

\[
F_{r,\text{max}} = \sigma_c A_c \tag{2.52}
\]

where \( F_{r,\text{max}} \) is the maximum hydrodynamic rupture force, \( \sigma_c \) is the fracture strength of the crystalline bridge, and \( A_c \) is the smallest cross-sectional area that is needed to form a stable bridge. If line contact between the particle doublet is assumed, as proposed by Liew et al. (Liew et al., 2003), the cross-sectional area is

\[
A_c = \lambda_W \tag{2.53}
\]

where \( \lambda \) has a length dimension and \( W \) is the width of the crystalline bridge. In contrast to Liew et al. we did not assume \( \lambda \) to be proportional to the particle size, but to be an empirical constant since no well-defined orientation of the crystals forming the agglomerate could be seen on SEM pictures.

The maximum hydrodynamic rupture force \( F_{r,\text{max}} \) has the form (Mumtaz et al., 1997):
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\[ F_{r, \text{max}} \propto \gamma L_{m}^{2}, \quad (2.54) \]

where \( L_{m} \) is the mean diameter of the doublet.

The critical cementation time is proportional to the time required to reach the width \( W \) with the growth rate \( G \) (Ilievski and Livk, 2006):

\[ t_{c} \propto \frac{W}{G}. \quad (2.55) \]

Combining Eqs. (2.52) to (2.55) yields:

\[ t_{c} \propto \frac{\gamma L^{2}}{\sigma_{c} \lambda_{c} G}. \quad (2.56) \]

Assuming that \( \lambda_{c} \) and \( \sigma_{c} \) are constant one obtains:

\[ t'_{c} = k_{c} \frac{\gamma L^{2}}{G}, \quad (2.57) \]

where \( k_{c} \) is a constant combining parameters of hydrodynamics, material properties and contact geometry. The expression for \( t_{c} \) derived by Baldyga reads as follows (Baldyga et al., 2003):

\[ t''_{c} = \frac{1}{f(L, \lambda)} \sqrt{\rho_{c} \left( \varepsilon / \nu \right)^{0.5} L_{m}}. \quad (2.58) \]

where \( f \) is the shape function, which describes the shape of the crystalline bridge as proposed by David (David et al., 1991), \( G \) is the growth rate, and \( L_{m} \) is the mean diameter of the doublet. Illievski and Li present a similar expression if point contact between the colliding particles is assumed (Ilievski and Livk, 2006):

\[ t'''_{c} = k_{c} \sqrt{\rho \nu \left( \varepsilon / \nu \right)^{0.5} L}. \quad (2.59) \]

If line contact is assumed one obtains:

\[ t^{iv}_{c} = k_{c} \frac{\rho \nu \left( \varepsilon / \nu \right)^{0.5} L}{G}. \quad (2.60) \]
The average interaction time $t_r$ is interpreted as the lifetime of the small turbulent eddies (Baldyga et al., 2003), which is equivalent to the Lagrangian time microscale $\tau_L$ in the case of the viscous subrange:

$$t_r^I = \tau_L \approx Re_\lambda^{0.5} \left( \frac{\nu}{\varepsilon} \right)^{0.5}, \quad (2.61)$$

where $Re_\lambda$ is the Taylor microscale Reynolds number. Alternatively several other approaches might be applied, like the one proposed by Hounslow and coworkers (Hounslow et al., 2001):

$$t_r^{II} = \tau_K = \left( \frac{\nu}{\varepsilon} \right)^{0.5}. \quad (2.62)$$

where $\tau_K$ is the Kolmogorov time microscale.

Rielly and Marquis state that the lifetime of a turbulent eddy is given by

$$t_r^{III} = \frac{C_{\mu}^{3/4} k}{\sqrt{2} \varepsilon}, \quad (2.63)$$

where $k$ is the turbulent kinetic energy and $C_{\mu} = 0.09$ is a model constant in the $k-\varepsilon$ turbulence model (Rielly and Marquis, 2001). In isotropic turbulence the following equation can be applied:

$$\varepsilon = A' \frac{k^{3/2}}{\Lambda}, \quad (2.64)$$

where $\Lambda$ is the integral scale of turbulence and $A'$ is a constant (Yu, 1993). By assuming $\Lambda$ is proportional to the impeller diameter $d_{imp}$, Eq. (2.64) becomes (Yu, 1993)

$$k = 1.5 \left( \frac{\varepsilon d_{imp}}{A' A''} \right)^{2/3}. \quad (2.65)$$

Laufhütte and Mersmann reported a value of $A'' = 6.5$ (Laufhütte and Mersmann, 1985).

In this study all the expressions for $t_c$ and $t_r$ reported above are compared in terms of accuracy in describing the experimental results. The results are presented in section 2.4.5.
2.4.3.3 **Empirical agglomeration kernel**

Another type of agglomeration kernels, which are not based on first principle models, describes the agglomeration process with power-law correlations to be fitted to experimental data. During the experiments described in section 2.3 it was found that the agglomeration of particles is enhanced with increasing growth rate $G$ and decreasing rate of energy dissipation $e$. Similar to other studies the size dependency was neglected (Collier and Hounslow, 1999; Wojcik and Jones, 1997). The expression for the empirical agglomeration kernel has the following form:

$$\beta = a_1 G^{a_2} e^{a_3},$$

with $a_1$, $a_2$ and $a_3$ being fitting parameters. The agglomeration kernel $\beta$ in Eq. (2.66) is given in m$^3$/s, $G$ in m/s and $e$ in m$^2$/s$^3$.

2.4.4 **Population balance model**

The population balance equation (PBE) is used to model the precipitation of L-glutamic acid and to estimate the unknown parameters in the growth rate expressions, as presented later. The PBE written in terms of length for a perfectly mixed batch process with constant volume and a size independent growth rate can be written as follows (Mersmann, 2001):

$$\frac{\partial n}{\partial t} = -G \frac{\partial n}{\partial L} + B - D,$$

where $n$ is the number density of particles, $t$ is the time, $G$ is the growth rate, $B$ and $D$ are the birth and death terms due to agglomeration as given in Eqs. (2.43) and (2.44), respectively. In Eq. (2.67) $L$ is the characteristic particle size. The use of Eq. (2.67) implies that the process is not affected by mixing. Thus, the method that we propose in this study for the determination of agglomeration kinetics is limited to conditions were mixing effects are negligible. This assumption will be verified in section 2.4.5.1.

The concentration $c$ of the solute can be obtained by the material balance and is given by the following equation:

$$\frac{dc(t)}{dt} = -3k_v \rho_v G(t) \int_{L_0}^\infty n(L,t) L^2 \, dL - k_v \rho_v J L_0^3,$$
where \( k_v \) is the volume shape factor, \( \rho_c \) the crystal density and \( L_0 \) is the nuclei size. The following initial and boundary conditions apply for the PBE and the material balance:

\[
\begin{align*}
    n(L_0, t) &= \frac{J}{G} \\
    n(L, 0) &= n_0 \quad \text{(2.70)} \\
    c(0) &= c_0, \quad \text{(2.71)}
\end{align*}
\]

where \( J \) is the nucleation rate, \( n_0 \) and \( c_0 \) are the initial PSD and solute concentration, respectively. The supersaturation \( S \), used for the calculation of the nucleation and growth rates, is defined as follows:

\[
S = \frac{c}{c^*}, \quad \text{(2.72)}
\]

with \( c \) and \( c^* \) being the concentration and solubility of \( \alpha \) L-glutamic acid, respectively. The solubility was determined previously at 25 °C as \( c^* = 10.9 \text{ g/kg} \) (Schöll et al., 2006a). In this work we have used values of \( \rho_c = 1540 \text{ kg/m}^3 \) for the crystal density, \( k_v = \frac{\pi}{6} \) for the volume shape factor and \( L_0 = 0 \) for the nuclei size. However, we have observed that the influence of the nuclei size on the simulation result is negligible in the range of \( L_0 \) from 0 to 100 nm.

### 2.4.4.1 Solution of the population balance equation

One approach for solving the hyperbolic partial differential equation (2.67) is to discretize along the length coordinate, which results in a set of ordinary differential equations and reduces the complexity of the problem drastically. Nevertheless, the solution of these equations, especially if growth and agglomeration are included, can be difficult. We used the method presented by Kumar and Ramkrishna in order to solve the PBE (Kumar and Ramkrishna, 1997). Thereby, the PBE is discretized and each finite size range is represented by a corresponding length, the pivot, and its lower and upper boundary. We used the arithmetic mean of the size of the lower and upper boundaries as size of the pivot. The moving pivot technique greatly reduces the problem of numerical diffusion and instability, while providing the applicability to an arbitrary grid to guarantee accuracy and reasonable computational effort (Kumar and Ramkrishna, 1997). The discretized form of equation (2.67) reads as follows:
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\[
\frac{dN_i(t)}{dt} = \frac{\sum_{j \geq k} (1 - 0.5\delta_{j,k}) \eta_{j,k} \beta(x_j, x_k) N_j N_k}{v_{i-1}(t) \leq v_j(t) + v_k(t) \leq v_{i+1}(t)}
\]

\[\text{Eq. (2.73)}\]

\[\text{and} \]

\[
\frac{dx_i}{dt} = G, \quad i > 1
\]

\[\text{Eq. (2.74)}\]

\[
\frac{dx_i}{dt} = \frac{1}{2} G
\]

\[\text{Eq. (2.75)}\]

where \(x_i\) is the size of the pivot, \(v_i\) is the corresponding volume, i.e. \(v_i = k_v x_i^3\), \(N_i\) is the number of particles in each finite size range and \(\delta_{j,k}\) is the Kronecker delta. The coefficient \(\eta\) is used for the preservation of number and mass:

\[
\eta = \begin{cases} 
\frac{v_{i+1}(t) - [v_j(t) + v_k(t)]}{v_{i+1}(t) - v_j(t)}, & v_j(t) \leq v_j(t) + v_k(t) \leq v_{i+1}(t) \\
\frac{v_{i-1}(t) - [v_j(t) + v_k(t)]}{v_{i-1}(t) - v_j(t)}, & v_{i-1}(t) \leq v_j(t) + v_k(t) \leq v_i(t).
\end{cases}
\]

\[\text{Eq. (2.76)}\]

Eqs. (2.73) to (2.76) were solved using the MATLAB ode45 solver.

2.4.4.2 Growth and nucleation kinetics

The growth rate of \(\alpha\) L-glutamic acid was determined as a function of supersaturation and temperature in section 2.2. For the simulations in this section a simplified growth rate expression being valid at 25 °C was used:

\[
G = 2.8 \times 10^{-7} (S - 1)^{5/6} \exp \left( \frac{-0.56}{S - 1} \right),
\]

\[\text{Eq. (2.77)}\]

where \(G\) is given in m/s.

Similarly, also for the nucleation rate of \(\alpha\) L-glutamic acid, which was determined in section 2.3, a simplified expression describing the nucleation rate in the two regimes at 25 °C was used for the simulations in this section:
\[ J = 7.6 \times 10^{28} \exp\left( \frac{-162.2}{\ln^2 S} \right) + 8.6 \times 10^9 \exp\left( \frac{-9.6}{\ln^2 S} \right), \]  

(2.78)

where \( J \) is given in \( \text{m}^{-3} \text{s}^{-1} \).

### 2.4.4.3 Shear rate distribution in stirred vessels

In stirred tank reactors the mechanisms of particle formation can be influenced by fluid dynamics and mixing (Marchisio et al., 2006b; Vicum et al., 2004). When the time scales of nucleation, growth or agglomeration are comparable to that of mixing a model based on computational fluid dynamics (CFD) is needed. However, if mixing is much faster than the other mechanisms mentioned above the PSD is independent of the spatial coordinate and Eq. (2.67) can be applied. Nevertheless, the agglomeration kernel still depends on the local value of the shear rate, and the spatial distribution of shear rates in the stirred tank has to be taken into account. A straightforward approach is to determine the volume averaged agglomeration kernel:

\[ \bar{\beta} = \int_0^\infty \beta(\varepsilon) f(\varepsilon) d\varepsilon, \]  

(2.79)

where \( f(\varepsilon) \) is the distribution of the energy dissipation in the reactor (Marchisio et al., 2006b). Such a distribution can be calculated from a CFD model of the stirred tank. We used the commercial CFD code FLUENT 6.1 and the standard \( k-\varepsilon \) model to simulate the reactor. The grid was adjusted until a grid-independent solution was obtained. The final grid consisted of 221,233 cells.

A contour plot of the velocity magnitude in the reactor for a stirring rate of 200 rpm is shown in Figure 2.23. In the model it is not accounted for the probe tips in the reactor. Based on the CFD model the energy dissipation distribution can be calculated, in which \( f(\varepsilon) d\varepsilon \) represents the volume fraction in the reactor with an energy dissipation between \( \varepsilon \) and \( \varepsilon + d\varepsilon \). The energy dissipation distribution for a stirring rate of 200 rpm is given in Figure 2.24.

An averaged agglomeration kernel can also be estimated based on a mean value of the energy dissipation, e.g. from a power number correlation:

\[ \bar{\varepsilon}_{PN} = \frac{N_p d_{imp}^5 n^3}{V}, \]  

(2.80)
where \( N_p \) is the power number for the stirrer, \( d_{imp} \) is the impeller diameter, \( n \) is the stirring rate and \( V \) is the reactor volume. For a four blade impeller the power number can be estimated as \( N_p = 0.6 \) (Kraume, 2003). The mean value of the agglomeration kernel based on the power number correlation can be determined as follows:

\[
\bar{\beta} = \beta(\bar{\varepsilon}_{PN}) .
\]  

(2.81)

A comparison of \( \bar{\varepsilon}_{PN} \) with a mean value of the energy dissipation for the CFD model \( \bar{\varepsilon}_{CFD} \), given by

\[
\bar{\varepsilon}_{CFD} = \int_0^\infty \varepsilon f(\varepsilon) d\varepsilon ,
\]

(2.82)

is shown in Figure 2.25. For low stirring rates the agreement is very good, whereas at higher stirring rates the CFD model predicts lower values of the mean energy dissipation compared to the power number correlation. The impact of these two approaches on the calculation of the mean agglomeration kernel, given by Eqs. (2.79) and (2.81), will be discussed in section 2.4.5.

Figure 2.23: Contour plot of velocity magnitude in m/s for a stirring rate of 200 rpm. The CFD simulations were carried out using FLUENT 6.1.
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Figure 2.24: Distribution of energy dissipation in the stirred reactor for a stirring rate of 200 rpm. The distribution was determined from the CFD simulations of the reactor flow field.

Figure 2.25: Mean energy dissipation rate as a function of stirring speed.
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2.4.4.4 Parameter estimation

The agglomeration kernels given in section 2.4.3 require the estimation of empirical parameters, namely $k_y$ for the first principle models and $a_1$, $a_2$, $a_3$ for the empirical model. This is done by an integral parameter estimation technique using a nonlinear optimization algorithm which minimizes the sum of squared residuals between the experimental and computed PSDs obtained using the PBE process model. The nucleation rate in the PBE model was set to zero for the parameter estimation since we did not observe significant nucleation during the agglomeration experiments as explained in section 2.3. The model parameters are estimated by minimizing the sum of squared residuals $SSR$, i.e.:

$$SSR = \sum_{i=1}^{N_e} \sum_{j=1}^{N_c} \left( m_{i,j}^{exp} - m_{i,j}^{sim} \right)^2,$$

where $N_e$ is the number of experiments, $N_c$ the number of channels in the particle size measurement device, $m_{i,j}^{exp}$ and $m_{i,j}^{sim}$ are experimental and simulated mass densities of particles, respectively. The experimental data of 13 seeded batch experiments, as given in Table 2.5, have been used. The optimization problem was solved using the *lsqnonlin* algorithm of the MATLAB optimization toolbox.

An estimate of the standard deviation $\sigma$ is given by:

$$\sigma = \sqrt{\frac{1}{N_t - p} \sum_{i=1}^{N_e} \sum_{j=1}^{N_c} \left( m_{i,j}^{exp} - m_{i,j}^{sim} \right)^2},$$

where $p$ is the number of model parameters $b_k$ ($k = 1, \ldots, p$) and $N_t = N_e N_c$. The standard deviation is used in section 2.4.5.1 to compare the results of the different models in terms of agreement with the experimental data.

Approximate confidence intervals of the model parameters can be determined by calculating the sensitivity matrix, i.e. the derivative of the model predictions with respect to the model parameters, based on a linearized model in the vicinity of the estimated model parameters (Beck and Arnold, 1977). The sensitivity matrix can be used to calculate the approximate covariance matrix of the parameter estimates. The standard error $s_{b,k}$ of the model parameters is given by the square root of the diagonal elements of this covariance matrix (Beck and
Arnold, 1977). The confidence intervals of the model parameters $b_k$ are then given by:

$$b_k \pm t_a \left( N_t - p \right) s_{b,k},$$

(2.85)

where $t_a \left( N_t - p \right)$ is the value of the t-distribution for $N_t - p$ parameters and a confidence interval $a$ (Beck and Arnold, 1977). We have used $a = 0.05$ leading to a 95% probability.

### 2.4.5 Results and discussion

In this section, first the empirical parameters in the agglomeration models given in section 2.4.3 are determined based on seeded batch desupersaturation experiments using the integral parameter estimation technique presented above. Secondly, two agglomeration models, one assuming a constant energy dissipation rate and the other a distribution of the energy dissipation rate in the vessel, are compared, and the validity of the model assumptions is verified. Then, the findings of the agglomeration experiments are presented and compared with the simulation results. Finally, the prediction quality of the precipitation model including nucleation, growth and agglomeration is assessed by comparison with unseeded precipitation experiments.

#### 2.4.5.1 Agglomeration model

The number of possible combinations of the different elements forming the agglomeration kernel, as presented in sections 2.4.3 and 2.4.4.3, is 96: there are in fact two equations for the collision kernel, two for the agglomeration efficiency, 12 combinations of $t_c$ and $t_r$, and two ways of determining an average value of $\beta$. During preliminary simulations it became clear that Eq. (2.50) for the agglomeration efficiency would not give reasonable results since the dependence on growth rate could not be expressed correctly. Thus, the number of combinations to be tested could be reduced to 48. It was found that a number of different combinations can describe the agglomeration process in the observed range of operating conditions with similar accuracy. Nevertheless, the best result in terms of sum of squares residuals (Eq. (2.83)) was obtained using the model given by combining Eqs. (2.46), (2.51), (2.57) and (2.63), i.e.:
\[ \beta = 1.3 \left( \frac{\epsilon}{\nu} \right)^{0.5} \left( \frac{L + \lambda}{2} \right)^3 \left( 1 + k_{\psi} \frac{(\epsilon/\nu)^{0.5} L_m^2 / G}{0.1162 k/\epsilon} \right)^{-1}, \]  

(2.86)

where \( \beta \) is given in \( m^3/s \). The parameter \( k_{\psi} \) was estimated as \( 2.039 \pm 0.025 \frac{s}{m} \) when using the CFD model (Eq. (2.79)) and as \( 1.738 \pm 0.022 \frac{s}{m} \) when assuming a mean energy dissipation based on a power number correlation (Eq (2.81)). The confidence intervals of the parameters are calculated for 95 \% probability using Eq. (2.85). The standard deviation between model and experiment was \( \sigma = 5.71 \times 10^2 \frac{m}{^{-1}} \) for the first case (Eq. (2.79)) and \( \sigma = 5.81 \times 10^2 \frac{m}{^{-1}} \) for the second (Eq. (2.81)). The next best combination had a standard deviation of \( \sigma = 6.09 \times 10^2 \frac{m}{^{-1}} \), while the worst combination had \( \sigma = 9.13 \times 10^2 \frac{m}{^{-1}} \). The standard deviation of each experiment is given in Table 2.6. It must be noted that the standard deviations seem to be randomly distributed, i.e. no specific operating condition is represented significantly better or worse than the average.

Even better results in terms of agreement between model results and agglomeration experiments could be obtained using the size-independent empirical correlation of Eq. (2.66) where the three parameters are estimated to be:

\[ a_1 = (6.0 \pm 1.5) \times 10^{-7} \]
\[ a_2 = (9.0 \pm 0.16) \times 10^{-1} \]  
\[ a_3 = (-7.7 \pm 0.48) \times 10^{-2}. \]  

(2.87)

The standard deviation obtained using Eq. (2.66) together with these parameters is \( \sigma = 4.52 \times 10^2 \frac{m}{^{-1}} \). However, it will be shown below that this empirical model is less effective in predicting the precipitation experiments presented in section 2.4.5.3. The confidence intervals of the parameters in Eq. (2.87) are somewhat larger than those in Eq. (2.86), most likely due to stronger correlation.
Comparison of agglomeration models

A comparison of the simulated final PSDs for the agglomeration model with constant energy dissipation (estimated from the power number correlation Eq. (2.81)) and with energy dissipation distribution (calculated from CFD model Eq. (2.79)) is given in Figure 2.26 for 150 and 300 rpm. The corresponding operating conditions are given as runs 4 and 5 in Table 2.5. The PSDs for the two models are for both stirring rates rather similar. The majority of the experiments in this study was conducted at 200 rpm and can be modeled equally well using either model. Only for smaller or larger stirring rates the differences become more pronounced. This indicates that the shape of the PSD is not influenced very much by using either constant energy dissipation or energy dissipation distribution. Yet, if the power number of the stirrer is not available the mean energy dissipation is difficult to estimate. Also for a scale-
up of the process one might use a combined PBE-CFD model. Especially if mixing becomes important, i.e. at high supersaturation and nucleation rates, a CFD model directly incorporating the population balance equations should be used (Vicum et al., 2004).

Figure 2.26: Comparison of simulation results for agglomeration model using CFD based (solid black line), power number based estimation of the energy dissipation rate (dashed line) and for empirical agglomeration kernel (solid grey line) for two stirring rates (runs 4 and 5).
In Figure 2.26 the simulation result for the empirical agglomeration kernel of Eq. (2.87) are plotted as well. The influence of stirring on agglomeration can be modeled with higher accuracy compared to the other models, mostly due to the fact that this model has three parameters, which can be used to tune supersaturation and stirring dependency separately.

Validity of model assumptions

During the experiments considered in this work no significant nucleation or breakage occurred. These two mechanisms also change the number of particles and should be prevented when determining the agglomeration kinetics. If significant nucleation occurred, as indicated by FBRM monitoring, the experiment was discarded and the operating conditions were changed, i.e. the initial supersaturation was decreased or the amount of seeds was increased. At short experimental times (< 30 min) and moderate stirring (≤ 400 rpm) no significant breakage could be observed. This was verified by measuring the PSD after certain time intervals using the Coulter Multisizer. Only after rather long and intense stirring an increase of finer particles in the PSD, indicating the breakage of agglomerates due to collisions with the stirrer, can be observed as shown in Figure 2.27.

In the population balance equation (2.67) it is assumed that the characteristic timescale for mixing is much shorter than those for nucleation, growth and agglomeration. The characteristic timescale for mixing is in this case the macro-mixing or circulation time $\tau_C$:

$$\tau_C = \frac{V}{C_1 N d_{\text{imp}}^3}, \quad (2.88)$$

where $C_1$ is a constant depending on the pumping capacity of the stirrer, which can be estimated as 1.5 for the impeller (Kraume, 2003). The maximum circulation time was $\tau_C = 1$ s at 150 rpm. The characteristic timescale for nucleation is the induction time $t_i$, which was measured in a previous study (Schöll et al., 2006b): the minimum time at a supersaturation of $S = 7.3$ was $t_i = 23$ s. The characteristic timescale for growth $\tau_G$ describes the rate of concentration decrease resulting from crystal growth and can be calculated as follows (Baldyga and Bourne, 1999):
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\[ \tau_G = \frac{c}{\rho_c a_c G}, \]  
\[ \text{(2.89)} \]

with \( a_c \) being the specific surface of the crystals in the reactor. A typical value for high solid loadings, as in run 12, with \( a_c = 350 \text{ m}^2/\text{m}^3 \), and a supersaturation of \( S = 7.3 \) is \( \tau_G = 120 \text{ s} \). The characteristic time scale for agglomeration \( \tau_A \) is given by the time interval between two consecutive agglomeration events (Marchisio et al., 2006a):

\[ \tau_A = \frac{1}{\beta \mu_0}, \]  
\[ \text{(2.90)} \]

where \( \mu_0 \) is the zeroth moment of the PSD, i.e. the number of particles per volume. We have calculated a minimum value of \( \tau_A = 13 \text{ s} \) for a supersaturation of \( S = 7.3 \) and high solid loading using Eq. (2.87). The comparison of the different timescales shows that for the operating conditions in this study the characteristic timescale for mixing is much smaller than all the other timescales, thus the application of Eq. (2.67) is feasible.

Figure 2.27: Influence of breakage on particle size distribution for a stirring rate of 400 rpm as a function of time. The PSD at 0 min corresponds to run 11 and 200 rpm, afterwards the stirring rate was increased to 400 rpm.
In the agglomeration model presented in section 2.4.3 it is assumed that during the formation of an agglomerate the volume of the two colliding particles is preserved and the diameter of the newly formed particle is that of a volume equivalent sphere. This assumption results in a decrease of surface due to agglomeration over the course of an experiment and a slower depletion of supersaturation. This in turn affects also the agglomeration rate. In reality the surface is approximately preserved during the agglomeration process when neglecting the decrease of available surface at the contact point. In Figure 2.28 the experimental supersaturation profile, which was measured using ATR-FTIR, and the simulated desupersaturation profile of run 7 are shown. Because of the good agreement between experiment and simulation it is reasonable to assume that for the conditions in this study the decrease in surface in the agglomeration model can be neglected.

Figure 2.28: Experimental and simulated desupersaturation profile for run 7. Circles: experiment; solid line: simulation.

2.4.5.2 Agglomeration experiments

The seeded batch procedure described in section 2.3 was applied to determine the agglomeration kinetics of L-glutamic acid in a broad range of operating conditions. The experimental conditions are given in Table 2.5. The influence of supersaturation, stirring rate, seed mass and particle size on the final PSD is
given in Figure 2.29 to Figure 2.32, respectively. In these figures the measured PSD of seed crystals (filled circles), measured final PSD (open circles), simulated final PSD (solid black line) and simulated PSD without agglomeration modeling (solid gray line) are shown. If not stated otherwise the agglomeration model accounting for a shear rate distribution, as given by Eqs. (2.79) and (2.86), is used.

Figure 2.29: Influence of supersaturation on final particle size distribution: (a) $S = 4.24$, run 2; (b) $S = 5.74$, run 3.
Figure 2.30: Influence of stirring rate on final particle size distribution: (a) 150 rpm, run 4; (b) 300 rpm, run 5.
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Figure 2.31: Influence of seed mass on final particle size distribution: (a) 5 g seed, run 11; (b) 7 g seed, run 12.
Figure 2.32: Influence of seed particle size on final particle size distribution: (a) F1 seed, run 7; (b) F3 seed, run 10.
The degree of agglomeration can be defined as:

\[ X = 1 - \frac{\mu_{0,\text{final}}}{\mu_{0,\text{initial}}} , \]  

(2.91)

where \( \mu_{0,\text{final}} \) is the final zeroth moment of the PSD, which corresponds to the final number concentration of particles, and \( \mu_{0,\text{initial}} \) is the zeroth moment of the initial PSD. A small extent of agglomeration corresponds to a low value of \( X \) and vice versa. This definition is reasonable since we can neglect significant nucleation and the change in particle number can only be attributed to agglomeration. The PBE model was used to determine the final number concentration of particles \( \mu_{0,\text{final}} \). The Coulter Multisizer was only applied to obtain the normalized PSDs, but not to measure the absolute number of particles. Since the final experimental and simulated PSDs are in good agreement, it is assumed that the use of a simulated \( \mu_{0,\text{final}} \) is reasonable for calculating the degree of agglomeration \( X \) corresponding to the different experimental conditions that we have explored. The influence of several operating conditions on the degree of agglomeration \( X \) is illustrated in Figure 2.33. The value of \( X \) is given in Table 2.5 for each experiment together with the mean particle size \( d_{43} \) of the seeds and of the experimental final PSD. The mean particle size for spheres is defined by:

\[ d_{43} = \frac{\mu_4}{\mu_3} , \]  

(2.92)

where \( \mu_3 \) and \( \mu_4 \) are the third and fourth moment of the PSD, respectively. The influence of supersaturation on the final PSD is shown in Figure 2.29 by considering runs 2 and 3. The operating conditions for the two experiments are the same, only the initial supersaturation is different. The size of the agglomerates is not only affected by agglomeration but also by growth of the seed crystals. Therefore, in Figure 2.29 the PSDs for simulations not accounting for agglomeration are displayed as well. Compared to simulations without agglomeration the PSD is broader and shifted towards larger particle sizes due to agglomeration. Measured and simulated PSDs including the agglomeration model are in good agreement. For the sake of comparison the mean particle size \( d_{43} \) of the final PSD is given in Table 2.5. The value of \( d_{43} \) increases with increasing supersaturation (run 1 to 3), thus indicating enhanced agglomeration at higher
supersaturation, as demonstrated also by the increasing value of $X$ shown in Figure 2.33.a.

Figure 2.33: Degree of agglomeration $X$ as a function of different operating conditions. (a) Initial supersaturation: runs 1, 2 and 3; (b) Stirring rate: runs 3, 4, 5 and 6; (c) Seed mass: runs 10, 11 and 12; (d) Mean diameter $d_{43}$ of the seed fraction: runs 7, 10 and 13. For details see text.

The influence of stirring rate on the final PSD is illustrated in Figure 2.30 for two stirring rates, namely 150 and 300 rpm corresponding to runs 4 and 5 in Table 2.5. With increasing stirring rate the final PSD is shifted towards smaller particle sizes, which corresponds to a smaller extent of agglomeration. The agreement between experiments and simulations is quite satisfactory. The values of $d_{43}$ for runs 4 to 6 given in Table 2.5 show the same trend of smaller particles at higher stirring rates. The influence of the stirring rate on the degree of
agglomeration is shown also in Figure 2.33.b. The decreasing value of $X$ for increasing stirring rates is due to disruption of the newly formed particle doublets under the action of the stirrer.

The influence of seed crystal mass on the course of the experiment is illustrated in Figure 2.31 with reference to runs 11 and 12. There are three effects. First, the available surface in the system increases with increasing seed mass, thus resulting in a faster depletion of the supersaturation, which in turn reduces the time available for agglomeration. As shown in Figure 2.33.a the agglomeration rate strongly depends on supersaturation. Secondly, the mass being deposited on each crystal is reduced, hence the final primary particles will be smaller. Thirdly, with increasing mass of seed crystals the number of particles is increased too; hence the collision of particles is more likely and the agglomeration rate should increase. As a result of these counteracting effects the degree of agglomeration increases with increasing seed mass, as shown in Figure 2.31 and Figure 2.33.c.

In literature it was often concluded that a size independent agglomeration kernel could best describe the experimental findings (Bramley et al., 1996; Ilievski, 2001; Ilievski and White, 1994; Mumtaz and Hounslow, 2000). We found that the influence of size cannot be neglected if one considers a broad range of particle sizes. The experimental and simulated final PSDs for experiments with two different seed fractions are shown in Figure 2.32. For a better comparability the simulation results omitting agglomeration are shown as well. For smaller particle size (run 7, seed fraction F1) the agglomeration extent is increased compared to larger particles (run 10, seed fraction F3). The same trend can be seen in Figure 2.33.d. This figure shows the degree of agglomeration not only for the same initial seed mass but also for the same initial number density as a function of the mean particle size $d_{43}$ of the seed fraction. For the same mass of seed crystals a smaller seed fraction consists of more particles than a larger seed fraction. Hence, the influence of particle size is difficult to estimate if one compares experimental results for different seed fractions but the same seed mass. Using the PBE model presented here the mass of the initial seeds can be increased until the initial suspension density, i.e. the initial number of particles, is equal for all seed fractions. The result of this simulation is shown in Figure 2.33.d. Also for the same initial suspension density the degree of agglomeration decreases for increasing mean particle size $d_{43}$. 
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2.4.5.3 Precipitation experiments and prediction quality of the model

The prediction quality of the precipitation model is assessed by comparing the PSDs of precipitation experiments with the model predictions including nucleation, growth and agglomeration. The unseeded batch experiments were carried out in a previous study for the determination of the induction time (Schöll et al., 2006b). The experimental conditions are reported in Table 2.5 as runs 14, 15 and 16. The measured PSDs in Figure 2.34.a are very similar over a wide range of supersaturation from \( S = 4.24 \) to \( S = 7.29 \). Also the mean particle size \( d_{43} \) reported in Table 2.5 is in a rather narrow range from 210 to 260 \( \mu m \).

In Figure 2.35 SEM micrographs of the final particles are shown. At low supersaturations the nucleation rate is low and so is the number density and agglomeration rate. The final particles are relatively large single crystals with a size of the longest diagonal of about 300 \( \mu m \) (see Figure 2.35.a). With increasing supersaturation the nucleation rate, suspension density and agglomeration rate are increased as well. The final particles consist of a larger number of small agglomerated crystals. The size of the longest diagonal of the single crystals is about 80 \( \mu m \), the agglomerates are in the range of 200 to 400 \( \mu m \) (see Figure 2.35.b and c). When modeling the precipitation process using only the nucleation and growth kinetics (Eqs. (2.77) and (2.78)) the results indicate a decreasing particle size with increasing supersaturation owing to larger nucleation rates and faster depletion of the supersaturation (Figure 2.34.b). The experimental final particle size distribution can not be predicted correctly. In Figure 2.34.c the results are shown for simulations including the agglomeration model, showing satisfactory accuracy in describing experimental results for all supersaturation levels. The degree of agglomeration \( X \), given in Table 2.5, also increases with increasing supersaturation, thus indicating enhanced agglomeration at higher supersaturation. For precipitation experiments \( \mu_{0,initial} \) in Eq. (2.91) is replaced by the final zeroth moment of the PSD from simulations without agglomeration modeling, i.e. simulations with nucleation and growth only. The experimental PSDs in Figure 2.34.a are slightly broadened compared to the simulations in Figure 2.34.c. For larger particle sizes a slight discrepancy exists between simulation results and experimental data. However, in this region the measurement consists only of a few particles and hence it is subject to error.
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Figure 2.34: Precipitation of L-glutamic acid for three different initial supersaturations (runs 14, 15 and 16): (a) Experimental results; (b) Simulation without agglomeration; (c) Simulations including size-dependent agglomeration model; (d) Simulations including empirical agglomeration model.

Furthermore, small variations in the kinetics might affect the shape of the final PSD drastically because of the strongly nonlinear character of nucleation and the coupling and interplay with growth and agglomeration. It is noticeable that the precipitation process can be predicted based on independently measured kinetics; particularly for the agglomeration kinetics the application of the model to particles smaller than 40 μm is an extrapolation.
When applying the empirical size-independent agglomeration kernel (Eq. (2.87)) to simulate the precipitation experiments it can be seen that the final PSD is less well predicted than with the rigorous model, as shown in Figure 2.34.d. Since in this model the size dependency is neglected already the newly formed nuclei start to agglomerate, thus resulting in larger final particles compared to the experiment. At higher supersaturations than displayed in Figure 2.34 the empirical model predicts even larger particles, which is not in agreement with experimental observation. This is also reflected by the higher values of the standard deviation reported in Table 2.6. Therefore, it can be concluded that the whole precipitation process can only be described correctly with the size dependent agglomeration kernel given by Eq. (2.86). Based on the SEM micrographs shown in Figure 2.35 and on the inspection of many similar pictures, we can conclude that most agglomerates consist of crystals larger than approximately 50 μm and that these crystals are non-agglomerated primary particles. It looks as if particles have to grow up to a certain size before they start to agglomerate. Hence, we believe that also from a physical point of view the agglomeration of L-glutamic acid crystals is a size-dependent process. With reference to Figure 2.34.c and d, it is worth noting that the sharp peak is not due to numerical errors, but it represents small crystals that are formed through a nucleation event occurring at the start of the process. This happens in all three cases, but the peak is smeared out under conditions of intense agglomeration, i.e. at higher supersaturation.
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Figure 2.36: Precipitation model of L-glutamic acid: (a) Final average particle size $d_{43}$; (b) Average number of primary particles per agglomerate $N_a$.

Once the precipitation kinetics of α L-glutamic acid is known the question which particle size can be obtained in a precipitation process by changing the operating conditions can be addressed. The influence of changing the initial supersaturation in a range from two to nine on the average particle size $d_{43}$ is illustrated in Figure 2.36.a. In this figure the results of simulations including the agglomeration model, i.e. for stirring rates of 200 and 400 rpm, and those of simulations without agglomeration are shown. In the latter case the precipitation process is not affected by stirring as to our model where mixing is assumed
to be perfect. For a stirring rate of 200 rpm the average particle size decreases with increasing supersaturation, reaches a region with a local maximum at about \( S = 6.4 \) and finally it further decreases. This local maximum in particle size is less pronounced at higher stirring rates, i.e. at lower agglomeration rates, and disappears if agglomeration is neglected. It is noticeable that in the case of agglomeration the final particles do not go below a certain size, while in the case of omitting agglomeration the final particle size decreases with increasing supersaturation. At the point where the particle size goes below the plateau value the nucleation regime changes (see Eq. (2.78)), thus increasing drastically the number of particles and decreasing the size of the primary particles. In Figure 2.36.b the average number of primary particles per agglomerate \( N_a = (1-X)^{-1} \) is plotted for the same simulations of Figure 2.36.a. The number of primary particles slowly increases with increasing supersaturation until the transition from one to the other nucleation regime occurs. At this point the number of primary particles in the agglomerate increases rapidly with increasing supersaturation. Nevertheless, the size of the primary particles is smaller and hence the size of the agglomerates decreases although the extent of agglomeration increases.

### 2.4.6 Conclusions

A method for the determination of agglomeration kinetics in precipitation processes is presented and applied to \( \alpha \) L-glutamic acid precipitated by pH-shift from an aqueous solution. The method is based on a population balance model and an optimization routine in order to estimate empirical parameters in the agglomeration kernel. Different in-situ measurement techniques, such as ATR-FTIR and FBRM, were applied to monitor solute concentration and particle formation in precipitation experiments. Initial and final particle size distributions were measured using a Coulter Multisizer.

We have assessed quantitatively a large number of expressions for the agglomeration kernel, the agglomeration efficiency and their combinations in terms of agreement between model and experiments. The combination describing the experimental results best can be used to model accurately the agglomeration process in a wide range of operating conditions, i.e. initial supersaturation, stirring rate, seed size and seed mass. It can also be extrapolated to precipitation experiments with much higher supersaturations and smaller particle sizes.
Moreover, we have developed an empirical model which does not depend on particle size. This model describes very well the seeded batch experiments, but is less predictive than the size-dependent kernel in the precipitation experiments.

A model that accounts for the dependence of the agglomeration rate on the heterogeneously distributed shear rate in stirred reactors has also been presented. Computational fluid dynamics (CFD) was used to calculate the shear rate distribution. Alternatively, the mean shear rate was also estimated using a power number correlation. Both approaches gave similar results in this study, but we believe that the proposed use of CFD is applicable under more general conditions, especially if the mean energy dissipation rate is not accessible, and can be used to account for scale-up effects.

The work shows how key mechanisms of particle formation, such as nucleation, growth and agglomeration, can be determined from batch experiments carried out in the same setup but applying different measurement protocols if the process is not affected by mixing. A timescale analysis was employed to check that this condition was fulfilled, i.e. that the characteristic timescales for mixing are much smaller than those for particle formation. The complete detailed model describes precipitation experiments satisfactorily.
2.5 Polymorph transformation*

The polymorph transformation of the metastable $\alpha$ to the stable $\beta$ polymorph of L-glutamic acid at 45 °C is monitored using in-situ Raman spectroscopy. In a series of seeded transformation experiments the effect of different operating conditions on the transformation is studied. Both increasing seed mass and increasing stirring rate decrease the transformation time, thus suggesting an attrition-based secondary nucleation mechanism of the $\beta$ polymorph. Moreover, it is found that no pure seed crystals of the metastable $\alpha$ polymorph can be produced and that different sieve fractions of the $\alpha$ polymorph contain different amounts of the $\beta$ polymorph, which is included within the $\alpha$ crystal. These inclusions have a significant effect on the transformation times meaning that in experiments with larger seeds the transformation is faster than in experiments with smaller seeds. Independent seeded batch desupersaturation experiments are conducted to determine the growth rate of the $\beta$ polymorph. On the basis of this growth rate and of the seeded transformation experiments the secondary nucleation rate of the $\beta$ polymorph is estimated using a population balance model. Together with nucleation and growth kinetics of the $\alpha$ polymorph, which were measured previously in sections 2.2 and 2.3, a fully descriptive model of the polymorph transformation process is developed.

2.5.1 Introduction

Polymorphism is of key importance in the pharmaceutical and fine-chemical industry since different polymorphs have different physical and chemical properties, such as solubility and reactivity. A process involving multiple polymorphs simultaneously, i.e. concomitant polymorphism, can produce more than one crystalline form or a mixture of different crystal structures depending on the operating conditions. In order to avoid production of undesired polymorphs and to obtain a robust crystallization process, thermodynamics and kinetics must be known (Bernstein et al., 1999; Hilfiker, 2006). Concerning the thermodynamics of a polymorph transformation, the Gibbs free energy of the involved polymorphic forms as a function of temperature determine if only one or multiple stable polymorphs exist. A compound is called monotropic or enantiotropic

* Portions of this chapter appear in Cornel et al., Cryst. Growth Des. (9) 2009.
2.5 Polymorph transformation

depending whether the same polymorph or different polymorphs, respectively, are stable at different temperatures. The kinetics of nucleation and growth of each polymorph determines which appears first and how long the transformation from the one, the metastable form, to the other, the stable form, takes. The overall kinetics results from a complex interplay between the involved physical phenomena, i.e. nucleation, growth and dissolution of the involved solid-state forms. Ultimately, accurate kinetic information allows process modeling and enables process design, optimization and control. Whereas the thermodynamic aspects of a solid-state transformation are relatively straightforward and simple to determine, the characterization of transformation kinetics has shown to be a nontrivial task (Borissova et al., 2005; Caillet et al., 2007a; Caillet et al., 2007b; Ono et al., 2004a; Ono et al., 2004b; Qu et al., 2006; Schöll et al., 2006a).

The development of in-situ monitoring techniques via spectroscopic, laser (back) scattering techniques or imaging, enables in-situ characterization of the liquid and the solid phase and results in a significant increase in the amount of information about a particular process. Although the number of publications that report utilization of in-situ characterization tools has increased significantly over the last decade (Aaltonen et al., 2007; Santos et al., 2004; Strachan et al., 2007), the measured quantities are rarely used to develop descriptive process models. Numerous publications describe a polymorphic transformation process quantitatively, however few consider in detail the underlying phenomena, i.e. nucleation, growth and dissolution of the individual solid-state forms. By employing population balance equations (PBEs) a wide variety of transformation processes can be described. Combination of PBE modeling with optimization routines enables estimation of unknown parameters characterizing the involved phenomena. Although PBEs and their numerical solution methods are well-known, few authors consider PBEs as a framework to model a polymorphic transformation. In a previous work (Schöll et al., 2006a), a PBE model of the solvent-mediated polymorphic transformation of L-glutamic acid was presented. However, the effect of various process conditions was not investigated. In a comparable study (Ono et al., 2004a), the same transformation was considered and a descriptive process model was obtained. Yet, a complete insight in the secondary nucleation mechanisms was not provided. Recently, a detailed and thorough work was published considering the solvent-mediated anhydrous to monohydrate transformation of citric acid (Caillet et al., 2007b; Fevotte et
The nucleation and growth rates were determined independently based on an appropriate number of experiments. Secondary nucleation mechanisms were suggested to govern transformation kinetics and a descriptive model was developed.

In this work, we applied Raman spectroscopy to characterize the liquid as well as the solid phase in-situ by means of multivariate data analysis techniques (Cornel et al., 2008b). Nucleation and growth rates of the α form were determined independently (see sections 2.2 and 2.3), leaving the growth and nucleation rates of the stable β polymorph to be determined through seeded batch de-supersaturation and polymorph transformation experiments at different process conditions, i.e. stirring rate, seed mass and seed size.

2.5.2 Materials and methods

L-glutamic acid has two known polymorphs (Schöll et al., 2006a), a metastable α and a thermodynamically stable β polymorph. Whereas the β-polymorph was purchased (≥ 99 %, Sigma-Aldrich, Buchs, Switzerland), the α polymorph is not commercially available and was obtained via pH-shift precipitation by mixing equal amounts of a 0.4 molar monosodium monohydrate solution with a 0.4 molar hydrochloric acid solution at 5 °C. The crystals were filtered 45 minutes after the onset of particle formation. The polymorphic form was verified using X-ray powder diffraction. The meta-stable prismatic α polymorph can also be clearly distinguished from the thermodynamically stable needle-shaped β polymorph by optical microscopy (Schöll et al., 2006a). L-glutamic acid is a monotropic compound, where the β polymorph is the thermodynamically stable solid-state form (Kitamura, 1989; Sakata, 1961; Schöll et al., 2006a).

Experiments were performed in a jacketed glass reactor of 100 mL volume. The reactor was temperature controlled using a Ministat 230-3 thermostat and a Pt 100 temperature sensor, and was equipped with a 4-blade glass impeller (LTS, Biel-Benken, Switzerland) with a diameter of 27.5 mm. This relatively small reactor volume was used to reduce the amount of α crystals required for the seeded transformation experiments.
2.5.2.1 Seeded desupersaturation experiments

Seeded batch desupersaturation experiments were used to estimate growth kinetics of the β polymorph at 45 °C. Two different sieve fractions of β L-glutamic acid were produced to estimate the growth kinetics. The initial PSDs of the seed crystals were measured using the Coulter Multisizer and are shown in Figure 2.37. In each experiment the seeds are added to a supersaturated solution and the change of supersaturation over time, also called desupersaturation profile, is monitored using ATR-FTIR spectroscopy as discussed in section 2.2. The supersaturation was created by mixing equimolar solutions of monosodium glutamate and of hydrochloric acid. The experimental conditions are given in Table 2.7.

2.5.2.2 Seeded transformation experiments

In order to elucidate the governing mechanisms and to estimate the parameters in the nucleation rate expression of the β polymorph of L-glutamic acid, an extensive set of seeded transformations experiments was performed. Different particle size distributions of α seed crystals were obtained via wet sieving. The obtained fractions and corresponding particle size distributions are shown in Figure 2.38. In the seeded experiments a certain seed mass with known particle size distribution was added to a saturated solution with respect to the α form that had been prepared by mixing a monosodium monohydrate solution and a hydrochloric acid solution. Raman spectra acquisition was started upon addition of the seed crystals. All seeded transformation experiments were performed at 45 °C under conditions reported in Table 2.8.

2.5.2.3 Unseeded transformation experiments

In contrast to earlier works (Ono et al., 2004a; Schöll et al., 2006a), where crash-cooling was applied, the desired supersaturation in unseeded experiments was created through addition of a hydrochloric acid solution to a monosodium monohydrate solution. The pH-shift method has two important advantages over crash-cooling: 1) supersaturation is created nearly instantaneously since mixing times are short, whereas during crash-cooling supersaturation is reached over a relatively long time period resulting in nucleation occurring within a range of temperatures instead of at one specific temperature level. 2) Crystals do not appear on the reactor walls as in the case of crash-cooling. It is worth noting
that the reproducibility of unseeded experiments was found to be relatively poor, probably due to a varying level of microscopic dust particles in the reactor resulting in varying heterogeneous nucleation rates.

Figure 2.37: Particle size distribution of β seeds used for growth rate experiments. The average particle sizes were $d_{43}(F_{\beta,1}) = 41 \mu m$ and $d_{43}(F_{\beta,2}) = 132 \mu m$.

<table>
<thead>
<tr>
<th>Run</th>
<th>Seed fraction</th>
<th>$S_\beta$</th>
<th>$\beta$ seed added</th>
<th>Stirring rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$F_{\beta,1}$</td>
<td>2.55</td>
<td>5</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>$F_{\beta,1}$</td>
<td>2.00</td>
<td>5</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>$F_{\beta,2}$</td>
<td>2.55</td>
<td>10</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>$F_{\beta,2}$</td>
<td>2.00</td>
<td>10</td>
<td>300</td>
</tr>
</tbody>
</table>

Table 2.7: Experimental conditions of seeded desupersaturation experiments at 45 °C. Each experiment was repeated once.
2.5 Polymorph transformation

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Figure 2.38: Particle size distributions of α seeds obtained by wet sieving. The following nominal size ranges of the sieves were used: 125 – 250 µm (Fα,1 sieve fraction, d43 = 188 µm), 250 – 355 µm (Fα,2 sieve fraction, d43 = 303 µm), >355 µm (Fα,3 sieve fraction, d43 = 412 µm).

2.5.3 Mathematical description of the polymorphic transformation

2.5.3.1 Population balance model

The mathematical description of the polymorphic transformation of L-glutamic acid is based on population balance equations (PBEs). Combined with an optimization routine, the model allows for estimation of unknown parameters in the kinetics expressions. Assuming a perfectly mixed batch process with constant volume, size independent growth and absence of agglomeration and breakage, the PBE reduces to (Mersmann, 2001):

\[ \frac{\partial n_i}{\partial t} + G_i \frac{\partial n_i}{\partial L} = 0 \quad (i = \alpha, \beta), \quad (2.93) \]

where \( t \) is the time, \( L \) is the crystal size, \( n_i \) is the number density of particles and \( G_i \) is the growth rate of the corresponding polymorph. Mixing effects are assumed to be negligible as discussed in section 2.4 and elsewhere (Schöll et al.,
2. L-glutamic acid pH-shift precipitation

2006b). Agglomeration effects could be neglected since supersaturation is low (see section 2.4).

<table>
<thead>
<tr>
<th>Run</th>
<th>Seed fraction</th>
<th>Seed mass α [g/kg]</th>
<th>β seed added [wt. %]</th>
<th>Stirring rate [rpm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fₐ₁</td>
<td>15</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>Fₐ₁</td>
<td>30</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>Fₐ₁</td>
<td>50</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>Fₐ₁</td>
<td>30</td>
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<td>210</td>
</tr>
<tr>
<td>5</td>
<td>Fₐ₁</td>
<td>30</td>
<td>-</td>
<td>440</td>
</tr>
<tr>
<td>6</td>
<td>Fₐ₂</td>
<td>15</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>7</td>
<td>Fₐ₂</td>
<td>30</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>8</td>
<td>Fₐ₂</td>
<td>50</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>9</td>
<td>Fₐ₃</td>
<td>15</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>10</td>
<td>Fₐ₃</td>
<td>30</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>11</td>
<td>Fₐ₃</td>
<td>50</td>
<td>-</td>
<td>300</td>
</tr>
<tr>
<td>12</td>
<td>Fₐ₃</td>
<td>30</td>
<td>-</td>
<td>440</td>
</tr>
<tr>
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<td>Fₐ₃</td>
<td>30</td>
<td>-</td>
<td>595</td>
</tr>
<tr>
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<td>300</td>
</tr>
<tr>
<td>15</td>
<td>Fₐ₁</td>
<td>30</td>
<td>3</td>
<td>300</td>
</tr>
</tbody>
</table>

Table 2.8: Experimental conditions of seeded transformation experiments at 45 °C. Each experiment was repeated at least once.

The concentration of the solute \( c \) can be obtained through the material balance and is given by the following equation:

\[
\frac{dc}{dt} = -3k_{v,\alpha} \rho_{c,\alpha} G_{\alpha} \int_{0}^{\infty} \frac{n_{\alpha} L^2 dL}{3k_{v,\beta} \rho_{c,\beta} G_{\beta} \int_{0}^{\infty} n_{\beta} L^2 dL}, \tag{2.94}
\]

where \( \rho_{c,i} \) and \( k_{v,i} \) are the solid density and the volume shape factor of the \( i \)th polymorph, respectively. The densities of both polymorphs were assumed to be the same and equal to 1540 kg/m³. Volume shapes factors of \( \pi/6 \) and 0.01 were assumed for the \( \alpha \) and the \( \beta \) polymorph, respectively (Schöll et al., 2006a;
2.5 Polymorph transformation

Schöll et al., 2007b). The following initial and boundary conditions apply for the PBE and material balance in case of seeded transformation experiments:

\[ n_i(0, L) = n_{i,0}(L) \quad (i = \alpha, \beta) \]  
\[ n_i(t, 0) = \frac{J_i}{G_i} \quad (i = \alpha, \beta) \]  
\[ c(0) = c_0 \]  

where \( J_i \) is the nucleation rate of the corresponding polymorphic form, and \( n_{i,0}(L) \) and \( c_0 \) represent the initial particle size distribution (PSD) of polymorph \( i \) and the initial concentration, respectively. The supersaturation with respect to the \( i \)th polymorph, \( S_i \), used to determine nucleation and growth rates, is defined as:

\[ S_i = \frac{c}{c_i^*}, \]  

with \( c_i^* \) being the solubility of polymorph \( i \). The solubilities of both polymorphs were determined previously as a function of temperature (Schöll et al., 2006a). The solubilities at 45 °C are 21.7 g/kg of solvent and 17.0 g/kg of solvent for the \( \alpha \) and \( \beta \) polymorph, respectively.

2.5.3.2 Nucleation kinetics

The nucleation kinetics of the \( \alpha \) polymorph is determined based on induction times measured using ATR-FTIR and FBRM as discussed in section 2.3. The nucleation rate at 45 °C used in this model is

\[ J_\alpha = 2.4 \times 10^8 S_\alpha \exp \left( -\frac{4.4}{\ln^2 S_\alpha} \right), \]  

where \( J_\alpha \) is given in \( \text{m}^{-3}\text{s}^{-1} \).

At low supersaturation levels the \( \beta \) polymorph nucleates only in the presence of the \( \alpha \) form, as verified by long-term experiments where no nucleation occurred after several days in a clear solution that was supersaturated with respect to \( \beta \) and slightly undersaturated with respect to \( \alpha \). At such low supersaturations, i.e. \( S_\beta < 1.27 \), primary nucleation of the \( \beta \) polymorph is negligible (Mersmann, 2001). Therefore, secondary nucleation mechanisms govern the formation of \( \beta \).
nuclei. These mechanisms could include surface and attrition based nucleation. A lumped expression for the secondary nucleation rate was proposed in the literature (Garside and Davey, 1980; Mersmann, 2001):

\[
J \sim f_1(\text{mechanics}) f_2(S) \varphi \overline{E},
\]

(2.100)

where \(f_1\) is the number of attrition fragments formed by collisions, \(f_2\) is the fraction of particles which grow and survive, \(\varphi\) is the volumetric crystal holdup, and \(\overline{E}\) is the mean specific power input. The mean specific power input \(\overline{E}\) can be estimated using a power number correlation:

\[
\overline{E} = \frac{N_p d_{\text{imp}}^5 n_s^3}{V},
\]

(2.101)

where \(N_p\) is the power number for the stirrer type used, \(d_{\text{imp}}\) is the impeller diameter, \(n_s\) is the stirring rate, and \(V\) is the reactor volume. For a four blade impeller, the power number can be estimated as \(N_p = 0.6\) (Kraume, 2003).

The effect of supersaturation could not be studied since during the transformation period the concentration stays constant at the solubility of the \(D\) polymorph. Thus, a simplified expression for the nucleation rate of \(E\) was applied:

\[
J_\beta = k_{j1} (m_a)^{k_{j2}} \overline{E}^{k_{j3}},
\]

(2.102)

where \(m_a\) is the mass of the \(\alpha\) polymorph, and \(k_{j1}, k_{j2}\) and \(k_{j3}\) are empirical parameters. The nucleation rate in Eq. (2.102) is given in \(\text{m}^{-3}\text{s}^{-1}\), \(m_a\) in \(\text{g/kg}\), and \(\overline{E}\) in \(\text{m}^2/\text{s}^3\). Recently, a similar rate expression was used by Fevotte and co-workers to model the transformation of the anhydrous form of citric acid to the monohydrate form (Caillet et al., 2007b). Yet, the effect of stirring was not investigated by these authors.

### 2.5.3.3 Growth and dissolution kinetics

The growth mechanism of the \(\alpha\) polymorph was found to be integration controlled and of the birth-and-spread type (Kitamura and Ishizu, 2000). The growth kinetics at 45 °C was measured in section 2.2 and is implemented as

\[
G_a = 9.6 \times 10^{-7} (S_a - 1)^{2/3} \left( \ln S_a \right)^{1/6} \exp \left( -\frac{0.54}{\ln S_a} \right),
\]

(2.103)
where $G_\alpha$ is given in m/s.

It has been shown by Davey and coworkers that in solvent-mediated polymorph transformations either dissolution or growth can be rate controlling (Davey et al., 1986). If during the transformation the liquid phase concentration stays at the solubility of the metastable dissolving polymorph, as shown later in this paper for L-glutamic acid, then the transformation is growth controlled. Dissolution of the $\alpha$ polymorph was estimated based on the Sherwood correlation and was incorporated as (Schöll et al., 2006a)

$$D_\alpha = 2.2 \times 10^{-4} \left( S_\alpha - 1 \right),$$  \hspace{1cm} (2.104)

where $D_\alpha$ is given in m/s. As shown previously (Schöll et al., 2006a), dissolution is not the rate-determining step in this transformation; hence a change of one order of magnitude in the coefficient given in Eq. (2.104) did not change the simulation results.

Nucleation and growth rates of the $\alpha$ form are only implemented in case of unseeded transformation experiments where $S_\alpha \geq 1$. If the concentration is lower than the solubility of $\alpha$, the dissolution rate $D_\alpha$ is used instead of the growth rate $G_\alpha$ in Eqs. (2.93), (2.94) and (2.96), and $J_\alpha$ is set to zero.

Growth of the $\beta$ polymorph was found to be of the birth-and-spread type as well (Kitamura and Ishizu, 2000). However, the parameters were unknown and had to be estimated from seeded batch experiments as shown in section 2.5.4.

$$G_\beta = k_{G_1} \left( S_\beta - 1 \right)^{5/6} \exp \left( -\frac{k_{G_2}}{S_\beta - 1} \right),$$  \hspace{1cm} (2.105)

where $G_\beta$ is given in m/s.

### 2.5.3.4 Solution of the population balance model

The model equations above were solved using the moving pivot technique proposed by Kumar and Ramkrishna (Kumar and Ramkrishna, 1997). Following this approach, the PBE is discretized, and each size range is represented by a corresponding length, the pivot, and its lower and upper boundary. We used the arithmetic mean of the size of the lower and upper boundaries as size of the pivot. The moving pivot technique greatly reduces the problem of numerical diffusion and instability, while providing the needed accuracy and requiring a
reasonable computational effort (Kumar and Ramkrishna, 1997). The discretized form of Eq. (2.93) is:

\[
\frac{dN_{i,j}}{dt} = J_i \delta_{j,1} \tag{2.106}
\]

\[
\frac{dx_{i,j}}{dt} = G_i, \quad j > 1 \tag{2.107}
\]

\[
\frac{dx_{i,1}}{dt} = \frac{1}{2} G_i, \tag{2.108}
\]

where \(N_{i,j}\) represents the total number of particles of the \(i\)th polymorph in the \(j\)th size range, \(\delta_{j,1}\) represents the Kronecker delta and \(x_{i,j}\) is the size of the \(j\)th pivot corresponding to the \(i\)th polymorph. Essentially, the right-hand-side of eq (2.106) reduces to zero for all size ranges except the smallest one. Equations (2.106), (2.107) and (2.108) were solved using the MATLAB \texttt{ode45} solver. In case of seeded transformation experiments, \(J_\alpha\) and \(G_\alpha\) are set to zero since \(S_\alpha\) is smaller than or equal to unity. It should be noted that the reactor volume was constant since all concentrations are given per cubic meter of solvent.

### 2.5.3.5 Parameter estimation

As discussed above, the growth rate parameters of the \(\beta\) polymorph were estimated on the basis of seeded batch desupersaturation experiments with \(\beta\) seed crystals. The unknown parameters were estimated using a nonlinear optimization algorithm that minimizes the sum of squared residuals between the experimental and the simulated values of the supersaturation of \(\beta\). The model parameters are estimated by minimizing the sum of squared residuals \(\text{SSR}\), written as

\[
\text{SSR} = \sum_{i=1}^{N_e} \sum_{j=1}^{N_d,i} (S_{i,j}^{\text{exp}} - S_{i,j}^{\text{sim}})^2, \tag{2.109}
\]

where \(N_e\) is the number of experiments, \(N_d,i\) the number of data points per experiment \(i\), and \(S^{\text{exp}}\) and \(S^{\text{sim}}\) the experimental and simulated supersaturation with respect to \(\beta\), respectively. The experimental data of seeded desupersaturation experiments given in Table 2.7 has been utilized. The MATLAB optimization algorithm \texttt{lsqnonlin} has been used to solve the optimization problem.
Then, the unknown parameters in the expression for the nucleation rate of $\beta$ were estimated using a nonlinear optimization algorithm that minimizes the sum of squared residuals between the experimental and simulated solid phase compositions resulting from the previously described PBE model, i.e.

$$SSR = \sum_{i=1}^{N_i} \sum_{j=1}^{N_{ij}} \left( w_{i,j}^{\text{exp}} - w_{i,j}^{\text{sim}} \right)^2,$$

(2.110)

where $w_{i,j}^{\text{exp}}$ and $w_{i,j}^{\text{sim}}$ are the experimental and simulated solid compositions expressed as weight percent $\alpha$ polymorph, respectively. The experimental data of seeded transformation experiments (runs 1 – 11) given in Table 2.8 has been utilized. The MATLAB optimization algorithm $fminsearch$ has been used to minimize Eq. (2.110) by varying the parameters in the nucleation rate expression of the $\beta$ polymorph.

$lsqnonlin$ is generally faster than $fminsearch$ and its convergence behavior was found to be good for the estimation of the growth rate parameters. However, for the estimation of the nucleation rate parameters $fminsearch$ was used since the objective function is very shallow close to the optimum, and only $fminsearch$ could find the optimum.

Approximate confidence intervals of the model parameters $b$ can be determined by calculating the sensitivity matrix, i.e. the derivative of the model predictions with respect to the model parameters, based on a linearized model in the vicinity of the estimated values (Beck and Arnold, 1977). The sensitivity matrix can be used to calculate the approximate covariance matrix of the parameter estimates. The standard error $s_k$ of the $k$th model parameter is given by the square root of the $k$th diagonal element of this covariance matrix (Beck and Arnold, 1977). The confidence intervals of the $k$th parameter are given by

$$b_k \pm t_{\alpha,\nu}s_k,$$

(2.111)

where $t_{\alpha,\nu}$ is the value of the $t$-distribution for confidence interval $\alpha$ in case of $\nu$ degrees of freedom. We have used $\alpha = 0.05$ leading to a 95% probability (Beck and Arnold, 1977).

### 2.5.4 Results and Discussion

In this section, first the growth rate of the $\beta$ polymorph is characterized based on seeded batch desupersaturation experiments. Then, the results of seeded
polymorph transformation experiments are reported and the parameters in the
expression for the nucleation rate of $\beta$ are estimated. Finally, the model is used
in a fully predictive manner to estimate the transformation times in unseeded
polymorph transformation experiments.

2.5.4.1 Seeded batch desupersaturation experiments

The experimental method requires that only the added seed crystals grow dur-
ding desupersaturation and that no new particles are formed. Therefore, FBRM
was used to ensure that no significant nucleation occurred during the experi-
ment. Nucleation can be detected by an increasing number of particle counts in
the small size range (Schöll et al., 2007b). In none of the growth experiments
nucleation was observed. The parameters in the growth rate expression were
estimated as described in section 2.5.3.5. The experimental conditions are given
in Table 2.7. Two different sieve fractions were used to check if a size-
dependent growth rate could be employed to describe the experimental data.
The experimental results of the desupersaturation experiments are shown in
Figure 2.39. The effect of different initial supersaturation can be observed in
Figure 2.39.a for the smaller seeds $F_{\beta,1}$ and in Figure 2.39.b for the larger seeds
$F_{\beta,2}$. It must be noted that for the $F_{\beta,1}$ seeds only half of the mass was used.
Thus, owing to the larger surface area of the $F_{\beta,1}$ seeds, the depletion of the
supersaturation is faster for this sieve fraction. However, experimental and
simulated desupersaturation profiles are in reasonably good agreement and the
growth rate parameters in Eq. (2.105) were estimated as:

$$k_{G1} = (5.7 \pm 0.1) \times 10^{-7} \text{ m s}^{-1} \quad (2.112)$$

$$k_{G2} = 0.95 \pm 0.01 \quad (2.113)$$

The $\alpha$ and the $\beta$ growth rates are plotted in Figure 2.40; the growth rates are
expressed in terms of growth of a volume equivalent sphere in order to allow
for direct comparison of the growth rates. The following equation was em-
ployed to calculate the growth rate $G$ of a volume equivalent sphere:

$$G = G_L \left( \frac{6k_v}{\pi} \right)^{1/3} \quad (2.114)$$
where $G_L$ is the growth rate of the characteristic dimension $L$, i.e. the length of the $\beta$ needle. It can be seen in Figure 2.40 that for $S_\alpha \geq 1.35$ the growth rate of $\alpha$ is larger than that of $\beta$, and vice versa. Thus, at supersaturations larger than 1.35 the formation of $\alpha$ over $\beta$ is most likely kinetically favored in agreement with Ostwald’s rule of stages (Cardew and Davey, 1985; Davey et al., 1986).

Figure 2.39: Desupersaturation profiles for two different seed fractions $F_{\beta,1}$ (a) and $F_{\beta,2}$ (b) given in Figure 2.37; Symbols: experimental data; Lines: simulation results.
2. L-glutamic acid pH-shift precipitation

Figure 2.40: Comparison of the growth rates of the $\alpha$ and the $\beta$ polymorph. Please note that the overall growth rate of a volume equivalent sphere is plotted for $\alpha$ and $\beta$, respectively.

2.5.4.2 Seeded polymorph transformations

Experimental results

Seeded batch experiments were conducted to estimate the nucleation rate of the $\beta$ polymorph. Moreover, the effect of different operating conditions, such as seed size, seed mass and stirring rate, was investigated. The operating conditions for the seeded polymorph transformation experiments are given in Table 2.8. Each experiment was carried out twice. The repeatability was found to be excellent, as shown by the very good agreement of the solid compositions and liquid phase concentrations in Figure 2.41 in the case of runs 1 and 2. In the following, the average of the two measured solid composition profiles, i.e. those corresponding to the repeated experiments, was taken in order to reduce the scattering in the measured solid compositions.

After addition of the $\alpha$ seed crystals to the saturated solution, the metastable $\alpha$ polymorph transforms slowly into the stable $\beta$ form as shown in Figure 2.41.a. Since nucleation and growth of the $\beta$ form are the rate limiting steps in the polymorph transformation of L-glutamic acid, the concentration stays at the
solubility of the $\alpha$ polymorph until the last $\alpha$ crystal has dissolved, and the concentration eventually approaches the solubility of $\beta$ (Figure 2.41.b).

![Graphs](image)

Figure 2.41: Experimental repeatability of seeded transformation experiments in terms of solid composition (a) and liquid phase concentration (b).

The effect of initial seed mass on the transformation time is shown in Figure 2.42 for the F$\alpha$, sieve fractions, i.e. the seeds between 125 and 250 $\mu$m. It can
be observed that with increasing mass of seed crystals the transformation time decreases. The results for the F_{a,2} and F_{a,3} sieve fraction, i.e. the seeds in the ranges of 250 – 350 and >350 μm, are shown in Figure 2.43 and Figure 2.44, respectively. Also for these two sieve fractions the transformation time decreases with increasing seed mass. However, for the same seed mass the transformation time increases with decreasing seed size. This is somehow in contradiction to the previously proposed nucleation mechanism, i.e. surface nucleation on the α crystals (Cashell et al., 2003a; Ferrari and Davey, 2004; Schöll et al., 2006a), where a larger surface would provide more sources of nucleation. We believe that our α seed crystals were not pure in terms of polymorph composition. This had a large effect on the transformation times and seemed to dominate the effect of a larger surface area. SEM micrographs of the α seeds are shown in Figure 2.45 and reveal the presence of β crystals within the α seed. This inclusion has been reported previously (Cashell et al., 2003b), and it was suggested that β nucleates on the surface of α and gets included in the α crystals by overgrowth owing to the higher growth rate of α, which is expected based on the growth rates shown in Figure 2.40. Typically, this happens during the very early stages of the process, i.e. when supersaturation is high. Thus, it is very likely that the largest seed crystals have the highest density of these β inclusions since they were formed at an earlier stage in the process. Unfortunately, it was possible neither by Raman spectroscopy nor by X-ray powder diffraction to quantify the amount of β inclusions in the α seeds. Furthermore, we tested the lower detection limit of β in α seeds. For this purpose we added to the α seeds with the lowest contamination (fraction F_{a,1}) a known amount of β crystals. It was found that below 5 wt.% no change in the Raman spectra could be observed. Nevertheless, in order to quantify the amount of β inclusion in the different sieve fractions we could estimate these parameters, i.e. the amount of contamination with β in the different α sieve fractions, together with the nucleation rate.

It must be noted that the slope of the polymorph composition curve increases with increasing size of the seed crystals. For the F_{a,1} seeds the slope is almost zero at the beginning of the transformation and gets steeper for the F_{a,2} and F_{a,3} seeds. It is obvious that for the latter cases some β crystals must be present in the very beginning otherwise it would take much longer until the polymorph composition changes significantly.
2.5 Polymorph transformation

Figure 2.42: Polymorph transformation with small seed crystals ($F_{a,1}$ fraction). Symbols: experimental data; Lines: simulation results.

Figure 2.43: Polymorph transformation with medium seed crystals ($F_{a,2}$ fraction). Symbols: experimental data; Lines: simulation results.
2. L-glutamic acid pH-shift precipitation

Figure 2.44: Polymorph transformation with large seed crystals (F_{α,3} fraction). Symbols: experimental data; Lines: simulation results.

Figure 2.45: SEM micrographs showing α seeds contaminated with β platelet particles.

The effect of stirring on transformation times is illustrated in Figure 2.46 and Figure 2.47 for two different sieve fractions. The transformation times decrease significantly with increasing stirring rates. In case we assume an integration limited growth mechanism of the β polymorph, which is highly justified at low supersaturations in a stirred vessel, the only mechanism being affected by the stirring rate and having an effect on the transformation time is the nucleation of the β polymorph.
2.5 Polymorph transformation

Figure 2.46: Effect of stirring on seeded polymorph transformation. $F_{\alpha,1}$ seeds with a concentration of 30 g/kg were used for all three stirring rates. Symbols: experimental data; Lines: simulation results.

Figure 2.47: Effect of stirring on seeded polymorph transformation. $F_{\alpha,3}$ seeds with a concentration of 30 g/kg were used for all three stirring rates. Symbols: experimental data; Lines: simulation results.
Typically, attrition based secondary nucleation mechanisms show a dependency of the stirring rate. If $\beta$ nucleation is induced by $\alpha$ surfaces, then the abrasion of $\alpha$ crystals will catalyze the nucleation rate of $\beta$ as previously observed (Ferrari and Davey, 2004).

**Simulation results and estimated nucleation rate**

The parameter estimation technique presented in 2.5.3.5 was used together with the population balance model and the experimental results of the seeded transformation experiments in order to determine the nucleation rate of the $\beta$ polymorph. To this aim runs 1 to 11 were employed for the parameter estimation and runs 12 to 15 were used for model validation. As discussed in the previous section no pure $\alpha$ seed could be produced and the initial contamination with $\beta$ could not be quantified experimentally. Thus, the initial amount and characteristic size of $\beta$ crystals in the $\alpha$ seed had to be estimated as well. It must be noted that simulations of the process without accounting for the initial contamination of the $\alpha$ seeds did not give satisfactory results. In these simulations the polymorph composition with respect to $\alpha$ was always overpredicted in the first half of the process, whereas it is was underpredicted in the second. The overall shape of the polymorph composition curve could never be predicted correctly. Based on these considerations, runs 1 to 11 were used to estimate seven parameters, namely those for the secondary nucleation of $\beta$ on $\alpha$ crystals, i.e. $k_{\beta1}$, $k_{\beta2}$ and $k_{\beta3}$ in Eq. (2.102), the average size of the $\beta$ crystals in the seeds, which is assumed to be the same for the three sieve fractions, and the percentage of $\beta$ impurities in each sieve fraction. The nucleation rate parameters were estimated to be:

$$k_{\beta1} = (7.6 \pm 0.2) \times 10^5 \text{ m}^{-3}\text{s}^{-1}$$  \hspace{1cm} (2.115)

$$k_{\beta2} = 2.29 \pm 0.01$$ \hspace{1cm} (2.116)

$$k_{\beta3} = 0.88 \pm 0.01.$$ \hspace{1cm} (2.117)

While $k_{\beta3}$ seems to be quite reasonable, i.e. in the range of 0.5 to 1, $k_{\beta2}$ appears to be rather large, though not unrealistic. For collisions with the impeller a value of 1 is expected and for particle-particle collisions a higher value of 2 can be derived. However, also larger values than 2 have been reported (Lacmann et al., 1999).

The initial amount of the $\beta$ crystals included in the $\alpha$ seeds was estimated to be:
The average size of the $\beta$ crystals in the $\alpha$ seeds was assumed to be constant for all three sieve fractions. We assumed a Gaussian distribution with a standard deviation of 20% of the mean since this gave reasonable PSDs as compared to measured PSDs of $\beta$ L-glutamic acid, e.g. the one given in Figure 2.37. The average size was estimated as $L_{\beta,0} = 26.6 \pm 0.7 \, \mu m$ which seems to be in good agreement with the SEM pictures, e.g. that in Figure 2.45. It must be noted that at the beginning of the experiments, the experimental polymorph composition is always very close to 100%. This is because, first, in the calibration model (Cornel et al., 2008b) the seeds were assumed to be pure, and second, very low concentrations of $\beta$ could not be measured by Raman spectroscopy as mentioned in the previous section. It is worth noting that the presence of $\beta$ crystals in the seeds speeds up the transformation just because the new $\beta$ phase can start to grow immediately as the experiment starts, the faster the larger the value of $w_{\beta,0}$.

To validate the nucleation kinetics determined above, polymorph transformation experiments with the $F_{\alpha,3}$ seeds and different stirring rates were conducted. It must be noted that the model is fully predictive at these conditions. The experimental data and the simulation results are shown in Figure 2.47. The transformation time decreases with increasing stirring rate and the trend is well predicted by the model. However, the agreement between model and experiment is less satisfactory than for the small seeds. The effect of attrition might be larger for the bigger seeds and hence the nucleation rate underpredicted.

In addition, we have tested whether the estimated contamination of the $\alpha$ seeds is reasonable. Therefore, we conducted transformation experiments with the $F_{\alpha,1}$ seeds and a seed concentration of 30 g/kg. To this we added a certain mass of $\beta$ crystals with known PSD, i.e. that corresponds to $F_{\beta,1}$ in Figure 2.37. Then, the transformation was monitored as described above. The results are shown in Figure 2.48. With increasing initial mass of $\beta$, expressed as weight percentage $\alpha$ seed mass, the transformation time decreases as expected. Moreover, the initial slope increases, thus showing the importance of $\beta$ contamination on the
course of the transformation. The agreement between the modeling results and the experiments is reasonably good.

Figure 2.48: Effect of initial amount of β polymorph on transformation time. The initial concentration is given as mass percentage of the initial α seeds ($F_{α,1}$ fraction with a concentration of 30 g/kg). Symbols: experimental data; Lines: simulation results.

The growth and nucleation rates at 45 °C of the two polymorph of L-glutamic acid were determined previously based on unseeded batch experiments (Schöll et al., 2006a). The comparison of these rates with those being presented here shows some discrepancy. We believe that this is due to the fact that in the work of Schöll nucleation and growth rates had been determined simultaneously, i.e. under conditions where they were highly correlated. Moreover, in that work the range of operating conditions was narrower than here and for example the effect of stirring was not investigated. This work represents a step forward in that the different kinetics have been measured independently in order to develop models with higher accuracy and prediction quality.
2.5 Polymorph transformation

2.5.4.3 Unseeded polymorph transformations

A series of unseeded transformation experiments has been performed at 45 °C. In each of these experiments a monosodium glutamate solution was mixed with a hydrochloric acid solution to create the initial supersaturation. The initial supersaturation with respect to the \( \alpha \) polymorph was varied from 1.75 to 3.75 by changing the initial concentrations. The stirring rate was kept constant at 300 rpm. A typical course of the solid phase composition and the solute concentration is shown in Figure 2.49a.

The kinetic parameters as obtained from seeded transformation experiments were used to simulate all the unseeded polymorphic transformations. The kinetic expressions and the estimated parameters are summarized in Table 2.9. In this case, the model accounts for growth and nucleation of both polymorphs, and is used in a fully predictive manner. The comparison between experiment and simulation for one specific case is illustrated in Figure 2.49a. From the simulation results induction time and endpoint were extracted and compared with experimental results. For further analyses, the total transformation period, i.e. induction time plus actual transformation period indicated as \( t_i \) and \( t_p \) in Figure 2.49a, respectively, was considered and plotted in Figure 2.49b. The lowest supersaturation as applied in the conducted induction time experiments equaled 2.0, hence the simulation results shown as dashed line are based on extrapolated nucleation kinetics.

In the simulations in Figure 2.49b, the total transformation time decreases for an increasing initial supersaturation. The experiments exhibit a similar trend, but there is a significant amount of scattering. The displayed experimental points are the result of at least three transformation experiments and the variance is given as error bars in the plot.

The large variability in the experimental data can be explained based on an analysis of an unseeded transformation experiment. After the formation of \( \alpha \) crystals and the depletion of the supersaturation, an unseeded polymorph transformation is governed by the same phenomena as a seeded transformation experiment, i.e. dissolution of the \( \alpha \) polymorph and nucleation and growth of the \( \beta \) polymorph. These phenomena are well reproducible as shown through the series of seeded transformation experiments as discussed in section 2.5.4.1, therefore the scattering in Figure 2.49b is most likely due to primary nucleation...
Figure 2.49: (a) A representative unseeded transformation experiment with initial supersaturation $S_a = 2.5$ where $t_i$ and $t_p$ represent induction time and transformation period, respectively. Lines represent simulation results and symbols experimental data. (b) Total transformation period ($t_i + t_p$), experimental (symbols) and simulated (line), as a function of the initial supersaturation. Experimental transformation times are the result of at least three transformation experiments and the variance is given as error bars in the plot.


<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$ nucleation, $J_\alpha$</td>
<td>$J_\alpha = 2.4 \times 10^8 S_\alpha \exp\left(-\frac{4.4}{\ln^2 S_\alpha}\right)$</td>
</tr>
<tr>
<td>$\alpha$ growth, $G_\alpha$</td>
<td>$G_\alpha = 9.6 \times 10^{-7} (S_\alpha - 1)^{2/3} \left(\ln S_\alpha\right)^{1/6} \exp\left(-\frac{0.54}{\ln S_\alpha}\right)$</td>
</tr>
<tr>
<td>$\alpha$ dissolution, $D_\alpha$</td>
<td>$D_\alpha = 2.2 \times 10^{-4} (S_\alpha - 1)$</td>
</tr>
<tr>
<td>$\beta$ nucleation, $J_\beta$</td>
<td>$J_\beta = 7.6 \times 10^7 m_\alpha^{2.29} \xi^{0.88}$</td>
</tr>
<tr>
<td>$\beta$ growth, $G_\beta$</td>
<td>$G_\beta = 5.7 \times 10^{-7} (S_\beta - 1)^{5/6} \exp\left(-\frac{0.95}{S_\beta - 1}\right)$</td>
</tr>
</tbody>
</table>

Table 2.9: Mechanisms and their kinetics expressions at 45 °C used in the population balance model.

of $\alpha$ and $\beta$ crystals during the induction period. Primary nucleation as a stochastic phenomenon is known to be difficult to reproduce and experiments conducted with great care may still exhibit a large variability (section 2.3 and (Teychene and Biscans, 2008). During the induction period, the $\alpha$ as well as the $\beta$ polymorph nucleate simultaneously, both with a certain variability. As discussed in section 2.5.4.1 and shown in Figure 2.48, small variations in the relative amount of the $\beta$ form as well as in the obtained particle size distribution have a significant effect on the transformation times and most likely result in the observed scattering in Figure 2.49b.

2.5.5 Conclusions

The quantitative use of in-situ Raman monitoring enables new insights in fundamental mechanisms of polymorph transformations. The solvent mediated polymorph transformation of L-glutamic acid is governed by nucleation,
growth and dissolution of the metastable α polymorph and the nucleation and
growth of the stable β polymorph. Raman spectroscopy is used to determine the
secondary nucleation rate of the stable β polymorph of L-glutamic acid at vari-
ous operating conditions. The proposed method is based on seeded transforma-
tion experiments and requires that the growth rate of the β polymorph is meas-
ured independently. Following the method proposed earlier (section 2.2), we
have measured the growth rate of the β polymorph on the basis of separate
seeded batch desupersaturation experiments. Then, the data of the polymorph
transformation experiments can be used together with a population balance
model and a non-linear least-squares optimization to determine the secondary
nucleation rate of the β polymorph, which is otherwise not directly accessible.
From the experimental observations it was concluded that an attrition-based
nucleation mechanism governs the transformation of the metastable α to the
stable β polymorph. To the best of our knowledge, for the first time, the effect
of stirring on the course of the polymorph transformation was modeled using a
population balance model and implementing the relevant kinetics. Finally, the
proposed model allows calculating the course of a polymorph transformation in
a fully predictive manner for seeded as well as for unseeded conditions under a
wide range of operating conditions.
2.6 Nomenclature chapter 2

Roman letters

\( a \)  
parameter in the nucleation rate \([\text{J mol}^{-1} \text{K}^{-1} \text{m}^{-3}]\)

\( a_c \)  
specific surface \([\text{m}^2 \text{m}^{-3}]\)

\( A \)  
kinetic parameter \([\text{m}^{-3} \text{s}^{-1}]\) or particle surface area \([\text{m}^2]\)

\( A_c \)  
cross-sectional area \([\text{m}^2]\)

\( b \)  
parameter in the nucleation rate [-]

\( B \)  
thermodynamic parameter [-] or birth rate \([\text{m}^{-4} \text{s}^{-1}]\)

\( c \)  
concentration \([\text{mol m}^{-3}]\) or \([\text{kg m}^{-3}]\)

\( c^* \)  
solubility \([\text{mol m}^{-3}]\)

\( c_c \)  
\( \rho_c / M \)

\( C_\mu \)  
constant in turbulence model [-]

\( C_1 \)  
stirrer dependent constant [-]

\( d_{\text{imp}} \)  
impeller diameter \([\text{m}]\)

\( d_{43} \)  
average particle size \([\text{m}]\)

\( D \)  
death rate \([\text{m}^{-4} \text{s}^{-1}]\) or dissolution rate \([\text{m s}^{-1}]\)

\( D_{AB} \)  
diffusivity \([\text{m}^2 \text{s}^{-1}]\)

\( f \)  
energy dissipation distribution \([\text{s}^3 \text{m}^{-2}]\)

\( F_{r,\text{max}} \)  
maximum rupture force \([\text{N}]\)

\( G \)  
growth rate \([\text{m s}^{-1}]\)

\( J \)  
nucleation rate \([\text{m}^{-3} \text{s}^{-1}]\)

\( k \)  
Boltzmann constant \([\text{J K}^{-1}]\) or turbulent kinetic energy \([\text{m}^2 \text{s}^{-2}]\)

\( k_a \)  
surface shape factor [-]

\( k_c \)  
constant in cementation time [-]

\( k_d \)  
mass transfer coefficient \([\text{m s}^{-1}]\)

\( k_v \)  
volume shape factor [-]

\( k_{\psi} \)  
parameter in efficiency factor [-]

\( K \)  
equilibrium constant [-]

\( L \)  
particle size \([\text{m}]\)

\( L_m \)  
mean particle size \([\text{m}]\)

\( L_0 \)  
nuclei size \([\text{m}]\)

\( n \)  
number density \([\text{m}^{-4}]\)
### 2. L-glutamic acid pH-shift precipitation

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n^* )</td>
<td>critical nucleus size [-]</td>
</tr>
<tr>
<td>( n_s )</td>
<td>stirring rate ([s^{-1}])</td>
</tr>
<tr>
<td>( m )</td>
<td>mass density ([m^{-4}])</td>
</tr>
<tr>
<td>( M )</td>
<td>molecular mass ([g \text{ mol}^{-1}]) or total mass ([kg])</td>
</tr>
<tr>
<td>( N )</td>
<td>number of particles ([m^{-3}])</td>
</tr>
<tr>
<td>( N_a )</td>
<td>number of primary particles per agglomerate [-]</td>
</tr>
<tr>
<td>( N_A )</td>
<td>Avogadro number ([\text{mol}^{-1}])</td>
</tr>
<tr>
<td>( N_p )</td>
<td>power number [-]</td>
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<tr>
<td>( r_0 )</td>
<td>molecule radius ([m])</td>
</tr>
<tr>
<td>( R_m )</td>
<td>mean residual [-]</td>
</tr>
<tr>
<td>( Re_\lambda )</td>
<td>Taylor microscale Reynolds number [-]</td>
</tr>
<tr>
<td>( s )</td>
<td>surface fraction [-]</td>
</tr>
<tr>
<td>( s_b )</td>
<td>standard error [-]</td>
</tr>
<tr>
<td>( S )</td>
<td>supersaturation [-]</td>
</tr>
<tr>
<td>( Sc )</td>
<td>Schmidt number [-]</td>
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<tr>
<td>( t )</td>
<td>time ([s])</td>
</tr>
<tr>
<td>( t_c )</td>
<td>cementation time ([s])</td>
</tr>
<tr>
<td>( t_i )</td>
<td>induction time ([s])</td>
</tr>
<tr>
<td>( t_r )</td>
<td>interaction time ([s])</td>
</tr>
<tr>
<td>( T )</td>
<td>temperature ([K])</td>
</tr>
<tr>
<td>( v )</td>
<td>volume of a pivot ([m^3])</td>
</tr>
<tr>
<td>( v_0 )</td>
<td>molecular volume ([m^3])</td>
</tr>
<tr>
<td>( V )</td>
<td>particle or reactor volume ([m^3])</td>
</tr>
<tr>
<td>( w )</td>
<td>solid composition ([\text{wt.%}])</td>
</tr>
<tr>
<td>( W )</td>
<td>width of the crystalline bridge ([m])</td>
</tr>
<tr>
<td>( x )</td>
<td>size of a pivot ([m])</td>
</tr>
<tr>
<td>( X )</td>
<td>degree of agglomeration [-]</td>
</tr>
</tbody>
</table>

#### Greek letters

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_v )</td>
<td>detectable volume fraction [-]</td>
</tr>
<tr>
<td>( \beta )</td>
<td>numerical factor [-] or agglomeration kernel ([m^3 \text{ s}^{-1}])</td>
</tr>
<tr>
<td>( \beta_{col} )</td>
<td>collision kernel ([m^3 \text{ s}^{-1}])</td>
</tr>
<tr>
<td>( \varepsilon )</td>
<td>energy dissipation rate ([m^2 \text{ s}^{-3}])</td>
</tr>
<tr>
<td>( \bar{\varepsilon} )</td>
<td>average power input ([\text{W kg}^{-1}])</td>
</tr>
</tbody>
</table>
\( \gamma \)  
interfacial energy \([\text{J m}^{-2}]\) or shear rate \([\text{s}^{-1}]\)

\( \eta \)  
dynamic viscosity \([\text{Pa s}]\)

\( \varphi \)  
volumetric crystal holdup \([-\text{]}\)

\( \lambda \)  
size of smaller particle \([\text{m}]\)

\( \lambda_c \)  
contact length \([\text{m}]\)

\( \lambda_K \)  
Kolmogorov microscale \([\text{m}]\)

\( \Lambda \)  
integral scale of turbulence \([\text{m}]\)

\( \mu_i \)  
i-th moment of PSD \([\text{m}^i \text{m}^{-3}]\)

\( \nu \)  
kinematic viscosity \([\text{m}^2 \text{s}^{-1}]\)

\( \theta \)  
temperature \([\text{°C}]\)

\( \rho \)  
fluid density \([\text{kg m}^{-3}]\)

\( \rho_c \)  
crystal density \([\text{kg m}^{-3}]\)

\( \sigma \)  
standard deviation \([\text{m}^{-1}]\)

\( \sigma_c \)  
fracture strength \([\text{N m}^{-2}]\)

\( \tau_A \)  
time scale of agglomeration \([\text{s}]\)

\( \tau_C \)  
circulation time \([\text{s}]\)

\( \tau_G \)  
time scale of particle growth \([\text{s}]\)

\( \tau_K \)  
Kolmogorov time microscale \([\text{s}]\)

\( \psi \)  
efficiency factor \([-\text{]}\)
3 Combined cooling/antisolvent crystallization of acetylsalicylic acid*

Design and optimization are important steps during the development of crystallization processes. The combined cooling/antisolvent crystallization of acetylsalicylic acid (ASA) in ethanol-water mixtures is studied by means of experiments and population balance modeling. Model-based approaches require accurate kinetics and thermodynamic data, which are obtained in this work using in-situ process monitoring techniques such as ATR-FTIR spectroscopy and focused beam reflectance measurement (FBRM). Solubility is measured in-situ as a function of temperature and solvent composition using a multivariate calibration model for the ATR-FTIR. Nucleation and growth kinetics are determined based on crystallization experiments by combination of a population balance model and an integral parameter estimation technique. The model is finally used to calculate optimal cooling and antisolvent addition profiles of the combined cooling/antisolvent crystallization process using a multiobjective optimization approach which optimizes the process with respect to product properties, i.e. particle size distribution, and performance, i.e. process time. It was found that the solubility exhibits a maximum at 17 wt% water and that the growth rate correlates well with the solubility. No effect of the solvent composition on the nucleation rate could be identified. The optimized trajectories for cooling and antisolvent could greatly reduce the number of nuclei formed as shown through modeling and experiment. The study shows that combining cooling and antisolvent crystallization allows both improving productivity and reducing the formation of fines, and illustrates how process analytical tools and population balance modeling are effective also in crystallization processes where temperature and solvent composition change.

* Portions of this chapter appear in Lindenberg et al., Cryst. Growth Des. (9) 2009.
3. Combined cooling/antisolvent crystallization of acetylsalicylic acid

3.1 Introduction

In recent years, the application of in-situ monitoring tools in crystallization processes has become more and more popular, also as a consequence of FDA’s process analytical technology initiative (FDA, 2004). Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy has been employed to measure the liquid phase concentration in precipitation (Schöll et al., 2007b), cooling (Cornel et al., 2008b; Dunuwila et al., 1994; Groen and Roberts, 2001; Lewiner et al., 2001) and antisolvent (Borissova et al., 2004; Schöll et al., 2007a) crystallization processes. The focused beam reflectance method (FBRM)(Barrett and Glennon, 1999; Sparks and Dobbs, 1993; Tadayyon and Rohani, 1998) has been used in crystallization processes to monitor the solid phase, either for tracking the evolution of the chord length distribution (Chew et al., 2007; Monnier et al., 1997; Shaikh et al., 2005) or for monitoring the particle size distribution by using an appropriate restoration method (Kempkes et al., 2008; Li and Wilkinson, 2005; Worlitschek et al., 2005). Further, it has been used to detect the onset of particle formation (Barrett and Glennon, 2002; Schöll et al., 2006b) or the point of complete dissolution (Zhou et al., 2006). Rohani and coworkers have recently estimated the nucleation and growth kinetics of paracetamol by a combination of population balance modeling and nonlinear regression with in-situ monitoring of supersaturation using ATR-FTIR and measuring chord length distribution using FBRM (Trifkovic et al., 2008). In the same work, optimal antisolvent flow rate profiles were obtained by applying nonlinear constrained single- and multi-objective optimization techniques. The multi-objective optimization approach was also applied by the same group to optimize seeded batch cooling (Sarkar et al., 2006) and reactive crystallization (Sarkar et al., 2007) processes, and to determine the optimal cooling profiles and feed flow rates, respectively. The application of the FBRM for the model based optimization of the particle size distribution in the batch cooling of paracetamol was also shown earlier (Worlitschek and Mazzotti, 2004). While a number of publications focus on the offline optimal control, i.e. the calculation of an optimal trajectory for the antisolvent (Nowee et al., 2008; Trifkovic et al., 2008) or the temperature (Miller and Rawlings, 1994; Sarkar et al., 2006; Worlitschek and Mazzotti, 2004), Braatz and coworkers have designed a pharmaceutical antisolvent crystallization process through feedback concentration control based on ATR-FTIR (Zhou et al., 2006). A comparison
between open-loop temperature control and closed-loop supersaturation control has shown that the latter, though more difficult and complex to implement, is less sensitive to disturbances, such as changing seed quality or impurity profile, than the former, hence it is more favorable for industrial applications (Fujiwara et al., 2005; Nagy et al., 2008a).

An overview about the different techniques for the measurement of nucleation and growth rates can be found elsewhere (Garside and Mersmann, 2002). Regarding antisolvent crystallization, the effect of solvent composition on the crystallization kinetics of paracetamol in acetone-water mixtures was investigated by Granberg and coworkers and a good correlation between growth rate and solubility was found (Granberg et al., 1999). For the same system and an equal supersaturation, the induction times depended on the solvent composition and the measured interfacial energies increased with decreasing solubility (Granberg et al., 2001). Also for paracetamol in isopropanol-water mixtures an effect of the antisolvent concentration on the parameters in the nucleation and growth rate was found (Trifkovic et al., 2008).

It is common practice in industrial cooling crystallization that an antisolvent is added in order to increase the yield of the process. From an engineering point of view the question arises how the cooling and the antisolvent addition should be combined. Recently, for the first time such combination has been considered systematically in the case of crystallization of lovastatin from water-acetone mixtures (Nagy et al., 2008b). The authors have applied a model-based design approach, i.e. equivalent to open-loop control, to choose the optimal policy in terms of combined cooling and antisolvent addition. Using newly measured solubility data together with literature expressions for nucleation and growth rates, different single-objective optimization problems, e.g. maximum average particle size, minimum coefficient of variation, etc., have been solved, thus showing that combining the combination of cooling and antisolvent addition is always better than either one or the other only.

Along similar lines, the goal of our study is the development and optimization of a combined cooling/antisolvent crystallization process of aspirin (acetylsalicylic acid, ASA) in ethanol(solvent)-water(antisolvent) solutions. This paper describes first the experimental setup used for solubility measurement and for the estimation of the nucleation and growth rates. Then, a process model based on the population balance equation is derived. This model is used together with
a nonlinear parameter estimation technique to regress the parameters of the nucleation and growth rates from the experimental data. Then, the model is used to calculate optimal temperature and antisolvent concentration trajectories, which yield a final product with large particle size, narrow particle size distribution and prismatic shape in the shortest process time, i.e. by solving the corresponding multi-objective optimization problem. Such optimal trajectories are then tested experimentally in an open-loop control mode. Finally, a practical implementation of the theoretical optimal trajectory is presented and discussed.

3.2 Experimental section

3.2.1 Experimental setup

The experiments were carried out in a jacketed 500 ml glass reactor equipped with a four-blade glass impeller and 45° inclined blades (LTS, Switzerland). The temperature was controlled using a Ministat 230-3 thermostat (Huber, Switzerland) and a Pt 100 temperature sensor. The stirrer had a diameter of 50 mm and was positioned 10 mm above the reactor bottom. The reactor diameter was 100 mm. The reactor was equipped with an FBRM and an ATR-FTIR probe. The probe tips were placed in zones of high fluid velocities and oriented toward the flow to prevent clogging and to obtain representative measurements by allowing the crystals to impinge on the probe window. The antisolvent was added using a Kp 2000 piston pump (Desaga GmbH, Germany) which could deliver flow rates from 10 to 5000 ml/hr. It has been reported that more consistent results are obtained if the antisolvent is added close to the impeller (O’Grady et al., 2007). However, in this study, the antisolvent was fed above the liquid level since addition close to the impeller led to clogging owing to the formation of incrustations in the inlet pipe. All experiments were carried out at a stirring rate of 250 rpm. A schematic of the setup is shown in Figure 3.1.

3.2.2 Materials

Acetylsalicylic acid (>99%, Sigma-Aldrich, Switzerland), ethanol (99.9%, Merck KGaA, Germany) and deionized water were used in all experiments. ASA has two known polymorphs, whereas form II was recently discovered and is obtained by crystallization of pure ASA in the presence of levetiracetam
from acetonitrile (Vishweshwar et al., 2005); form I is the well-known drug aspirin. In all our experiments form I was obtained since form II crystallizes at completely different operating conditions. Moreover, we employed a RA 400 Raman spectrometer (Mettler-Toledo, Switzerland) to exclude that solvates or hydrates of ASA have been obtained.

Figure 3.1: Schematic of the 0.5 L batch reactor used for the experiments. The setup allows for employing two in-situ probes at the same time, namely FBRM and ATR-FTIR.

Two seed fractions of ASA were produced and are shown in Figure 3.2. The S seed were obtained by grinding and the L seed by collecting purchased crystals which were sieved in the size range of 90 – 200 μm.
3. Combined cooling/antisolvent crystallization of acetylsalicylic acid

3.2.3 In-situ characterization techniques

ATR-FTIR spectroscopy was employed to measure the liquid phase concentration of ASA and of the antisolvent water. The ATR technique enables to measure exclusively the liquid phase in the presence of solid material due to the low penetration depth of the IR beam (Dunuwila et al., 1994). Spectra were collected using a ReactIR 4000 system from Mettler-Toledo (Switzerland), equipped with a 11.75 inch DiComp immersion probe and a diamond ATR crystal. Spectra were collected in the 650 – 4000 cm⁻¹ region with a resolution of 2 cm⁻¹, and were recorded over 20 sec (16 scans) or 120 sec (128 scans), respectively, depending on the required temporal resolution.

The FBRM allows for in-situ measurements of the chord length distribution CLD (Kempkes et al., 2008; Li and Wilkinson, 2005; Worlitschek et al., 2005). In principle, the actual particle size distribution (PSD) can be restored from the obtained CLD (Kempkes et al., 2008; Worlitschek et al., 2005). In this work, a laboratory-scale FBRM 600L from Lasentec (Redmond, USA) has been applied to detect the onset of particle formation during the ATR-FTIR calibration measurements and to verify that no significant nucleation occurred during the growth experiments.

Figure 3.2: Particle size distribution of the two seed fractions, where S seed were produced by grinding and L seed by sieving.
3.2.4 Offline characterization techniques

Particle size distributions were measured using a Multisizer 3 from Beckman Coulter (Nyon, Switzerland). This device uses the Coulter Principle to measure the number and volume particle size distribution with a high resolution in the range of 0.4 to 1200 µm. Every measurement consisted of at least 50,000 particles and PSDs were smoothed with a moving average filter. A saturated ethanol-water solution with 25 wt% ethanol and 1 wt% sodium chloride (>99%, Fluka, Switzerland) was used as electrolyte. In all experiments the PSD was measured after drying the crystals.

Optical microscopy using a Zeiss Axioplan microscope (Feldbach, Switzerland) was employed to quickly assess qualitative information about the particle size and shape of the crystals.

3.3 Population balance model

The population balance equation (PBE) is used to model the crystallization process of ASA. The PBE written in terms of length $L$ for a perfectly mixed semi-batch process with size-independent growth reads as follows (Randolph and Larson, 1988):

$$\frac{\partial (Vn)}{\partial t} + VG \frac{\partial n}{\partial L} = 0,$$

where $n$ is the particle number density, $V$ is the reactor volume, $t$ is the time and $G$ is the growth rate. Assuming that the change in reactor volume depends only on the volume flow rate of the antisolvent, $Q$, Eq. (3.1) can be recast as:

$$\frac{\partial n}{\partial t} + G \frac{\partial n}{\partial L} = -\frac{n}{V} Q.$$

The concentration of ASA in solution, $c$, can be obtained by the material balance, i.e. by the following equation:

$$\frac{dc}{dt} = -\frac{3}{M} k_v \rho_c G \int_0^\infty n L^2 dL - \frac{c}{V} Q,$$

where $M$ is ASA’s molecular mass, $k_v$ is its volume shape factor and $\rho_c$ is its crystal density. In this work we have used values of $\rho_c = 1400$ g/kg for the crys-
tal density and $k_v = \pi/6$ for the volume shape factor. The following initial and boundary conditions apply to the PBE and the material balance:

$$n(L_0, t) = J / G$$  \hspace{1cm} (3.4)
$$n(L, 0) = n_0$$  \hspace{1cm} (3.5)
$$c(0) = c_0,$$  \hspace{1cm} (3.6)

where $J$ is the nucleation rate, $n_0$ and $c_0$ are the initial PSD and solute concentration, respectively. The supersaturation $S$ is defined as follows:

$$S = c / c^*,$$  \hspace{1cm} (3.7)

with $c^*$ being the solubility of ASA. The solubility $c^*$ is not a constant, but depends on the temperature $T$ and the water concentration $w$ as discussed in the following section. Temperature and water concentration are functions of time, and their profiles, which realize the selected crystallization strategy, are input to the model. Moreover, nucleation and growth rates depend on temperature, concentration and solvent composition as discussed in section 3.5.

### 3.3.1 Solution of the population balance model

The PBE is solved using the moving pivot technique proposed by Kumar and Ramkrishna (Kumar and Ramkrishna, 1997). Thereby, the PBE is discretized and each size range is represented by a corresponding length, the pivot, and its lower and upper boundary. The arithmetic mean of the size of the lower and the upper boundaries was used as size of the pivot. The moving pivot technique greatly reduces the problem of numerical diffusion and instability, while providing the applicability to an arbitrary grid to guarantee accuracy and reasonable computational effort (Kumar and Ramkrishna, 1997). The discretized form of Eq. (3.2) is:

$$\frac{dN_i}{dt} = J \delta_{i,1} - \int_{b_i}^{h_i} \frac{n(L_1, t)}{V} QdL = J \delta_{i,1} - \frac{N_i}{V} Q$$  \hspace{1cm} (3.8)

$$\frac{dx_i}{dt} = G, \ i > 1$$  \hspace{1cm} (3.9)
$$\frac{dx_i}{dt} = \frac{1}{2} G,$$  \hspace{1cm} (3.10)
where \( N_i \) represents the total number of particles in the \( i \)th size range, \( \delta_{i,1} \) is the Kronecker delta and \( x_i \) is the size of the \( i \)th pivot. Eqs. (3.8), (3.9) and (3.10) were solved together with the material balance Eq. (3.3) using the MATLAB `ode45` solver.

### 3.4 Multivariate data analysis

Liquid properties such as temperature and composition have an influence on the IR absorbance. The pure component IR spectra of ASA and water in ethanol are shown in Figure 3.3. The spectra overlap in the whole range of wavenumbers of interest, thus making a univariate calibration based on peak height or peak area not feasible. Since the water concentration changes in the course of the experiment the ethanol-water background cannot be simply subtracted as often done in cooling crystallization. Therefore, a multivariate calibration model is used in this study.

![Figure 3.3: Pure component spectra of ASA and water in ethanol indicating overlapping signals in the whole range of wavenumbers.](image)

3.4.1 Calibration set

A calibration set covering the supersaturated as well as the undersaturated region was designed to obtain a calibration model, which is applicable over a
Combined cooling/antisolvent crystallization of acetylsalicylic acid

A wide range of process conditions, as described elsewhere (Cornel et al., 2008b; Togkalidou et al., 2001). The experimental procedure is described in Figure 3.4. An undersaturated solution was prepared by dissolving a known amount of ASA. After having confirmed complete dissolution by zero FBRM counts and a constant IR signal, the solution was cooled at 5 °C/h and spectra were collected every 2 min. A rapid increase in counts of the FBRM signal indicated nucleation, hence subsequent samples were discarded since the formation of particles decreased the solute concentration by an unknown amount. This procedure was repeated for several different initial concentrations of ASA and temperatures as shown in Figure 3.4 for a water concentration of 0 wt%, and then also employed for different water concentrations, namely 10, 25, 40, 55 and 75 wt%, whereas the initial concentration of ASA was decreased for larger water concentrations. In total, the calibration set consists of 740 samples in a temperature range from 20 to 60 °C and a concentration range of ASA from 50 to 650 g/kg.

![Figure 3.4: Temperature and concentration of the samples used for IR calibration. An undersaturated solution with known concentration is cooled down until nucleation is detected through FBRM monitoring (dashed line).](image-url)
3.4.2 Calibration model

In the calibration, a relation between the measured spectra and the independent data, e.g. ASA and water concentration, is sought. Since spectroscopic data are highly correlated, the corresponding regression problem is ill-conditioned and suitable approaches such as partial least squares regression (PLSR) have to be applied (Geladi and Kowalski, 1986; Nadler and Coifman, 2005). The whole fingerprint region, i.e. from 650 – 1500 cm\(^{-1}\), resulting in 443 variables, was used for building the calibration model.

Because of signal drifts induced by external effects, such as non-constant temperature in the laboratory, a linear baseline correction was required to obtain constant results. Moreover, the data were mean-centered to remove unwanted variation in the data, hence to improve model performance (Cornel et al., 2008b).

In PLSR a small number (1 – 10) of variables, which are linear combinations of the measured spectra, is used to regress the independent data. These combinations are called latent variables and their number has a great influence on the model performance. The optimal number of latent variables is found through a cross-validation procedure during which parts of the calibration set are left out, a calibration model is built based on the remaining subset, and this model is used to estimate the set that was left out (Cornel et al., 2008b). This procedure is repeated for different subsets – we used the leave-one-out method – and the root-mean-square error of cross-validation (RMSECV) is calculated. The RMSECV is used to find the optimal number of latent variables, i.e. the number where the value of RMSECV reaches a minimum, or, if no minimum exists, to find the number where the RMSECV does not change significantly if the number of latent variables is increased. The best model performance was found for a PLSR model using 4 latent variables. The corresponding RMSECV was 5.20 g/kg for the ASA concentration and 0.81 wt% (on a solute free basis) for the water concentration, which corresponds to 1.3% and 3.5% of the mean concentrations as used in the calibration set, respectively. These figures can be assumed to be the average error made in measuring the corresponding concentrations using the abovementioned calibration.
3. Combined cooling/antisolvent crystallization of acetylsalicylic acid

3.4.3 Solubility measurement

The calibration model described in the previous section was used to measure the solubility of ASA in a temperature range from 25 to 50 °C and an antisolvent concentration from 0 to 75 wt% water (on a solute free basis). A saturated solution, i.e. a solution with an excess of ASA crystals, was slowly heated from 25 to 50 °C at a rate of 1 °C/h. At 37.5 °C the temperature was held constant for 3 h to verify equilibrium conditions during the course of the experiment. This approach has been applied previously for non-isothermal solubility measurements (Togkalidou et al., 2002). Figure 3.5.a shows the measured solubility as a function of time and the corresponding temperature in pure ethanol. The procedure was repeated at 10, 25, 40, 55 and 75 wt% water. The measured solubilities as a function of solvent composition and temperature are given in Figure 3.6. It can be observed that the solubility is strongly increasing with temperature and that it exhibits a maximum at about 17 wt% water. In Figure 3.6 a surface described by a 2D polynomial which is fitted on the experimental data is shown as well. This polynomial is used in the simulations to determine the solubility at each required combination of solvent composition and temperature. It must be noted that the polynomial is valid only in the temperature range from 25 to 50 °C and for water concentrations between 0 and 75 wt%, and cannot be used for extrapolation. A 2D polynomial of 6th order giving 28 coefficients was used to fit the experimental solubility data of acetylsalicylic acid in a least-squares sense. The polynomial is arranged as follows:

\[
c(\theta, w) = p_{0,0}\theta^0w^0 + p_{1,0}\theta^1w^0 + p_{0,1}\theta^0w^1 + p_{2,0}\theta^2w^0 + p_{1,1}\theta^1w^1 + p_{0,2}\theta^0w^2 + \ldots + p_{0,10}\theta^0w^{10},
\] (3.11)

where \(c\) is the solubility in g per kg on a solute free basis, \(\theta\) is the temperature in °C and \(w\) is the water concentration in wt% on a solute free basis. The coefficients \(p_{i,j}\) are the elements of the \(i\)th column and \(j\)th row given Table 3.1.

The solubility can also be measured by slowly adding the antisolvent at constant temperature. The procedure is shown in Figure 3.5.b for an antisolvent addition rate of 20 ml/h and a temperature of 25 °C. Besides the ASA concentration also the water concentration was measured. It can be observed that in the very beginning of the experiment and after 2.5 h the water concentration stays approximately constant. At this point the pump sucked air, thus almost no antisolvent was added and also the ASA concentration changes only slowly.
This experiment is plotted in Figure 3.6 as well and a good agreement with the data measured at constant water content can be observed. The presented approach enables the continuous in-situ measurement of the solubility for processes with varying temperatures and solvent composition.

Figure 3.5: Measured solubility and corresponding temperature in pure ethanol (a), and measured solubility and corresponding measured water concentration at 25 °C as a function of time (b).
Figure 3.6: Measured ASA solubility (black solid lined) as a function of solvent composition and temperature. The grey surface is a 2D polynomial fitted on the experimental data, whose equation can be found in the supporting material.

Table 3.1: Parameters of the 2D polynomial describing the solubility of ASA.

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in a temperature-controlled shaker, after 24 h the solution was filtered off, the solvent was evaporated completely and the mass of the remaining crystals was determined. The agreement to the values measured by ATR-FTIR is very good and the relative error is below 3 %. However, for high water content, hence low ASA concentration, the agreement is worse with deviations up to 12.5 %. In this case the gravimetrically determined solubility is always higher, most likely due to residues of water in the crystal which could not be removed during drying.

<table>
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<th>$w$ [wt%]</th>
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<th>$c^*_{(IR)}$ [g/kg]</th>
<th>$c^*_{(grav.)}$ [g/kg]</th>
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Table 3.2: Solubility $c^*$ in g/kg of solvent determined by ATR-FTIR spectroscopy and gravimetry for different water concentrations $w$ and temperatures $T$. 
3.5 Growth and nucleation kinetics

3.5.1 Parameter estimation

The parameters in the kinetic expressions for nucleation and growth were estimated based on batch desupersaturation experiments using a nonlinear optimization algorithm that minimizes the sum of squared residuals, $SSR$, between the experimental and simulated supersaturation values:

$$SSR = \sum_{i=1}^{N_e} \sum_{j=1}^{N_{d,i}} (S_{i,j}^{\text{exp}} - S_{i,j}^{\text{sim}})^2,$$  \hspace{1cm} (3.12)

where $N_e$ is the number of experiments, $N_{d,i}$ is the number of data points per experiment $i$, and $S_{i,j}^{\text{exp}}$ and $S_{i,j}^{\text{sim}}$ are the experimental and simulated supersaturation, respectively. The optimization problem was solved using the \textit{lsqnonlin} algorithm of the MATLAB optimization toolbox.

Approximate confidence intervals of the model parameters $b$ can be determined by calculating the sensitivity matrix, i.e. the derivative of the model predictions with respect to the model parameters, based on a linearized model in the vicinity of the estimated values (Beck and Arnold, 1977). The sensitivity matrix can be used to calculate the approximate covariance matrix of the estimated parameters. The standard error $s_k$ of the $k$th model parameter is given by the square root of the $k$th diagonal element of this covariance matrix (Beck and Arnold, 1977). The confidence intervals of the $k$th parameter are given by

$$b_k \pm t_{\alpha, v} s_k,$$  \hspace{1cm} (3.13)

where $t_{\alpha, v}$ is the value of the $t$-distribution for confidence interval $\alpha$ in the case of $v$ degrees of freedom. We have used $\alpha = 0.05$ leading to a 95% confidence interval (Beck and Arnold, 1977).

3.5.2 Growth rate

The overall growth rate can be controlled by diffusion or surface integration. There is a wide variety of growth mechanisms which take place in competition and lead to different growth regimes (Mersmann, 2001). In this work, the following semi-empirical expression for the growth rate was employed (Mersmann, 2001):
3.5 Growth and nucleation kinetics

\[ G = k_{G_1} \exp \left( -\frac{k_{G_2}}{RT} (c - c^*)^{k_{G_3}} \right), \]  

(3.14)

where \( k_{G_1}, k_{G_2} \) and \( k_{G_3} \) are empirical parameters that have to be determined from experiments. The effect of the antisolvent concentration on the growth rate given by Eq. (3.14) is implicitly accounted for by the dependence of solubility on it.

3.5.2.1 Seeded batch protocol

A series of seeded batch desupersaturation experiments was performed at different temperatures and solvent compositions to determine the growth kinetics of ASA. In each of these experiments a certain amount of ASA crystals was dissolved completely in the ethanol-water solution by heating it up. The solution was cooled to the desired set temperature. Then, the temperature was kept constant and the seed crystals were added. The experimental method for the estimation of the parameters of the growth rate requires that only the added seed grow during the experiment and that nucleation is absent (Schöll et al., 2007b). FBRM was used to ensure that no significant nucleation occurred during the experiment. Nucleation can be detected by an increasing number of counts in the small size range of the FBRM. If nucleation were detected, which was the case at supersaturation levels higher than 1.4, the experiment would be discarded and not used for parameter estimation. All experiments that were used for parameter estimation are summarized in Table 3.3. The experiments were all carried out with the same initial suspension density of ASA seed crystals, i.e. 0.2 g\text{seed}/kg\text{solvent} of the L seed shown in Figure 3.2. The value of the suspension density was chosen based on a trade off between the need of having relatively slow desupersaturation to allow for monitoring of the process, which would require low suspension densities, and that of avoiding nucleation, that would occur if it were too low. Each experiment was carried out twice and a good repeatability was observed in all cases, as illustrated in Figure 3.7.a where as a representative example both experiments at 25 °C in pure ethanol are shown and the two curves overlap. The experimental protocol has already been applied successfully to determine the growth kinetics of several other compounds (Cornel et al., 2008a; Schöll et al., 2007a; Schöll et al., 2007b).
3. Combined cooling/antisolvent crystallization of acetylsalicylic acid

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<td>55</td>
<td>1.21</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Table 3.3: Experimental conditions of the growth experiments. All experiments were carried out twice.

3.5.2.2 Results

The parameter estimation technique presented in section 3.5.1 was used together with the population balance model and the experimental data of the seeded batch desupersaturation experiments (Table 3.3) to determine the growth rate of ASA. The following growth rate parameters in Eq. (3.14) were estimated:

\[
k_{g1} = (3.21 \pm 0.18) \times 10^{-4} \text{ m s}^{-1} \tag{3.15}
\]
\[
k_{g2} = (2.58 \pm 0.14) \times 10^4 \text{ J mol}^{-1} \tag{3.16}
\]
\[
k_{g3} = 1.00 \pm 0.01. \tag{3.17}
\]

The parameters do not depend on the solvent composition in this case, unlike suggested by other authors (Granberg et al., 1999; Nowee et al., 2008; Trifkovic et al., 2008). It was found that the proposed correlation describes the experimental data rather well and the use of more parameters was not justified. The $R^2$ values of the growth experiments are given in Table 3.3. It can be observed that the agreement with the experiment is good, as indicated by a high value of $R^2$, and that no systematic error exists, i.e. all temperatures and solvent compositions are represented equally well by the model.

A comparison of experimental and modeled desupersaturation profiles is reported in Figure 3.7. The effect of temperature is shown in Figure 3.7.a for pure ethanol. It can be observed that the initial supersaturations decrease with in-
creasing temperature since the supersaturation had to be adjusted in order to avoid nucleation. Despite the lower initial supersaturations at higher temperatures the desupersaturation curve is steeper, thus indicating a higher growth rate at elevated temperatures.

Figure 3.7: Growth experiments with ASA in pure ethanol and at different temperatures (a; runs 1 – 3), and at a constant temperature of 25 °C and different solvent compositions (b; runs 5 – 7). Symbols: experimental data; Lines: simulation results. The good repeatability is shown exemplarily for pure ethanol and 25 °C (run 1).
The effect of solvent composition is shown in Figure 3.7.b for a constant temperature of 25 °C. It can be observed that the supersaturation is depleted faster at lower concentrations of water, hence higher concentrations of ASA. This is only true for water concentrations up to 17 wt%, i.e. the maximum solubility. For lower concentrations of water the growth rate is decreasing again (not shown in the figure).

The growth rate as a function of solvent composition and supersaturation is shown in Figure 3.8 for a temperature of 45 °C. It can be observed that the maximum growth rate at fixed supersaturation is at the maximum of the solubility, i.e. at 17 wt% water. It is noticeable that the growth rate scales linearly with the supersaturation, thus suggesting a diffusion limited growth mechanism or a first-order reaction mechanism. Below the surface in Figure 3.8 the outline of the growth rate surface at 35 °C is plotted as well. This confirms that the growth rate depends strongly on temperature as accounted for by the Arrhenius-type temperature dependence in Eq. (3.14).

![Figure 3.8: Estimated growth rate of ASA as a function of solvent composition and supersaturation for a temperature of 45 °C (surface). The dotted line below the surface shows the outline of the growth rate surface at 35 °C.](image)
3.5.3 Nucleation rate

There are different nucleation mechanisms for the formation of crystals in solution: homogeneous and heterogeneous primary nucleation and secondary nucleation. In our experiments it was observed that nuclei form in clear solution; thus, a primary nucleation mechanism was assumed. Even though secondary nucleation could not be ruled out a priori, there was no experimental evidence that this mechanism contributed significantly to the formation of new crystals. The following empirical nucleation rate expression was used in this study:

\[ J = k_{j1} \exp \left( -\frac{k_{j2}}{RT} \right) \exp \left( -\frac{k_{j3}}{\ln^2 S} \right). \]  

(3.18)

It must be noted that Eq. (3.18) does not include any explicit effect of the solvent composition; however, as shown below, it can describe accurately the experimental data. A more physically meaningful expression which accounts for the effect of interfacial energy on the nucleation kinetics (Mersmann, 1990; Mersmann, 2001) was also tested, but did not give satisfactory results.

3.5.3.1 Unseeded batch protocol

A series of unseeded batch desupersaturation experiments has been performed at different temperatures and solvent compositions to determine the nucleation kinetics of ASA. In each of these experiments a certain amount of ASA crystals was loaded into an ethanol-water solution. The solution was heated up till the crystals were dissolved completely. Then, the solution was crash-cooled (at a rate of 50 K/h) to the desired set temperature and from that time on the temperature was kept constant. The process was monitored using ATR-FTIR and FBRM. The operating conditions for the nucleation experiments which were used for parameter estimation are given in Table 3.4. Each experiment was carried out twice. The repeatability was satisfactory but worse than in the growth experiments, most likely due to the stochastic nature of nucleation and to different amounts of microscopic dust, which is difficult to control and might promote heterogeneous nucleation. The effect of the stirring rate on nucleation kinetics, which was observed elsewhere (O’Grady et al., 2007), was not investigated here and the stirring rate was kept constant at 250 rpm in all experiments to guarantee similar mixing conditions.
3. Combined cooling/antisolvent crystallization of acetylsalicylic acid

3.5.3.2 Results

The protocol for the estimation of the parameters in the nucleation rate expression is similar to that for the growth rate, but it is based on the nucleation experiments summarized in Table 3.4. With reference to Eq. (3.18), the following nucleation rate parameters were estimated:

\[ k_{j1} = (1.15 \pm 0.51) \times 10^{21} \text{ m}^3 \text{ s}^{-1} \]  \hspace{1cm} (3.19)
\[ k_{j2} = (7.67 \pm 0.11) \times 10^4 \text{ J mol}^{-1} \]  \hspace{1cm} (3.20)
\[ k_{j3} = 0.16 \pm 0.01. \]  \hspace{1cm} (3.21)

<table>
<thead>
<tr>
<th>Run</th>
<th>( T ) [°C]</th>
<th>( w_{\text{H}_2\text{O}} ) [wt%]</th>
<th>( S_0 )</th>
<th>( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>0</td>
<td>1.52</td>
<td>0.92</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>0</td>
<td>1.51</td>
<td>0.87</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>0</td>
<td>1.22</td>
<td>0.77</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>25</td>
<td>1.40</td>
<td>0.79</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>25</td>
<td>1.75</td>
<td>0.81</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>25</td>
<td>2.00</td>
<td>0.86</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>25</td>
<td>1.48</td>
<td>0.96</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>40</td>
<td>1.50</td>
<td>0.76</td>
</tr>
<tr>
<td>9</td>
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<td>40</td>
<td>1.50</td>
<td>0.75</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>55</td>
<td>1.50</td>
<td>0.81</td>
</tr>
<tr>
<td>11</td>
<td>25</td>
<td>55</td>
<td>1.95</td>
<td>0.80</td>
</tr>
<tr>
<td>12</td>
<td>35</td>
<td>55</td>
<td>1.51</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Table 3.4: Experimental conditions of the nucleation experiments. All experiments were carried out twice.

The \( R^2 \) of the nucleation experiments are given in Table 3.4. It can be observed that the agreement between model and experiment is rather good, and that no systematic error regarding the effect of temperature and antisolvent concentration is observed. However, the values of \( R^2 \) are a bit lower than for the growth experiments. It is worth noting that although the confidence interval on the parameter \( k_{j1} \) looks rather large, namely \( \pm 44\% \), the effect of this uncertainty on the course of nucleation is minor as illustrated in Figure 3.9.a, where as a repre-
sentative example the experiment at 25 °C in pure ethanol is simulated with the estimated value of the parameter as well as with the two values at the upper and lower end of the confidence interval and the three curves do not differ much. The experimental results of the unseeded batch desupersaturation experiments with pure ethanol as solvent are given in Figure 3.9. In each experiment, first, the supersaturation increases due to cooling (Figure 3.9.a). Then, at a certain level, the supersaturation decreases rapidly because of particle formation and growth. At that point the temperature is typically above the final set-point given in Table 3.4, and the solution is cooled further till it reaches the set temperature (Figure 3.9.b). In some experiments the supersaturation reaches a plateau after the first rapid decrease. The reason for this behavior is that the solution heats up during particle formation and growth, since these are exothermic phenomena. Then, the solution is cooled down again through the action of the thermostat, whereas some overshooting of the temperature can be observed. This course of the temperature is also reflected by the experimental course of the supersaturation. The maximum supersaturation that is reached in an experiment decreases with increasing temperature due to an increasing nucleation and growth rate. It must be noted that for each experiment the temperature profile is measured, then imported and used in the corresponding simulation as input. The simulation results are plotted in Figure 3.9.a as well and a rather good agreement with the experimental data can be observed. However, there is a discrepancy between simulation results and experimental data in the phase of the experiment when the solution heats up due to nucleation and growth. This discrepancy is observed in all experiments, sometimes to a larger and sometimes to a smaller extent, and occurs most likely due to the temperature effect, which is not captured completely by the model. A study with different initial concentrations of ASA (runs 4 to 6 in Table 3.4) revealed that the maximum attainable supersaturation is not affected thereby. If the initial ASA concentration is larger, the nucleation just starts at a higher temperature. A comparison of the experimental and simulated desupersaturation profiles for different solvent compositions is illustrated in Figure 3.10. It must be noted that the data of the different experiments are shifted in time to allow for a better readability. The course of the supersaturation and the maximum supersaturation value are rather similar for the different solvent compositions. Thus, as anticipated above, no direct effect of solvent composition on the nucleation rate was
included in the model. Also for these experiments the agreement with the model is relatively good, whereas the same discrepancy as for the experiments described in the previous paragraph was observed.

Figure 3.9: Nucleation experiments with ASA in pure ethanol and at different temperature levels (runs 1 – 3). The course of the experimental (symbols) and modeled (lines) supersaturation is shown in (a) and of the temperature in (b). The dotted lines show exemplarily the effect of the uncertainty in the nucleation parameter $k_{ji}$ on the simulation results for pure ethanol and 25 °C (run1).
Figure 3.10: Nucleation experiments with ASA at different solvent compositions and at constant final temperature of 25 °C (runs 1, 5, 11). The course of the experimental (symbols) and modeled (lines) supersaturation is shown in (a) and of the temperature in (b).

3.6 Process optimization

The process model with the kinetic expressions which have been presented in sections 3.3 and 3.5 is used in this section to optimize the process, i.e. to calculate an optimal trajectory for the cooling and antisolvent addition. Such trajectory is then implemented experimentally. A crystallization process can be optimized in different respects, i.e. targeting optimal particle size and particle size
distribution, shape, purity, residual solvent content, yield and process time. In this study, a seeded semi-batch process is considered where the supersaturation is generated by cooling and antisolvent addition, whereas the antisolvent is added to increase the yield. At which antisolvent concentration the maximum yield is obtained depends on the solubility behavior of the specific substance; the maximum yield is in fact obtained at the final conditions where the mass gain due to change in solubility is the largest as compared to the loss due to dilution. In this study, the yield was fixed by choosing a specific and constant value of the final antisolvent concentration. The solution was cooled from 35 to 25 °C, and the initial and final antisolvent concentration were 25 and 60 wt%, respectively. The theoretical crystal yield obtained by cooling from 35 to 25 °C at a water concentration of 25 wt% was 128.9 g/kg, the yield obtained by changing the water concentration from 25 to 60 wt% at a temperature of 25 °C was 143.0 g/kg, and hence the total theoretical yield was 271.9 g/kg, i.e. 110% more than by cooling only.

Particle shape, purity and residual solvent content were also not used as parameters to be optimized, since for the first no criterion was available, whereas the latter two features did not seem to represent a problem. Therefore, the process was optimized with respect to time and particle size distribution. While the multi-objective optimization of cooling (Sarkar et al., 2006) or antisolvent crystallization (Trifkovic et al., 2008) and the single-objective optimization of the combined cooling/antisolvent crystallization (Nagy et al., 2008b) have been reported previously, we focus in this study on the multi-objective optimization of the combined cooling/antisolvent crystallization.

### 3.6.1 Optimal trajectory

The objective for the process optimization was the minimization of process time and of the difference between the calculated and a specified optimal PSD. The following multi-objective optimization problem was formulated where the cooling and the antisolvent flow rate profile are the manipulated variables:
3.6 Process optimization

\[
\begin{align*}
\text{Minimize} & \quad t_p, \\
\text{subject to} & \quad \int_0^\tau J \, dt \\
& \quad \frac{dT}{dt} \leq 30 \text{ K/h} \\
& \quad Q \leq 1.29 \text{ g/s}
\end{align*}
\]  

(3.22)

The following initial and final conditions were applied: \( S_0 = 1.05, \ T_0 = 35 \degree C, \ w_0 = 25 \text{ wt\%}, \ T_{\text{end}} = 25 \degree C, \ w_{\text{end}} = 60 \text{ wt\%}. \) The initial seed mass was \( 6.25 \times 10^{-2} \text{ g per kg of solvent} \) and the S seed shown in Figure 3.2 were used. The cooling and the antisolvent profile are discretized in time in 6 equidistant steps. This results in 13 parameters to be optimized: 2 process times for cooling and antisolvent addition, respectively, 5 temperatures (initial and final temperature were fixed) and 6 antisolvent flow rates. The particle size distribution was not directly optimized, but the number of crystals formed by nucleation was minimized as to Eq. (3.22). In a seeded process with negligible nucleation and size independent growth the final PSD is just the initial one shifted to the right along the crystal size coordinate of an extent that fulfils the material balance, i.e. it is consistent with the mass being deposited on the seed crystals by crystal growth. The constraints in Eq. (3.22) are determined by the maximum cooling and feed rates in our experimental setup.

The multi-objective optimization problem was solved by combining the two objective functions into a single one consisting of a weighted average (Deb, 2001). The optimization problem was solved using the \texttt{fmincon} algorithm of the MATLAB optimization toolbox. By varying the weights the Pareto-optimal solutions, which are illustrated in Figure 3.11, could be calculated. It can be observed that the two objectives are conflicting, i.e. short process time results in a larger nucleation rate and vice versa. The following Pareto-optimal point was chosen and used for further studies:

\[
\begin{align*}
t_p &= 1298 \text{ s} \quad (3.23) \\
\int_0^\tau J \, dt &= 2.60 \times 10^4 \text{ m}^{-3}. \quad (3.24)
\end{align*}
\]
Figure 3.11: Pareto-optimal set of the two-objective optimization problem (solid line); the region below the Pareto set is not feasible. The dotted line is the boundary due to the maximum cooling rate. The open circles correspond to process alternatives where the antisolvent is added at the beginning (case 1) or at the end (case 2). The filled circle gives the Pareto-optimal set that was implemented (case 3). The dashed line corresponds to a strategy of industrial relevance in which constant cooling and antisolvent addition rates are applied. The inset shows schematically the corresponding cooling and flow rate profiles.

The optimized trajectory is compared with two other process alternatives, a fast addition of the antisolvent in the beginning followed by cooling (case 1) and cooling followed by the addition of the antisolvent in the end (case 2), which are the extreme cases of the combined cooling/antisolvent crystallization. In these cases the cooling and the antisolvent addition are decoupled. These process strategies are interesting as they are often applied in industry. Initial conditions (concentrations of ASA and water, temperature, seed size and mass) and final conditions (water concentration and temperature) were the same as for the optimal trajectory. The optimized trajectory (hereafter called case 3) and the trajectories of case 1 and 2 are shown in Figure 3.12. In case 1 and 2 a maximum cooling rate of 30 K/h is applied, either after or before the antisolvent addition (Figure 3.12.a). In the optimized case, first, the solution is cooled at
maximum rate, and then the cooling rate is lowered in the second interval, till it increases again to the maximum rate. The antisolvent addition is shown in Figure 3.12.b. In case 1 and 2 the antisolvent is added at the maximum rate, i.e. 77.4 g/min, and for a duration 108.5 s. In the optimized case, the antisolvent flow rate decreases in the second interval and increases afterward gradually till the end of the process.

Figure 3.12: Cooling profile (a) and antisolvent flow rate (b) as a function of time. Dashed line: antisolvent addition in the beginning (case 1); Dotted line: antisolvent addition in the end (case 2); Solid line: optimized trajectory (case 3).
Combined cooling/antisolvent crystallization of acetylsalicylic acid

Figure 3.13: Concentration trajectory of the three process alternatives as a function of water concentration and temperature. Dashed line: antisolvent addition in the beginning (case 1); Dotted line: antisolvent addition in the end (case 2); Solid line: optimized trajectory (case 3); surface: solubility.

The process trajectories as function of temperature and solvent composition are plotted together with the solubility in Figure 3.13. It can be observed that the optimized trajectory follows approximately the steepest descent on the solubility surface and that the concentration is always close to the solubility, thus the supersaturation is low. In case 1 the concentration is much larger than the solubility in the beginning of the process, while in case two it is the largest in the end. In both cases the highest supersaturation is attained during the antisolvent addition. The course of the supersaturation as a function of process time is plotted in Figure 3.14.a. The supersaturation stays at a low value of about 1.1 and is relatively constant throughout the whole process in the optimal case 3. A supersaturation as high as 1.9 is attained if the antisolvent is added in the beginning (case 1), and a slightly lower maximum supersaturation of 1.7 is reached if the antisolvent is added in the end. If the antisolvent is added in the end the available crystal surface is larger as compared to the case where it is added in the
beginning, thus the rate of concentration decrease by growth is larger resulting in a lower supersaturation.

Figure 3.14: Supersaturation (a) and nucleation rate (b) as a function of time. Dashed line: antisolvent addition in the beginning (case 1); Dotted line: antisolvent addition in the end (case 2); Solid line: optimized trajectory (case 3).

The nucleation rates corresponding to the three process alternatives are plotted in Figure 3.14.b. It can be observed that the nucleation rate in cases 1 and 2 is by at least six orders of magnitude larger than in the optimized case. The effect of this higher nucleation rate on the simulated PSDs is illustrated in Figure
3.15. In case 3 a unimodal distribution with large crystals in the range 350 to 400 μm is obtained. This case is identical to a simulation with growth only and without nucleation. In case 1 the particles are much smaller and the PSD is bimodal. The first peak stems from the nucleation event in the beginning of the process and the second from the grown seed crystals. In case 2 the PSD is also bimodal, however, the grown seed crystals are almost as big as in case 3. The first peak on the left hand side of the plot stems from the crystals nucleated at the end of the process during the antisolvent addition.

Figure 3.15: Final simulated particle size distributions of the three process alternatives. Dashed line: antisolvent addition in the beginning (case 1); Dotted line: antisolvent addition in the end (case 2); Solid line: optimized trajectory (case 3).

The process alternatives 1 and 2 are shown as open circles in Figure 3.11. It can be observed that for the same process time the number of nuclei formed in case 1 and 2 is about 5 to 6 orders of magnitude larger than in the optimal case 3. However, the optimal antisolvent addition profile (Figure 3.12.b) is relatively complicated and might not be applicable in industrial processes. Therefore, a strategy with constant cooling and antisolvent addition rate was considered as well. In this case cooling and antisolvent feeding time are equal and the same initial and final conditions in terms of concentration and temperature as for the
optimal case were applied. The corresponding cooling and antisolvent addition rates are plotted schematically in the inset of Figure 3.11. The number of nuclei formed as a function of process time is shown as well, and it can be observed that for the same process time as in cases 1–3, i.e. around 1300 sec, the number of nuclei is 3 orders of magnitude larger than in the optimized case 3, and about 2 to 3 orders of magnitude smaller than in cases 1 and 2. Thus, we conclude that for industrial purposes an addition of the antisolvent over the whole cooling (process) time should be favored as compared to processes where the antisolvent is added all at once at the beginning or end of the cooling ramp.

3.6.2 Implementation and results

A comparison of experimental and simulated concentration of ASA is shown in Figure 3.16. A good agreement is observed, which is remarkable since in this case the model is used in a fully predictive mode. Besides the concentrations also the counts of the FBRM are plotted. It can be observed that in case 1 and 2 the addition of the antisolvent coincides with a rapid decrease of the ASA concentration and a sharp increase of the FBRM counts.

The comparison of Figure 3.14.b and Figure 3.16 shows that the increase in FBRM counts is related to the nucleation of ASA crystals. This confirms that the FBRM can serve as a valuable tool to detect nucleation events. In case 3 no significant increase of FBRM counts can be observed since the nucleation rate is very low. However, there is a slow but steady increase of the FBRM counts due to crystal growth since it is more likely for the FBRM to detect larger particles (Kempkes et al., 2008). It must also be noted that in cases 1 and 2 temperature effects were observed after the fast antisolvent addition owing to the mixing enthalpy and heat of crystallization. However, these effects were accounted for by the model since the actual temperature profiles from the experiments were monitored and used in the simulations.

The measured number distributions of the final particles are shown in Figure 3.17.a. A comparison with Figure 3.15 shows that in all cases the experimental PSDs are much broader than the simulated ones, but that the general trend is well predicted. If the antisolvent is added at the beginning (case 1), the final particles are much smaller due to nucleation. Adding the antisolvent at the end (case 2) leads to a bimodal PSD, whereas applying the optimized trajectory (case 3) yields a unimodal distribution. The measured mass distributions are
bimodal in case 1, whereas unimodal distributions are observed in cases 2 and 3 (Figure 3.17.b). However, the mass distribution of case 2 is broader and shifted towards larger particle sizes as compared to that of the optimized case 3, mainly due to a larger extent of agglomeration in case 2.

Figure 3.16: Experimental and modeled ASA concentration and FBRM counts as a function of time for the three process alternatives: antisolvent addition in the beginning (a), antisolvent addition in the end (b) and optimized trajectory (c). Circles: experimental data; Black line: simulation results; Grey line: FBRM data.
3.6 Process optimization

Figure 3.17: Final measured number (a) and mass densities (b). Grey circles: antisolvent addition in the beginning (case 1); Open black circles: antisolvent addition in the end (case 2); Filled black circles: optimized trajectory (case 3).

The broader PSDs in the experiments as compared to the simulations might be attributed to secondary effects, such as agglomeration, as can be seen on the microscope pictures in Figure 3.18. The final crystals are elongated in case 1, whereas they are more compact in cases 2 and 3. The difference might be explained by the different solvent compositions. In case 1 the solvent composition
is about 60 wt% water almost throughout the whole process. The lowest average water concentration occurs in case 2 since the antisolvent is added at the end of the process. The optimal case is such that the antisolvent concentration varies continuously during crystallization as shown in Figure 3.13. The comparison of the final crystals from the different runs shows that the solvent composition affects the ratio of the growth rates of different crystal faces, i.e. the shape of the crystal changes and the crystals become more elongated at higher water concentrations. This effect was also observed in the nucleation experiments presented in section 3.5.3. In case 2 a large number of small crystals can be observed which have been formed due to the high supersaturation at the end of the process, and the large particles are slightly agglomerated. A mild agglomeration of crystals can also be observed in case 3.

Figure 3.18: Microscope pictures of the final ASA crystals of case 1 (antisolvent addition in the beginning, left), case 2 (antisolvent addition in the end, middle) and case 3 (optimized trajectory, right). All pictures have the same magnification.

### 3.7 Conclusions

The optimized combined cooling/antisolvent crystallization of acetylsalicylic acid from ethanol-water solutions has been studied, showing that process performance can be improved as compared to conventional process alternatives which are commonly applied in industry, i.e. the addition of the antisolvent either at the beginning or at the end of the cooling process. In particular, a uni-
modal particle size distribution at a minimum process time has been obtained. The advantage of the combined process was shown through both modeling and experiments. The model-based optimization required the knowledge of solubility, nucleation and growth kinetics of acetylsalicylic acid, which were measured using process analytical technologies, such as ATR-FTIR and FBRM, and by applying previously development experimental protocols. A process model based on a population balance equation was used for a multiobjective process optimization. More specifically, the resulting Pareto-optimal solutions showed that the two objectives are conflicting, i.e. short process time results in a larger nucleation rate and vice versa, and yielded the corresponding optimal cooling and antisolvent flow rate profiles. However, these profiles are complex and difficult to implement in industrial processes. Therefore, a strategy with constant cooling and antisolvent addition, where cooling and feeding time were equal, was considered. Although this strategy is suboptimal, it outperformed processes where the antisolvent is added all at once at the beginning or at the end of the cooling ramp, and hence it should be favored. To the best of our knowledge, for the first time, multiobjective optimization was applied to a combined cooling/antisolvent crystallization, and solubilities as well as nucleation and growth kinetics of acetylsalicylic acid were determined as a function of temperature and solvent composition.
3.8 Nomenclature chapter 3

**Roman letters**

- $b$: vector of parameters [-]
- $c$: concentration [mol m$^{-3}$]
- $c^*$: solubility [mol m$^{-3}$]
- $G$: growth rate [m s$^{-1}$]
- $J$: nucleation rate [m$^{-3}$ s$^{-1}$]
- $k$: empirical parameter [-]
- $k_v$: volume shape factor [-]
- $L$: particle size [m]
- $n$: number density [m$^{-4}$]
- $N$: number of particles [m$^{-3}$]
- $M$: molecular mass [g mol$^{-1}$]
- $Q$: antisolvent flow rate [m$^3$ s$^{-1}$]
- $R$: ideal gas constant [J mol$^{-1}$ K$^{-1}$]
- $s$: standard error [-]
- $S$: supersaturation [-]
- $t$: time [s]
- $T$: temperature [K]
- $V$: reactor volume [m$^3$]
- $w$: antisolvent concentration [wt% on a solute free basis]
- $x$: size of a pivot [m]

**Greek letters**

- $\alpha$: weighting factor [-]
- $\gamma$: interfacial energy [J m$^{-2}$]
- $\rho_c$: crystal density [kg m$^{-3}$]
4 Mixing characterization*

Mixing in static mixers is studied using a set of competitive-parallel chemical reactions and computational fluid dynamics (CFD) in a wide range of operating conditions. Two kinds of mixers, a wide angle Y-mixer and a two jet vortex mixer, referred to as Roughton mixer, are compared in terms of reaction yields and mixing times. It is found that the Roughton mixer achieves a better mixing performance compared to the Y-mixer. The effect of flow rate ratio on mixing in the Roughton mixer has been studied as well and it is shown that the mixing efficiency is not affected by the flow rate ratio. Moreover, experimental results and model predictions are in good agreement for all mixer geometries and operating conditions. CFD is used to calculate absolute mixing times based on the residence time in the segregated zone and it is shown that mixing times of less than one millisecond can be achieved in the Roughton mixer. In addition, CFD provides insight in local concentrations and reaction rates and serves as a valuable tool to improve or to scale-up mixers.

4.1 Introduction

In precipitation processes carried out at high supersaturations, i.e. at conditions where the kinetics of particle formation are very fast, the course of the process as well as the properties of the final crystalline product can depend on the mixing conditions (Baldyga et al., 2005; Baldyga et al., 2007; Vicum and Mazzotti, 2007). If the timescales of mixing are comparable to or larger than those of precipitation the resulting spatial inhomogeneity of the concentration can lead to undesired product properties, e.g. large crystal size and broad crystal size distribution, due to the highly non-linear relation between supersaturation and nucleation rate. Moreover, if the process is scaled-up the mixing conditions can change and the product properties might be different.

Static mixers such as confined impinging jet (CIJ), T- and Y-mixers were employed for the production of micro and nano sized particles. Johnson and Prud’homme have used the CIJ mixer to precipitate organic substances and

stabilize the nanoparticles using block copolymers (Johnson and Prud'homme, 2003b). Crystallization in a Y-mixer has been investigated using a combined CFD process simulation approach by Choi and coworkers (Choi et al., 2005). The authors found that the mixing effect was important even though micromixing was neglected in their model. The precipitation of barium sulfate nanoparticles in a T-mixer was studied by Schwarzer and Peukert (Schwarzer and Peukert, 2004). The authors have shown that with increasing Reynolds number, i.e. improved mixing, the particles are smaller and the particle size distribution is narrower.

Another application of these fast mixing devices is the determination of nucleation and growth kinetics at high supersaturation. These conditions are typically attained by mixing two solutions where one contains the substance to be crystallized and the other an antisolvent (Mahajan and Kirwan, 1993; Mahajan and Kirwan, 1994), or a reactant (Blandin et al., 2001; Stahl et al., 2001). If the solute solution is mixed with an antisolvent the solubility is decreased drastically, thus initiating the precipitation. If the solute solution is mixed with a reactant solution, e.g. an acid in the case of pH-shift precipitation (Schöll et al., 2007b; Schöll et al., 2006b), the reaction product has a lower solubility which leads to a supersaturated solution. Sparingly soluble inorganic crystals, such as barium sulfate, are obtained by mixing two solutions containing the salts of the respective counter-ion (Nielsen, 1961; Vicum et al., 2003). A Y-mixer has been used by Haberkorn and coworkers to investigate the early stages of particle formation using small-angle X-ray scattering (Haberkorn et al., 2003). In all these processes it is desirable to achieve complete mixing prior to nucleation in order to have a uniform concentration distribution in the reactor.

Laser induced fluorescence (LIF) has been used by Unger and Muzzio to quantify mixing in impinging jet reactors (Unger and Muzzio, 1999). However, the application of LIF is relatively complicated and limited to low Reynolds numbers and larger characteristic sizes of the setup. Furthermore, it has been reported that CIJ mixers exhibit self-sustained oscillations in a certain Reynolds range (Johnson and Wood, 2000). Micromixing effects in a two impinging jet precipitator have been studied by Mahajan and Kirwan using a competitive-consecutive reaction system (Mahajan and Kirwan, 1996). For their configuration micromixing times as small as 65 ms were achieved. Johnson and Prud’homme have studied micromixing in a CIJ mixer using competitive-
parallel chemical reactions (Johnson and Prud'hommme, 2003a). They determined mixing times below 9.5 ms. However, the methodology and the definition of the mixing time are not directly comparable. In two recent studies, mixing in the CIJ has been studied using CFD (Gavi et al., 2007; Liu and Fox, 2006).

Besides fast mixing, static mixers used for precipitation processes should have a rounded geometry and no internals, e.g. grids and blades, to avoid clogging of the mixer. The aim of this work is to develop experimental and numerical techniques in order to design improved mixing devices and allow for a simple scale-up of these mixers. Mixing can be characterized experimentally using a set of chemical reactions with well-known kinetics. In this study we use the reaction system consisting of the neutralization of hydrochloric acid with sodium hydroxide and the hydrolysis of 2,2-dimethoxypropane with hydrochloric acid (Baldyga et al., 1998) in order to study the effect of mixing on the reaction yield. In addition, the experimental data are used to check the accuracy and the prediction capability of a CFD model of the process. Finally, this model is used to determine mixing times and to visualize mixing and reaction zones in the mixer.

4.2 Experimental section

4.2.1 Experimental setup

In the mixer the fluid streams have to be mixed at high flow rates with minimal flow rate fluctuations to ensure good mixing. Owing to the high pressure drop over the mixing chamber the maximum differential pressure that the pumps have to overcome is also relatively high, i.e. in the order of 20 bar for a flow rate of 220 g/min. A custom-made setup, consisting of two Pneumatix PWD 8 pressure tanks with a maximum pressure of 25 bar and a maximum liquid capacity of 6.4 liters, has been developed (Schöll, 2006). The flow sheet of the setup is shown in Figure 4.1.a.
Figure 4.1: Experimental setup with different pump configurations: pressure tank (a), syringe pump (b), gear pump (c).
Prior to each experiment the solutions are fed into the setup through the valves V-4 and V-5. Then, the tanks are pressurized with nitrogen. It must be noted that the gas has no contact with the solution since gas and solution are separated by a membrane. The pressure can be set using a pressure regulator. Flow rate (coriolis force flowmeter Rheonik RHM 01, Germany), pressure and temperature are measured for both streams. The flow rate ratio can be adjusted using a needle valve between the flowmeter and the mixer. Finally, at the outlet of the mixer the solution can be quenched or collected for sample analysis. The same setup has also been used with syringe pumps (Havard PHD 22, United States) and gear pumps (Ismatec MCP-Z, Switzerland) as shown in Figures 1.b and 1.c, respectively. The syringe pump can deliver very accurate (±0.35%) and pulsation-free flows, while pressure is limited to approximately 2 bar and flow to 60 g/min for our configuration. They were used in this study to characterize mixing at very low flow rates since at these conditions the pressure tank setup did not give reasonable and reproducible results. The gear pump is limited to relatively low pressures of about 5.2 bar, but can deliver flow rates up to 7200 ml/min. Although this pump is not pulsation-free it was tested in this study because of the possibility of continuous operation, which makes it highly relevant for industrial applications.

A two jet vortex mixer, also called Roughton mixer, was proposed by Söhnel and Garside for precipitation processes with fast nucleation and growth kinetics (Söhnel and Garside, 1992). On the basis of that work an optimized Roughton geometry has previously been developed using CFD (Schöll, 2006) and is shown in Figure 4.2.a. The mixing chamber has a diameter of 1.5 mm and a height of 1.75 mm. The inlet tubes have a diameter of 0.5 mm, the outlet tube has a diameter of 0.75 mm and a length of 15 mm. The Y-mixer design was based on mixer geometries published in other precipitation studies (Blandin et al., 2001; Eble, 2000; Haselhuhn and Kind, 2003; Roelands et al., 2003). As shown in Figure 4.2.b, our Y-mixer is designed with an inlet tube diameter of 0.5 mm, an impingement angle of $\alpha = 160^\circ$, and an outlet tube with 1 mm diameter and a length of 15 mm. Adapters of different length with the same diameter can be used to extend the outlet tube. Both mixing devices consist of stainless steel and were manufactured in our workshop.
4.2.2 Reaction kinetics

Competitive-parallel chemical reactions can be used experimentally to determine mixing times (Johnson and Prud'homme, 2003a). Usually, the reaction set consists of a fast and a slow reaction. If the timescale of mixing of the two segregated streams is much smaller than the reaction timescale of the slower reaction, this reaction will practically not take place. In contrast, if the timescale of mixing is similar to or larger than the timescale of the slower reaction, the yield of this reaction can be used to quantify mixing timescales (Baldyga and Bourne, 1999; Johnson and Prud'homme, 2003a).

The competitive-parallel reaction scheme studied by Baldyga and coworkers (Baldyga et al., 1998; Walker, 1996) has been used in this study to characterize mixing.

\[
H^+ + OH^- \xrightarrow{k_1} H_2O \tag{4.1}
\]

\[
H^+ + CH_3C(\text{OCH}_3)_2CH_3 + H_2O \xrightarrow{k_2} H^+ + CH_3COCH_3 + 2CH_3OH \tag{4.2}
\]
The first reaction is the fast neutralization of sodium hydroxide with hydrochloric acid. The second order rate constant is $k_1 = 1.4 \times 10^8 \text{ m}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 298 K (Baldyga et al., 1998). The second reaction is a relatively slower hydrolysis of 2,2-dimethoxypropane (DMP) forming acetone and methanol. The rate of the hydrolysis reaction can be simplified to second order due to ubiquity of water:

$$k_2 = 7.32 \times 10^7 \exp\left(-5556 / T\right)10^{0.05434+7.07 \times 10^5 \text{c}_S}$$  \hspace{1cm} (4.3)

where $k_2$ is given in $\text{m}^3 \text{ mol}^{-1} \text{ s}^{-1}$. The rate constant is valid for sodium chloride concentrations $c_S$ of 100 to 1200 mol/m$^3$, HCl and DMP concentrations of 25 to 1333 mol/m$^3$, respectively, a temperature range of 298 to 313 K and an ethanol concentration of 25 wt.% (Baldyga et al., 1998). Ethanol was added to the solution to increase the solubility of DMP. Sodium chloride was added since the reaction rate (Eq. (4.3)) was determined in the presence of sodium chloride. The following expressions for density and viscosity as a function of process parameters were obtained by Johnson and Prud'homme (Johnson and Prud'homme, 2003a):

$$\rho = 1143.9 - 0.60916 T + 0.020894 c_{in} + 0.014989 c_{NaOH}$$  \hspace{1cm} (4.4)

$$\eta = 36780 \exp\left(-0.03296 T\right) + 1.20 \times 10^{-4} (1-X) c_{in} + 7.00 \times 10^{-4} c_{NaOH}$$ \hspace{1cm} (4.5)

where $\rho$ is the density in kg/m$^3$, $\eta$ is the dynamic viscosity in mPas, $c_{in}$ is the initial concentration of DMP or HCl before mixing, $c_{NaOH}$ is the NaOH concentration in the stream of interest and $X$ the fraction of DMP converted:

$$X = 1 - \frac{c_{DMP}}{c_{DMP}^0}$$ \hspace{1cm} (4.6)

with $c_{DMP}$ being the final concentrations of DMP after mixing and reaction and $c_{DMP}^0$ being the concentration of DMP after mixing as if no reaction had occurred. Since $k_1$ is many orders of magnitude higher than $k_2$ the characteristic reaction time can be defined as the time constant of the slow pseudo first-order reaction of DMP (Johnson and Prud'homme, 2003a):

$$t_r = \frac{1}{k_2 c_{DMP}^0}$$ \hspace{1cm} (4.7)
4.2.3 Experimental protocol

2,2-dimethoxypropane (98%, Sigma-Aldrich, Switzerland), ethanol (99.8%, Merck KGaA, Germany), sodium chloride (99.5%, L.T. Baker, Netherlands), hydrochloric acid (1.000 molar standard, Merck KGaA, Germany) and sodium hydroxide (1.000 molar standard, Merck KGaA, Germany) were used in all experiments. The initial solutions were produced such that after mixing a ratio of $c_{NaOH}^0 : c_{HCl}^0 : c_{DMP}^0$ was obtained. The details about the initial concentration for each run are given in Table 4.1. NaOH was added in excess to have a pH larger than 8 after mixing which ensures no further reaction of DMP. Both reaction streams contained 90 mmol/L of NaCl and a solvent consisting of 25 wt.% ethanol in deionized water. All experiments were carried out at room temperature. Although the temperature rose of about 1–2 °C during mixing due to reaction enthalpy and energy dissipation, we assumed a constant temperature of 25 °C for the calculation of the reaction rate constant, density and viscosity. For each concentration, an experimental run started with the lowest flow rate. After the flow rates had stabilized, samples were taken. Then, the flow rate was gradually increased till the maximum allowable pressure or flow rate was reached. For each setpoint of the flow rate two samples were taken and analyzed using a gas chromatograph. Hence, the experimental values of the DMP conversion $X$ reported in this work represent always the average of two measurements.

The samples were analyzed on a Varian 3800 gas chromatograph equipped with a 30 m Varian column (VA-125103-20) and a flame ionization detector. An injection volume of 1 μL and a split ratio of 1:10 were employed. The oven temperature was held at 40 °C for 7.5 min and then increased with a ramp of 25 °C/min to 180 °C. Each sample was injected three times and the average of measured concentration was taken for further analysis. For each experimental run calibration standards were produced using methanol (99.8%, L.T. Baker, Netherlands) in a solvent of 25 wt.% ethanol in deionized water. The calibration standards corresponded to the maximum attainable concentration of methanol and a dilution by a factor 10, 100 and 1000. The concentration of methanol was measured and ethanol was taken as internal standard to increase reproducibility. The calibration curve of all analysis can be described by a single straight line and is valid in a range of methanol concentration from 0.1 to 600 mmol/L:
\[ c_{MeOH} = 1.017 \times 10^4 \frac{A_{MeOH} \cdot w_{EtOH}}{A_{EtOH}}, \quad (4.8) \]

where \( A_{MeOH} \) and \( A_{EtOH} \) are the peak areas of methanol and ethanol in the chromatogram, respectively, and \( w_{EtOH} \) is the absolute concentration of ethanol in weight percent. The concentration of DMP is given by the following equation:

\[ c_{DMP} = c_{DMP}^0 - 0.5 c_{MeOH}. \quad (4.9) \]

Samples were analyzed within 24 hours after the experiment. Decomposition of DMP was not observed within 14 days of storage.

<table>
<thead>
<tr>
<th>Run</th>
<th>Mixer type</th>
<th>Pump configuration</th>
<th>( Q_1/Q_2 ) [g/min]</th>
<th>( c_{HCl,1} ) [mmol/kg]</th>
<th>( c_{DMP,2} ) [mmol/kg]</th>
<th>( t_r ) [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>syringe pump</td>
<td>1</td>
<td>600</td>
<td>600</td>
<td>4.9</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>syringe pump</td>
<td>1</td>
<td>200</td>
<td>200</td>
<td>14.9</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>pressure tank</td>
<td>1</td>
<td>600</td>
<td>600</td>
<td>4.9</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>pressure tank</td>
<td>1</td>
<td>200</td>
<td>200</td>
<td>14.9</td>
</tr>
<tr>
<td>5</td>
<td>R</td>
<td>pressure tank</td>
<td>1</td>
<td>100</td>
<td>100</td>
<td>29.7</td>
</tr>
<tr>
<td>6</td>
<td>R</td>
<td>gear pump</td>
<td>1</td>
<td>600</td>
<td>600</td>
<td>4.9</td>
</tr>
<tr>
<td>7</td>
<td>R</td>
<td>gear pump</td>
<td>1</td>
<td>200</td>
<td>200</td>
<td>14.9</td>
</tr>
<tr>
<td>8</td>
<td>R</td>
<td>gear pump</td>
<td>1</td>
<td>100</td>
<td>100</td>
<td>29.7</td>
</tr>
<tr>
<td>9</td>
<td>R</td>
<td>pressure tank</td>
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<td>300</td>
<td>150</td>
<td>14.9</td>
</tr>
<tr>
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<td>120</td>
<td>14.9</td>
</tr>
<tr>
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<td>600</td>
<td>600</td>
<td>4.9</td>
</tr>
<tr>
<td>12</td>
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<td>1</td>
<td>200</td>
<td>200</td>
<td>14.9</td>
</tr>
<tr>
<td>13</td>
<td>Y</td>
<td>pressure tank</td>
<td>1</td>
<td>200</td>
<td>200</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Table 4.1 Experimental conditions. Mixer type, pump configuration, flow rate ratio, initial concentration of HCl and DMP, and corresponding reaction time constant.
4.3 Mathematical model

4.3.1 CFD model

The material balance and the momentum balance (Navier-Stokes) equations are closed using the RNG $k-\epsilon$ model, i.e. a standard turbulence model (Fluent, 2006). The CFD code Fluent 6.2.16 was employed to solve the turbulence model and the additional scalar transport equations. The grid consists of 193600 cells for the Roughton mixer and 169000 cells for the Y-mixer, and was refined until a grid-independent solution was obtained. It must be noted that at low Reynolds number the outlet tube had to be extended thus increasing the number of cells accordingly. The enhanced wall treatment model was used to model near wall flow, and the differential viscosity model was employed to account for low Reynolds number effects (Fluent, 2006). The solver was set to second-order upwind for all transport equations. Other turbulence models, such as the standard $k-\epsilon$ model, the realizable $k-\epsilon$ model and the Reynolds stress model, which are all available in Fluent, were tested as well. All models gave similar results for a reference case at a Reynolds number of 2227 if a second order upwind discretization was applied. However, we employed the RNG $k-\epsilon$ model because it allows for the prediction of swirling and transitional flows (Fluent, 2006). Furthermore, it is less computational intensive and has good convergence properties, compared to the Reynolds stress model (Fluent, 2006). Different near-wall models were tested too, however a comparison of the results showed only minor differences. We decided to use the enhanced wall treatment since it has been suggested to describe satisfactorily low-$Re$ and complex 3D flows (Chen and Patel, 1988; Fluent, 2006), as in the mixer employed here. Another way of solving the Navier-Stokes equations is via direct numerical simulation (DNS), which has a number of advantages over conventional Reynolds-averaged models, i.e. it describes the flow field more accurately especially in the case of transitional flows. Moreover DNS allows for the prediction of symmetry breaking phenomena, which are neglected by the Reynolds-averaged models but occur in reality, for example in T- and confined impinging jet mixers (Bothe et al., 2006; Schwertfirm et al., 2007). However, the DNS approach was not followed in this work because of the excessive computational effort.
4.3 Mathematical model

4.3.2 Turbulent mixer model

In this section, the turbulent mixer model, which has been developed and applied previously by other authors to model small-scale mixing, is presented (Baldyga, 1989; Baldyga and Henczka, 1995; Vicum and Mazzotti, 2007; Vicum et al., 2004). The turbulent mixer model describes the mixing of a passive tracer $T$ with concentration $c_T$, which is injected into the mixer with concentration $c_{T0}$. The average normalized tracer concentration $\langle f \rangle$ reads as follows:

$$\langle f \rangle = \frac{c_T}{c_{T0}}.$$  \hfill (4.10)

The concentration of $f$ changes under the action of convection and turbulent diffusion. The distribution of $\langle f \rangle$ can be calculated from the following equation:

$$\frac{\partial \langle f \rangle}{\partial t} + \langle u_i \rangle \frac{\partial \langle f \rangle}{\partial x_i} = \frac{\partial}{\partial x_i} \left[ (D + D_T) \frac{\partial \langle f \rangle}{\partial x_i} \right],$$  \hfill (4.11)

with $D$ and $D_T$ being the molecular and turbulent viscosity, respectively. The mixture structure on small-scale can be characterized by the concentration variance $\sigma^2$ of the local concentration distribution of $f$ around its average value $\langle f \rangle$, where $\sigma^2$ can be divided into three parts related to the scale of segregation and the mechanism of mixing (Baldyga and Orciuch, 2001), i.e. inertial convective ($\sigma^2_1$), viscous-convective ($\sigma^2_2$) and viscous-diffusive ($\sigma^2_3$):

$$\sigma^2 = \langle (f - \langle f \rangle)^2 \rangle = \sigma^2_1 + \sigma^2_2 + \sigma^2_3.$$  \hfill (4.12)

The evolution of the local mixture structure, which is expressed by the evolution of the concentration variances, can be calculated using the following transport equations:

$$\frac{\partial \sigma^2_i}{\partial t} + \langle u_i \rangle \frac{\partial \sigma^2_i}{\partial x_i} = \frac{\partial}{\partial x_i} \left[ (D + D_T) \frac{\partial \sigma^2_i}{\partial x_i} \right] + R_{pi} - R_{di} \quad (i = 1, 2, 3),$$  \hfill (4.13)

where $R_{pi}$ and $R_{di}$ stand for production and dissipation terms of the different variances. These terms are defined by (Baldyga and Orciuch, 2001):
where $\varepsilon$ is the energy dissipation rate, $k$ is the turbulent kinetic energy, $\nu$ is the kinematic viscosity and $Sc$ is the Schmidt number. The parameter $R$ in Eq. (4.15) is the ratio of the time scale for the decay of velocity fluctuations to the time scale for the decay of concentration fluctuations. In turbulence modeling this parameter is often set to $R = 2$. However, as explained by Liu and Fox the value of $R$ is smaller at low Reynolds numbers, and in order to describe the reaction rate correctly one has to account for low-Reynolds-number-effects in the mixing model (Liu and Fox, 2006). The authors suggest to describe the dependence of $R$ on the local turbulent Reynolds number $Re_1$ using the following expression (Liu and Fox, 2006):

$$R = \sum_{n=0}^{6} a_n \left( \log Re_1 \right)^2 \quad \text{for } Re_1 \geq 0.2 ,$$

where $a_0 = 0.4093$, $a_1 = 0.6015$, $a_2 = 0.5851$, $a_3 = 0.09472$, $a_4 = -0.3903$, $a_5 = 0.1461$ and $a_6 = -0.0164$. The local turbulent Reynolds number is defined as:

$$Re_1 = \frac{k}{\varepsilon \nu^{0.5}} .$$

### 4.3.3 Mixing-reaction model

The neutralization reaction (Eq. (4.1)) is assumed to be instantaneous and hydrolysis reaction (Eq. (4.2)) to be fast:

$$A + B \overset{k_1 \to \infty}{\longrightarrow} P_1$$

$$A + D \overset{k_2}{\longrightarrow} A + P_2 + 2P_3 ,$$
where $A$ is $H^+$, $B$ is $OH^-$, $D$ is DMP, $P_1$ is water, $P_2$ is acetone, and $P_3$ is methanol. The simplest way to compute the average local reaction rates $\langle r \rangle$ is to consider them as a function of the local average reactant concentrations $\langle c_j \rangle$ only, i.e.:

$$\langle r_1 \rangle = k_1 \langle c_A \rangle \langle c_B \rangle$$  \hspace{1cm} (4.22)
$$\langle r_2 \rangle = k_2 \langle c_A \rangle \langle c_D \rangle.$$  \hspace{1cm} (4.23)

However, using this approach the effects of small-scale mixing are neglected. Another possibility is to model the small-scale mixture structure, e.g. using the turbulent mixer model presented in the previous section. The information about the local mixture structure can be used to account for the effect of the concentration fluctuations on the reaction rate, i.e. to close the reaction rate term properly:

$$\langle r_1 \rangle = k_1 \langle c_A c_B \rangle = k_1 \left( \langle c_A \rangle \langle c_B \rangle + \langle c'_A c'_B \rangle \right)$$  \hspace{1cm} (4.24)
$$\langle r_2 \rangle = k_2 \langle c_A c_D \rangle = k_2 \left( \langle c_A \rangle \langle c_D \rangle + \langle c'_A c'_D \rangle \right).$$  \hspace{1cm} (4.25)

The closure requires expressing the local instantaneous concentrations $c'_j$ as functions of the concentration of the non-reacting tracer $f$. Under the assumption of an infinitely fast neutralization reaction it follows that reactants $A$ and $B$ cannot coexist in the same fluid element. Thus, it is convenient to replace them by a single variable $Y$ which is defined as follows (Baldyga and Bourne, 1999):

$$Y(f) = \frac{c_A(f) - c_B(f)}{c_{A0}}.$$  \hspace{1cm} (4.26)

It is worth noting that the variable $Y$ behaves like a non-reacting tracer in Eqs. (4.20) and (4.21). The local instantaneous value of $Y$ is then given by (Baldyga and Bourne, 1999):

$$Y(f) = f(1 + \beta) - \beta,$$  \hspace{1cm} (4.27)

where $\beta$ is defined as:

$$\beta = \frac{c_{B0}}{c_{A0}}.$$  \hspace{1cm} (4.28)
with $c_{A0}$ and $c_{B0}$ being the initial concentrations of $A$ and $B$, respectively. The local instantaneous concentrations of $A$ and $B$ can be recalculated from $Y(f)$:

$$c_A(f) = \frac{[Y(f)] + Y(f)}{2} c_{A0} \quad (4.29)$$

$$c_B(f) = \frac{[Y(f)] - Y(f)}{2} c_{B0}. \quad (4.30)$$

The method for calculating the value of the normalized concentration of $C$

$$C(f) = \frac{c_D(f)}{c_D0} \quad (4.31)$$

is based on linear interpolation of $C(f)$ between two limiting cases: $C^\infty$ and $C^0$ corresponding to instantaneous and infinitely slow reaction, respectively (Baldyga and Bourne, 1999):

$$C^\infty(f) = \begin{cases} 1 - f \frac{1+\beta}{\beta} & f < \frac{\beta}{1+\beta} \\ 0 & f > \frac{\beta}{1+\beta} \end{cases} \quad (4.32)$$

and

$$C^0(f) = 1 - f. \quad (4.33)$$

The method of linear interpolation using the local average concentrations gives the local instantaneous value of $C(f)$

$$C(f) = C^\infty(f) + \frac{\langle C \rangle - \langle C^\infty \rangle}{\langle C^0 \rangle - \langle C^\infty \rangle} \left( C^0(f) - C^\infty(f) \right), \quad (4.34)$$

where

$$\langle C^\infty \rangle = \int_0^1 C^\infty(f) \phi(f) df \quad (4.35)$$

and

$$\langle C^0 \rangle = 1 - \langle f \rangle. \quad (4.36)$$
The probability density function (PDF) can be used to describe the local mixture structure; in this work we have approximated the composition PDF with the beta-function \( \phi(f) \) (Baldyga and Henczka, 1995):

\[
\phi(f) = \frac{f^{w-1} (1-f)^{v-1}}{I_1(u^{w-1} (1-u)^{w-1})}, \quad (4.37)
\]

with

\[
v = \langle f \rangle \frac{\langle f \rangle (1-\langle f \rangle)}{\sigma_v^2 - 1}, \quad (4.38)
\]

and

\[
w = (1-\langle f \rangle) \frac{\langle f \rangle (1-\langle f \rangle)}{\sigma_v^2 - 1}. \quad (4.39)
\]

The beta-function should be determined at every point in the system using the local values of the concentration variance \( \sigma_v^2 \) coming from the turbulent mixer model described above, thus linking the local mixture structure with the calculation of the average reaction rates. The local average rate of the second reaction (Eq. (4.25)) is then given by (Baldyga and Bourne, 1999):

\[
\langle r_2 \rangle = k_2 \langle c_A c_D \rangle = k_2 c_{A0} c_{D0} \int_0^1 \phi(f) \left| \frac{Y(f)}{2} \right| C(f) df . \quad (4.40)
\]

The distribution of the average concentrations is calculated using the Reynolds averaged transport equations and the mixing reaction model. The transport equation for the reactants reads as follows:

\[
\frac{\partial \langle Y \rangle}{\partial t} + \langle u_i \rangle \frac{\partial \langle Y \rangle}{\partial x_i} = \frac{\partial}{\partial x_i} \left[ (D + D_r) \frac{\partial \langle Y \rangle}{\partial x_i} \right] \quad (4.41)
\]

\[
\frac{\partial \langle C \rangle}{\partial t} + \langle u_i \rangle \frac{\partial \langle C \rangle}{\partial x_i} = \frac{\partial}{\partial x_i} \left[ (D + D_r) \frac{\partial \langle C \rangle}{\partial x_i} \right] - \frac{\langle r_2 \rangle}{c_{D0}} . \quad (4.42)
\]

Eqs. (4.11), (4.13), (4.41) and (4.42) are implemented in Fluent as user-defined scalars. Since the turbulent flow field is independent of the scalar fields the turbulent flow field can be solved first, followed by solving the scalar transport equations.
4.4 Results and discussion

4.4.1 Experimental results

The yield of the DMP reaction $X$ was determined experimentally for different mixer geometries, flow rates, flow rate ratios, concentrations and pump configurations. The experimental conditions of the different runs are reported in Table 4.1.

4.4.1.1 Effect of mixer type

In Figure 4.3.a, the experimental values of the DMP conversion are shown for the Roughton and the Y-mixer as a function of the jet Reynolds number, which is given by:

$$Re_j = \frac{\bar{u}d}{\nu}, \quad (4.43)$$

where $\bar{u}$ is the mean jet velocity and $d$ is the diameter of the inlet pipes. The values of $X$ in the Roughton mixer for a characteristic reaction time (see Eq. (4.7)) of $t_r = 4.9 \text{ ms}$ (run 1, $c_{\text{DMP},2} = 600 \text{ mmol/L}$) and $t_r = 14.9 \text{ ms}$ (run 2, $c_{\text{DMP},2} = 200 \text{ mmol/L}$) are shown as filled triangles and filled circles, respectively. The faster the two streams are completely mixed on all scales, the less DMP will react with H$^+$-ions since the DMP reaction stops as soon as the solution is neutralized. As expected, for both reaction times the value of $X$ decreases with increasing Reynolds number, thus indicating improved mixing. Furthermore, the value of $X$ is larger for smaller values of the reaction time constant, which corresponds to higher initial concentrations of HCl and DMP. The higher the concentration, the higher the reaction rate of the DMP reaction. Thus, at higher concentrations DMP and OH$^-$ compete more to react with H$^+$ and the yield of the DMP reaction increases. In Figure 4.3.a, the yield of the DMP reaction is plotted for the Y-mixer as well (runs 11 and 12). The Y-mixer exhibits a similar behavior concerning the effect of concentration and Reynolds number as the Roughton mixer. The mixing performance of the Roughton mixer is better, which is shown by more than two times smaller values of $X$ for $Re_j > 300$, if mixing is compared with respect to the jet Reynolds number.
Figure 4.3: Experimental results of the DMP conversion $X$ as a function of Reynolds number for Roughton and Y-mixer (a), where the flow is delivered by syringe pumps (runs 1, 2, 11, and 12). DMP conversion as a function of pressure drop (b), where the flow is delivered by syringe pump and pressure tank (runs 2, 4, 12, and 13).

However, different mixers should be compared also in terms of specific power input, which is related to the pressure drop across the mixer. Such a comparison
is given in Figure 4.3.b for \( t_r = 14.9 \) ms. It can be seen that up to a pressure drop of 0.8 bar the values of \( X \) are almost identical for the two mixers. But for higher pressure drops, as shown as inset in Figure 4.3.b, the yield of the DMP reaction is higher for the Y-mixer as compared to the Roughton mixer, thus indicating a better mixing performance of the Roughton mixer also in this representation.

Compared to the confined impinging jet (CIJ) mixer studied by Johnson and Prud’homme (Johnson and Prud'homme, 2003a) the values of the DMP conversion are much lower in the Roughton mixer. In the study of Johnson and Prud’homme the DMP conversion was determined experimentally for different Reynolds numbers and reaction times: at \( Re_j = 1000 \) and \( t_r = 28 \) ms the value of \( X \) was about 0.04 and at \( t_r = 4.8 \) ms \( X \) was about 0.3 in the CIJ (Johnson and Prud'homme, 2003a). The corresponding values of \( X \) measured in this study for the Roughton mixers are almost by a factor 10 lower, and for the Y-mixer about a factor 3 lower. Thus, it can be concluded that in both the Roughton and the Y-mixer mixing is much faster compared to the CIJ mixer, whereas the Roughton mixer shows the best mixing performance. However, this conclusion holds only if mixing is compared in terms of jet Reynolds number. Unfortunately, pressure drops of the CIJ were not available, thus a comparison in this respect was not possible.

### 4.4.1.2 Effect of pump configuration

Syringe pumps were used for low flow rates since they are pulsation-free and very precise. The syringe pumps used in this work were limited to a pressure difference of about 2 bar and a maximum flow rate of 60 g/min (\( Re_j \approx 1500 \)). Therefore, at higher flow rates the pressure tank setup was employed. However, for an industrial applications gear pumps are typically used, since they allow for high flow rates and pressures, and can be operated continuously. Since gear pumps are not pulsation-free we wanted to investigate if the pulsations had an influence on mixing. The effect of the different pump configurations is illustrated in Figure 4.4 for the Roughton mixer. For Reynolds numbers larger than 300 the values of \( X \) are in satisfactory agreement for the syringe and the gear pump. For lower Reynolds numbers the agreement is worse, i.e. the values of \( X \) are larger for the gear pumps, most probably as a result of pulsations in the gear pumps. However, at higher flow rates the effect of pulsations seems to be neg-
ligible. The values of $X$ for Reynolds numbers lower than 1000 are not shown for the pressure tank setup since at these conditions the results were scattered and not reproducible. At a Reynolds number of 1000 the agreement with respect to the DMP conversion is good for all three pump configurations. Since the DMP conversion is not very much affected by the pump configuration in a wide range of Reynolds numbers, it was concluded that all three pump systems can be used for a fast mixing of the streams in the static mixer.

![Figure 4.4: Effect of pump configuration on DMP conversion $X$ in the Rough-ton mixer. The plot shows the experimental results of runs 1 – 4, 6, and 7.](image)

### 4.4.2 Simulation results

In this section, first, the experimental and simulated DMP conversion $X$ is compared for the Roughton mixer and a flow rate ratio of 1:1. Second, the effect of different flow rate ratios on the DMP conversion is studied for the Roughton mixer. Since the mixer should be applicable for fast precipitation processes, e.g. precipitation with an antisolvent where the flow rate ratio is typically different from 1:1, it is important that a good mixing performance is achieved at these conditions too. Third, the values of experimental and simulated $X$ are shown for the Y-mixer.
Figure 4.5: Comparison of experimental and simulated DMP conversion $X$ in the Roughton mixer. Symbols: experimental data; lines: CFD simulations with PDF closure. The experimental data represent the results of all three pump configurations (runs 1 – 8).

In Figure 4.5, experimental and simulated DMP conversion values are presented for three different initial concentrations of DMP (reaction time constants, as to Eq. (4.7)). The yield $X$ decreases with increasing jet Reynolds number and decreasing concentration. The simulations agree very well with the experimental data for all Reynolds numbers and DMP concentrations. It is worth noting that CFD studies below a Reynolds number of 300 were not conducted since the required downstream length for modeling complete mixing would have been excessively long. The simulations presented in Figure 5 were obtained by applying the PDF closure, i.e. by accounting for the effect of small scale mixing on the reaction rate. The outlet concentration of DMP was calculated by its mass-weighted average, which is computed as follows (Fluent, 2006):
where $c_{Di}$ is the facet value of the DMP concentration and $|\bar{\vec{u}}_i \cdot \vec{A}_i|$ is the absolute value of the dot product of the velocity vector and the facet area. The averaged reaction rate $r_2$ was always zero at the outlet, thus mixing was completed. A comparison of the results of CFD simulations with and without the application of the PDF closure is shown in Figure 4.6 for a reaction time constant of $14.9 \text{ ms}$.

If sub-grid scale mixing is neglected, i.e. instantaneous complete mixing on sub-grid scale is assumed, the calculated DMP conversion is lower than in the case where sub-grid mixing is accounted for. This is true for all simulations that were carried out in this study. A detailed analysis will be given below in section 4.4.3. It can be observed that the differences between simulation with and
without applying the closure decrease with increasing Reynolds number. At high Reynolds numbers small scale mixing is improved due to the increased energy dissipation and the concentration variances decay faster.

Experimental and simulated DMP conversion for a reaction time constant of 14.9 ms and flow rate ratios of 1:2 and 1:5 are shown in Figure 4.7 and Figure 4.8, respectively. The Reynolds number in these cases is defined as

\[ Re_j = \frac{Re_{j1} + Re_{j2}}{2}, \]  

(4.45)

where \( Re_{j1} \) and \( Re_{j2} \) are the jet Reynolds numbers of the two inlet streams, respectively. It must be noted that for a flow rate ratio of 1:1 \( Re_j = Re_{j1} = Re_{j2} \).

![Figure 4.7: Results of DMP conversion \( X \) for CFD model of the Roughton mixer and a flow rate ratio of 1:2. The experimental data represent the results of the pressure tank configuration (run 9).](image)

At the same Reynolds number \( Re_j \) the experimental DMP conversion values are almost the same for all three flow ratios. The initial concentrations have to be adjusted if the flow rate ratio is different from 1:1 to give the same final concentration of DMP, \( H^+ \) and \( OH^- \) after mixing (see Table 4.1) and thus the same
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reaction rate constant as to Eq. (4.7). Therefore, with increasing local concentrations the reaction rate and the DMP conversion would be higher if one assumes that the mixing conditions stay the same. A comparison of the simulated values of $X$ obtained using the closure as given in Figure 4.6 to Figure 4.8 shows that for Reynolds numbers smaller than 5000 the values of $X$ at the same Reynolds number increase with decreasing flow rate ratio, while for Reynolds numbers larger than 5000 the opposite occurs. It can be observed that the difference between the model with and without applying the PDF closure becomes smaller with decreasing flow rate ratio, especially at high Reynolds numbers. It must be noted that for the same Reynolds number the pressure drop slightly increases with decreasing flow rate ratio.

Figure 4.8: Results of DMP conversion $X$ for CFD model of the Rougthon mixer and a flow rate ratio of 1:5. The experimental data represent the results of the pressure tank configuration (run 10).

A comparison of experimental and simulated DMP conversion in the Y-mixer is shown in Figure 4.9 for two different concentrations, which correspond to reaction time constants of 4.9 and 14.9 ms, respectively. For both concentrations the simulations agree very well with the experiments if the PDF closure is
applied. Simulations below a Reynolds number of 500 were not run because of the required tube length to be simulated to attain complete mixing. Compared to the Roughton mixer the DMP conversion is at least twice as high in the Y-mixer for Reynolds number larger than 1000. As for the Roughton mixer, the simulated values of $X$ without applying the closure are smaller than the values with closure, and the difference between the two models is getting smaller at higher Reynolds numbers.

Figure 4.9: Experimental and simulated results of DMP conversion $X$ in the Y-mixer. The experimental data represent the results of the syringe pump and the pressure tank configuration (runs 11 – 13).

The good agreement between experimental and simulated DMP conversion values for a wide range of operating conditions and for different mixer geometries allows for estimating the mixing times based on the CFD model. A detailed analysis of mixing times and a comparison of mixing in the different mixers are presented in section 4.4.4.
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4.4.3 Mixing and reaction zones

A contour plot of the concentration of a passive non-reacting tracer $\langle f \rangle$ is shown in Figure 4.10.a and Figure 4.10.c for a jet Reynolds number of 557 and 5568, respectively. For both Reynolds numbers the value of $\langle f \rangle$ is 0.5 at the outlet of the mixing chamber, thus indicating that macro-mixing is complete. Figure 4.10.b and Figure 4.10.d show the concentration variance $\sigma_s^2$ for a jet Reynolds number of 557 and 5568, respectively. At $Re_j = 557$ the concentration variance is still larger than 0.05 at the outlet, i.e. the mixing on meso- and micro-scale is not complete. On the contrary, at $Re_j = 5568$ the concentration variance is less than 0.001, which is considered here as a threshold for complete mixedness. It is notable that at $Re_j = 5568$ also the maximum value of the concentration variance is smaller than at $Re_j = 557$.

A contour plot of the reaction rate $\langle r_s \rangle$ when applying the PDF closure is shown in Figure 4.11.a for $Re_j = 557$ and a reaction time constant of 4.9 ms. It can be observed that the reaction is not completed as it takes place everywhere in the mixing chamber and in the outlet pipe. Figure 4.11.b shows the simulation results for the same operating conditions but without applying the PDF closure. In this case the reaction takes place completely in the mixing chamber and only in the zone of the mixer where the mean pH value is acidic, i.e. $\langle c_A \rangle > \langle c_B \rangle$. At higher flow rates, e.g. at $Re_j = 5568$, the reaction zone is smaller since the concentration variances decay faster as can be seen in Figure 11.c for the CFD model with PDF closure. Figure 4.11.d shows the reaction rate without application of the closure. The distribution of reaction rates is very similar to those at $Re_j = 557$; however the maximum value is slightly higher. A comparison of Figure 4.11.c and Figure 4.11.d reveals that at high Reynolds numbers the distributions of the reaction rate for the model with and without applying the closure become more similar. This can be attributed to the improved meso- and micro-mixing since the model without PDF closure is an extreme case of the model with closure if the mixing is very good.
4. Mixing characterization

Figure 4.10: Concentration $\langle f \rangle$ and variance $\sigma_f^2$ of a passive tracer in the Roughton mixer. (a) $\langle f \rangle$ at $Re_j = 557$; (b) $\sigma_f^2$ at $Re_j = 557$; (c) $\langle f \rangle$ at $Re_j = 5568$; (d) $\sigma_f^2$ at $Re_j = 5568$.

Figure 4.11: Reaction rate $\langle r_2 \rangle$ in the Roughton mixer. (a) $\langle r_2 \rangle$ at $Re_j = 557$ with applying the PDF-closure; (b) $\langle r_2 \rangle$ at $Re_j = 557$ without applying the PDF-closure; (c) $\langle r_2 \rangle$ at $Re_j = 5568$ with applying the PDF-closure; (d) $\langle r_2 \rangle$ at $Re_j = 5568$ without applying the PDF-closure.
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Figure 4.12: Effect of flow rate ratio on the variance $\sigma_s^2$ of a passive tracer in the Roughton mixer at $Re_j = 335$. (a) flow rate ratio 1:1; (b) flow rate ratio 1:2; (c) flow rate ratio 1:5.

The effect of the flow rate ratio on the mixing zone, which is represented by the distribution of the concentration variance, is displayed in Figure 4.12 for a Reynolds number of 335. It can be observed that with decreasing flow rate ratio, i.e. 1:1 (Figure 4.12.a), 1:2 (Figure 4.12.b), 1:5 (Figure 4.12.c) the mixing zone becomes smaller. For a 1:1 ratio the distribution of $\sigma_s^2$ is symmetrical while with decreasing flow rate ratio the region of the largest concentration variance is shifted to the inlet zone of the slower inlet stream on the upper left-hand side of the mixer.

Concentration $\langle f \rangle$ and variance $\sigma_s^2$ are shown for the Y-mixer in Figure 4.13. Mixing in the collision plane is relatively good, yet macro mixing is much slower compared to the Roughton mixer because of limited radial exchange of fluid elements. Furthermore, the point were $\langle f \rangle$ reaches 0.5 across the whole mixer cross section moves towards the outlet with increasing Reynolds number as shown in Figure 4.13.a and Figure 4.13.c. Thus, the mixing zone changes with Reynolds number. On the contrary, meso- and micro-mixing improves with increasing Reynolds number as can be seen from the distribution of $\sigma_s^2$ in Figure 4.13.b and Figure 4.13.d.
A contour plot of the reaction rate in the Y-mixer is shown in Figure 4.14.a for the model with PDF closure, a Reynolds number of 557 and a reaction time constant of 4.9 ms. The reaction takes place in the whole cross-section of the outlet pipe and is completed at about 35 times the pipe diameter (not shown in the figure). Figure 4.14.b shows the result for the same operating conditions but without applying the closure. It can be seen that the reaction in this case takes place only in the left-hand side of the mixer where $\langle c_A \rangle > \langle c_B \rangle$, i.e. where the solution is acidic. Compared to Figure 4.14.a the maximum reaction rate is much higher. However, the reaction zone is smaller, thus the conversion of DMP decreases as already shown in Figure 4.9. At higher Reynolds numbers the reaction takes place more in the left-hand side of the mixer, also if the PDF closure is applied as shown in Figure 4.14.c. This segregation is due to the fact that at higher flow rates there is more macroscopic segregation of the fluids as already shown in Figure 4.13.c. Furthermore, the distribution of the reaction
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rate in Figure 4.14.c is similar to the simulation results without closure given in Figure 4.14.d. Therefore, it can be concluded that at high Reynolds numbers the reaction rate is less affected by meso- and micro-mixing, i.e. it resembles more the “ideal mixing” in the model without closure.

Figure 4.14: Reaction rate $\langle r_2 \rangle$ in the Y-mixer. (a) $\langle r_2 \rangle$ at $Re_j = 557$ with applying the PDF-closure; (b) $\langle r_2 \rangle$ at $Re_j = 557$ without applying the PDF-closure; (c) $\langle r_2 \rangle$ at $Re_j = 5568$ with applying the PDF-closure; (d) $\langle r_2 \rangle$ at $Re_j = 5568$ without applying the PDF-closure.

4.4.4 Mixing times

The mixing times in this work are calculated based on the residence time in the zone of incomplete mixing. We have used the pathlines of a number of evenly distributed fluid elements entering the mixer in order to calculate the average mixing time according to the following equation:

$$t_{m,i} = \frac{1}{N_p} \sum_{k=1}^{N_p} (t_k^{max} - t_k^{min}) \quad i = 1, 2, 3$$

(4.46)
\[ t_{ms} = \frac{1}{N_p} \sum_{k=1}^{N_p} \left( t_k^{\text{max}} - t_k^{\text{min}} \right), \quad (4.47) \]

where \( N_p \) is the number of pathlines, namely 252 in the Roughton and 194 in the Y-mixer, \( t_k^{\text{max}} \) is the time needed along the pathline \( k \) to reduce the concentration variance (\( \sigma_i^2 \) or \( \sigma_s^2 \)) below a threshold of 0.001, and \( t_k^{\text{min}} \) is the time along the pathline \( k \) till the concentration variance is the first time above 0.001. It must be noted that at the inlets of the mixer the fluids are completely segregated and the concentration variance is zero. Thus, the difference between \( t_k^{\text{max}} \) and \( t_k^{\text{min}} \) represents the time between the first contact of the two different fluids and the time when they are completely mixed. Eq. (4.46) defines the mixing times corresponding to the different mixing mechanisms, i.e. inertial convective (\( \sigma_i^2 \)), viscous-convective (\( \sigma_s^2 \)) and viscous-diffusive (\( \sigma_s^2 \)), and Eq. (4.47) gives the mixing time with respect to the total concentration variance \( \sigma_s^2 \). The pathlines depend on the macroscopic flow pattern in the mixer which is determined by geometry, velocity, and viscosity. Thus, the action of macro-mixing enters into the calculation of mixing times by using pathlines. Plots of the pathlines colored by the residence time at a jet Reynolds number of 2227 are shown for the Roughton and the Y-mixer in Figure 4.15.

The typical course of the concentration variance \( \sigma_s^2 \) along a path through the Roughton and the Y-mixer is plotted in Figure 4.16.a for a jet Reynolds number of 2227. It can be seen that in the Roughton mixer the concentration variance is zero at the inlet, then it increases when the fluid element on the pathline has its first contact with the other stream, and finally it decays towards zero at about 1 ms. The course of the concentration variance in the Y-mixer is similar up to 1 ms but then it takes much longer, about 5 ms in the case shown here, for the value of \( \sigma_s^2 \) to go down to zero. The reason for the different behavior is that in the Roughton mixer the two streams are almost completely mixed after the mixing chamber due to highly swirling flow, while in the Y-mixer the mixing is good only in the collision plane and the radial exchange of fluid elements is rather poor. Though average mixing times are much longer in the Y-mixer the distribution of mixing times resulting from different paths is much narrower compared to the Roughton mixer.
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Figure 4.15: Pathlines colored by the residence time for $Re_j = 2227$. (a) Roughton mixer; (b) Y-mixer.

The standard deviation of the concentration fluctuations, $\sigma_T^2$, from the final totally mixed concentration, $\bar{f}$, has to be considered as well to quantify mixing. The standard deviation $\sigma_T^2$ is defined by the following equation:

$$\sigma_T^2 = \langle (f - \bar{f})^2 \rangle = \sigma_s^2 + \langle (f - \bar{f}) \rangle^2 .$$

(4.48)

In Figure 4.16.b the values of $\langle (f - \bar{f}) \rangle^2$ are plotted for the same paths as for the Roughton and the Y-mixer in Figure 16.a, respectively. It can be seen that the values of $\langle (f - \bar{f}) \rangle^2$ start at 0.25 and decay to zero. While $\sigma_s^2$ represents mixing on micro- and meso-scale, in turn the term $\langle (f - \bar{f}) \rangle^2$ characterizes the macroscopic mixing. The comparison of Figure 4.16.a and Figure 4.16.b as well as the results shown in Figure 4.10 and Figure 4.13 reveal that $\langle (f - \bar{f}) \rangle^2$ and $\langle f \rangle$ decrease much faster to zero across the mixer than $\sigma_s^2$. Thus, it is sufficient to calculate the mixing times only based on the course of $\sigma_T^2$. 
Figure 4.16: Typical pathlines of concentration variance $\sigma_x^2$ (a) and the variance of $\langle f \rangle$ around the final totally mixed concentration $\bar{f}$ (b) in the Roughton and the Y-mixer for $Re_j = 2227$. 
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Figure 4.17: Mixing times based on the mean residence time in the zones of inertial convective \( t_{m1} \), dotted line), viscous-convective \( t_{m2} \), solid line) and viscous-diffusive mixing \( t_{m3} \), dashed line) in the Roughton and the Y-mixer.

The mixing times corresponding to the distribution of \( \sigma_1^2 \), \( \sigma_2^2 \) and \( \sigma_3^2 \), labeled \( t_{m1} \), \( t_{m2} \) and \( t_{m3} \), respectively, are shown in Figure 4.17 for the Roughton and the Y-mixer. It can be seen that for all Reynolds numbers the mixing times are smaller in the Roughton mixer. For both mixing devices \( t_{m2} \) is the largest for all Reynolds numbers. In the Roughton mixer, \( t_{m1} \) is first lower than \( t_{m2} \) and \( t_{m3} \), but at a Reynolds numbers higher than 1200 it is in between \( t_{m2} \) and \( t_{m3} \). In the Y-mixer, the behavior is similar; however the change is at a higher Reynolds number of 2500. In general, all mixing times follow the same trend, i.e. they decrease with increasing Reynolds number and the differences between the different mixing times become smaller.

The average mixing times, based on Eq. (4.47), are plotted in Figure 4.18 as a function of pressure drop to allow for a direct comparison of the two mixers in terms of mixing efficiency. The mixing times in the Y-mixer are always larger, going from 25 ms at \( \Delta p = 0.1 \) bar to 1.3 ms at \( \Delta p = 16 \) bar. The Roughton mixer with a flow rate ratio of 1:1 gives mixing times which range from 20 ms at \( \Delta p = 0.1 \) bar to 0.4 ms at \( \Delta p = 16 \) bar. For pressure drops larger than 3 bar the mixing time in the Roughton mixer is about 3 times smaller than in the Y-
mixer. For lower flow rate ratios, i.e. 1:2 and 1:5, the mixing times are almost identical with the values for the 1:1 ratio and for the sake of clear presentation the mixing times for flow rate ratios 1:2 and 1:5 are not displayed. A plot of the mixing time as a function of Reynolds number shows that in the Roughton mixer the mixing time scales approximately as $Re_j^{-1.5}$ for $Re_j < 1000$ and as $Re_j^{-1}$ for $Re_j > 6000$, while in the Y-mixer the mixing time scales approximately as $Re_j^{-1}$ for $Re_j > 2000$.

![Graph showing mixing time vs. pressure drop](image)

Figure 4.18: Average mixing times $t_{ms}$ based on the mean residence time in the mixing zone for Y-mixer and for Roughton mixer with a flow ratio of 1:1 as a function of the pressure drop.

### 4.4.5 Pressure drop

The pressure drops across the mixers were measured in the experiments for the Roughton and the Y-mixer and are presented in Figure 19 as symbols. It must be noted that the pressure drops in the pipe between the pressure sensor and the mixer have been measured separately and have been subtracted from the overall pressure drop, i.e. pressure drop in the pipe plus pressure drop in the mixer, to obtain the pressure drop across the mixer as given in Figure 4.19.
Figure 4.19: Experimental (symbols) and simulated pressure drops (lines) across the Roughton and the Y-mixer.

The pressure drop in the Roughton mixer is approximately four times larger than in the Y-mixer. The larger pressure drop is a result of the higher energy dissipation in the Roughton mixer which also results in higher mean velocity convection, turbulent diffusion and viscous-convective deformation and hence improved mixing as discussed in the previous section. Thus, mixing in different mixers should be compared with respect to pressure drop too, particularly if the attainable flow rate is limited by the maximum allowable pressure drop, as in most industrial setups where rotary or gear pumps are used. The simulated pressure drops from the CFD model are shown in Figure 19 as lines. The agreement between model and experiment is good, yet at high Reynolds numbers the pressure drop is slightly underestimated by the model, whereas the differences are larger for the Y-mixer. It must be noted that only pressure drops for a 1:1 flow rate ratio are shown and that the pressure drop slightly increases with decreasing flow rate ratio. However, for the sake of a clear presentation the pressure drops for the 1:2 and the 1:5 flow rate ratios are not displayed in Figure 19.
4.5 Additional studies*

4.5.1 Effect of viscosity

In antisolvent precipitation processes, the two streams to be mixed typically have different viscosities. The effect of viscosity ratio on the mixing efficiency was investigated for the confined impinging jet (CIJ) mixer (Wang et al., 2006). It was found that for viscosity ratios larger than 3 rapid mixing is not possible in the CIJ mixer. Moreover, the effective use of the CIJ mixer is limited by the requirement that the momentums of the solute and the antisolvent stream must be equal (Liu et al., 2008).

In this section, the effect of different viscosity ratios on the mixing efficiency of a Roughton and a Y-mixer is characterized using competitive-parallel chemical reactions and CFD.

4.5.1.1 Experimental procedure

The composition of the solution is consistent with the solutions given in section 4.2.3. The only difference is that part of the water is replaced by hydroxypropyl methylcellulose (HPMC), a polymer often used as emulsifier and thickening agent. HPMC is added only to the basic solution since it was reported that HPMC degrades at acidic conditions in a relatively short period of time (ShinEtsu, 1998).

The viscosity of the ethanol–water–DMP solution was measured at 25 °C using a Haake Viscotester VT 550 (Offenbach, Germany). The measured viscosity of the basic DMP solution is given in Figure 4.20. In all experiments, the solution contained 200 mmol/kg DMP, 210 mmol/kg NaOH, 90 mmol/kg NaCl and a solvent consisting of 25 wt% ethanol and deionized water. The average measurement error was 0.078 mPas. The stability of the solution regarding the viscosity was checked by remeasuring the viscosity after a certain period of time. It was found that the solutions were stable for at least one month. The viscosity as a function of the HPMC concentration can be described using the following polynomial:

\[
\eta = 3.704w_{\text{HPMC}}^3 + 4.331w_{\text{HPMC}}^2 + 4.068w_{\text{HPMC}} + 2.469, \quad (4.49)
\]

4.5 Additional studies

Figure 4.20: Measured viscosity of the ethanol-water-DMP solution as a function of the HPMC concentration at 25 °C.

where \( \eta \) is given in mPas and \( w_{\text{HPMC}} \) in wt\%.

The gas chromatograph used for sample analysis in the mixing experiments was calibrated using calibration standards, and the calibration curve coincides with the one given by Eq. (4.8).

In the mixing experiments, the initial solutions have a concentration of 200 mmol/kg, which corresponds to a reaction time constant of \( t_r = 14.9 \) ms, and are prepared according to section 4.2.3. HPMC is added to the DMP solution to increase the viscosity. The addition of 1 and 1.5 wt\% HPMC yield solutions with a viscosity ratio between the DMP and the HCl solution of:

\[
\frac{\eta_{\text{DMP,1}} (1 \text{ wt\% HPMC})}{\eta_{\text{HCl,2}}} = \frac{14.7 \text{ mPas}}{2.49 \text{ mPas}} \approx 6
\] (4.50)

and

\[
\frac{\eta_{\text{DMP,1}} (1.5 \text{ wt\% HPMC})}{\eta_{\text{HCl,2}}} = \frac{30.7 \text{ mPas}}{2.49 \text{ mPas}} \approx 12,
\] (4.51)

respectively. The viscosity of the HCl solution was calculated using Eq. (4.5). It is assumed that density, diffusivity and reaction rates are not affected by the
presence of a low-weight polymer at low concentrations (Johnson and Prud'homme, 2003a).

4.5.1.2 Experimental results

The yield of the DMP reaction $X$ was determined experimentally for the two different mixers and for different flow rates and viscosity ratios. The results for the Roughton mixer are presented in Figure 4.21, where the experimental values of $X$ are plotted as a function of the mass flow rate of the inlet streams. The values of $X$ decrease with increasing flow rate, as expected, and for the same flow rate they are lower for lower viscosity ratios.

![Figure 4.21: Comparison of experimental and simulated DMP conversion $X$ in the Roughton mixer for different viscosity ratios. Symbols: experimental data; lines: CFD simulations.](image)

The experimental yields $X$ for the Y-mixer are given in Figure 4.22. Also in this case, the values of $X$ decrease with decreasing viscosity ratio. Compared to the Roughton mixer and for the same flow rate, the values of $X$ are larger in the Y-mixer.
4.5.1.3 Simulation results

The simulations are carried out using the CFD model presented in section 4.3. The only difference with the simulations presented above is that now Eq. (4.49) is implemented to describe the dependence of the viscosity on the local average HPMC concentration \( \langle w_{\text{HPMC}} \rangle \), which is given by

\[
\langle w_{\text{HPMC}} \rangle = w_{\text{HPMC},0} \left( 1 - \langle f \rangle \right)
\]  

(4.52)

with \( \langle f \rangle \) being the average normalized tracer concentration and \( w_{\text{HPMC},0} \) being the inlet HPMC concentration. In Fluent, the flow field cannot be considered being independent of the local HPMC concentration. Thus, first, the flow field is solved together with Eq. (4.11) for the tracer concentration and employing Eqs. (4.49) and (4.52). Then, the scalar transport equations for the concentration variances (Eqs. (4.13), (4.41) and (4.42)) are solved.

Figure 4.22: Comparison of experimental and simulated DMP conversion \( X \) in the Y-mixer for different viscosity ratios. Symbols: experimental data; lines: CFD simulations.

In Figure 4.21 experimental and simulated values of the DMP conversion \( X \) are compared for the Roughton mixer and different viscosity ratios. The simulation
results are in good agreement with the experimental data. It must be noted that CFD simulations for flow rates below 60 g/min were not carried out due to the extremely long downstream length that would be required to model complete mixing. All simulations were obtained by applying the PDF closure as presented in section 4.3.3.

The simulated values of $X$ for a viscosity ratio of 1, which were discussed already in section 4.4, are plotted in Figure 4.21 too. It can be observed that with increasing flow rate the values of $X$ approach one another, i.e. the influence of viscosity on mixing performance is decreasing with increasing flow rate, i.e. increasing turbulence.

The agreement between experiments and simulations is good also for the Y-mixer as shown in Figure 4.22. It can be observed that the lines for the different viscosity ratios cross each other. Unlike in the Roughton mixer, at large flow rates the yield is higher for low viscosity ratios, i.e. mixing improves as the viscosity ratio increases.

A contour plot of the dynamic viscosity in the Roughton mixer is shown in Figure 4.23 for a flow rate of 60 g/min. For all viscosity ratios the viscosity approaches a constant value at the outlet of the mixing chamber. The final viscosity increases with increasing viscosity ratio.

The distribution of the concentration variance of a passive tracer $s^2$ in the Roughton mixer is shown in Figure 4.24 for different viscosity ratios and a flow rate of 60 g/min. It can be observed that the mixing zone, i.e. the zone with a concentration variance larger than 0.001 which is considered here as a threshold for complete mixedness, becomes larger with increasing viscosity ratio. A contour plot of the reaction rate $\langle r_2 \rangle$ when applying the PDF closure is shown in Figure 4.25 for different viscosity ratios and a flow rate of 60 g/min. It can be observed that at a viscosity ratio of 1 the reaction takes place almost entirely in the mixing chamber. With increasing viscosity ratio the reaction zone increases and moves downstream. This behavior is a consequence of the poor mixing and results in a larger yield of the DMP reaction as presented in Figure 4.21.

The average mixing times $t_{ms}$ are calculated based on the residence time in the zone of incomplete mixing as described in section 4.4.4 and are plotted as a function of the flow rate in Figure 4.26 for the Roughton and the Y-mixer. As expected, the average mixing time decreases with increasing flow rate. At fixed
4.5 Additional studies

flow rate the mixing time increases with increasing viscosity ratio. As a matter of fact this difference is less pronounced at large flow rates.

Figure 4.23: Contour plot of the dynamic viscosity in the Roughton mixer for different viscosity ratios. The flow rate of the two inlet streams is 60 g/min in all three cases.

Mixing times in the Y-mixer are always larger than in the Roughton mixer if the values are compared at the same flow rate. It should be mentioned that this difference becomes smaller if the mixing times are compared for the same pressure drop as discussed in section 4.4.4.

An interesting characteristic of the Y-mixer is that at large flow rates mixing is improved for larger viscosity ratios despite the larger average viscosity in this case. The reason for this behavior can be explained with the help of Figure 4.27 where the distribution of the concentration variance $\sigma_s^2$ is plotted for different viscosity ratios and for a relatively large flow rate of 600 g/min. The maximum value of $\sigma_s^2$ increases with increasing viscosity ratio. However, the size of the mixing zone decreases with increasing viscosity ratio and therefore mixing times decrease as well. This is caused by the symmetry breaking at large viscosity ratios and the corresponding improved radial exchange of fluid elements.
4. Mixing characterization

Figure 4.24: Distribution of the concentration variance $\sigma_x^2$ of a passive tracer in the Roughton mixer for different viscosity ratios. The flow rate of the two inlet streams is 60 g/min in all three cases.

Figure 4.25: Distribution of the reaction rate $\langle r_2 \rangle$ in the Roughton mixer for different viscosity ratios. The flow rate of the two inlet streams is 60 g/min in all three cases.
4.5 Additional studies

Figure 4.26: Average mixing time $t_{\text{ms}}$ based on the mean residence time in the mixing zone for different viscosity ratios.

Figure 4.27: Distribution of the concentration variance $\sigma_s^2$ of a passive tracer in the Y-mixer for different viscosity ratios. The flow rate of the two inlet streams is 600 g/min in all three cases.
4.5.2 Effect of large flow rate ratios

In this section, the effect of large flow rate ratios on the mixing efficiency is studied using the CFD model presented in sections 4.3 and 4.5.1.3. The goal of this industry-relevant study is to clarify if for a specific antisolvent precipitation fast mixing can be achieved. In this case it is desirable that mixing is fast enough to allow for decoupling mixing and precipitation as discussed in section 5.1. Methanol ($\eta = 0.6$ mPas, $\rho = 0.8$ g/L) is mixed with an aqueous solution containing the solute ($\eta = 12$ mPas, $\rho = 1.36$ g/L) in the Roughton mixer. Mixing is studied at various flow rates (60-600 g/min) and flow rate ratios (1:1 to 50:1). It is assumed that local viscosities and densities can be described by a linear interpolation of the values for the pure solutions.

The average mixing times $t_{ms}$ are calculated based on the residence time in the zone of incomplete mixing as described in section 4.4.4, and are plotted as a function of the pressure drop for a flow rate ratio of 1 in Figure 4.28. It can be observed that for the same pressure drop the mixing time is longer for the methanol-solute mixture with a viscosity ratio of 20 as compared to the water-ethanol mixtures with a viscosity ratio of 1 (simulation data from section 4.4.4).

The main reason for this behavior is the higher viscosity of the methanol-solute mixture as compared to the water-ethanol mixture. The effect of flow rate ratio is shown in Figure 4.29 as a function of pressure drop. It must be noted that the largest pressure drop is reported, i.e. the pressure drop between the inlet with the higher velocity and the outlet. The mixing time decreases with increasing flow rate ratio in the range of flow rate ratios from 1:1 to 10:1, and increases again for larger flow rate ratios. At low pressure drops the mixing times for flow rate ratios larger than 1 are always lower than the one for a flow rate ratio of 1. However, at high pressure drops all mixing times for flow rate ratios larger than 20:1 are longer than the one for a flow rate ratio of 1. The reason for this behavior is that the average viscosity decreases with increasing flow rate ratio (main effect at low pressure drops), and that the flow profile changes with varying the flow rate ratio (main effect at high pressure drops).
Figure 4.28: Average mixing time $t_m$ in the Roughton mixer for different viscosity ratios of the inlet streams and a flow rate ratio of 1.

Figure 4.29: Average mixing time $t_m$ in the Roughton mixer for different flow rate ratios.
The distribution of the tracer concentration $\langle f \rangle$ is shown in Figure 4.30 for a flow rate of the larger stream of 120 g/min and flow rate ratios of 1:1, 10:1 and 50:1, which corresponds to a pressure drop of 3.8, 2.7 and 3.3, respectively. It can be observed that for a flow rate ratio of 10:1 the mixing zone is decreasing as compared to the 1:1 case. In fact, mixing takes place mainly in the vicinity of the inlet of the low flow rate stream into the mixing chamber. However, for larger flow rate ratios, e.g. 50:1, the mixing zone is pushed into the inlet pipe; the stream is retained and mixing efficiency decreases.

Figure 4.30: Distribution of the tracer concentration $\langle f \rangle$ in the Roughton mixer for different flow rate ratios. The flow rate of the larger stream is 120 g/min in all three cases.

4.5.3 Scale-up

Scale-up of the Roughton mixer requires the knowledge of a correlation between mixing time, characteristic size of the mixer, e.g. the jet diameter, and flow rate. We have looked at a scale-up with respect to the jet diameter by factor 5 and 10 corresponding to an inner diameter of the inlet tube of 2.5 and 5 mm, respectively.

In industry, for example on a pilot or production scale, the required flow rate might be in the range from 300 to 1300 kg/h. Standard high-pressure centrifugal pumps can deliver about 2 m$^3$/h at a pressure of 20 bar. Scale-up by a factor of 10, i.e. changing the jet diameter from 0.5 to 5 mm, yields for an inlet velocity of 5 m/s a flow rate of 350 kg/h and for 20 m/s a flow rate of 1400 kg/h, assuming water is pumped. Besides knowing the mixing time also the corresponding pressure drop should be determined to meet the pump specifications.
The model presented in section 4.3 was also used in the scale-up study. The distribution of the velocity and the tracer concentration are shown for the original mixer and for a scale-up by factor 5 and 10, respectively, in Figure 4.31. The inlet velocity is constant at 10.5 m/s in the three cases. It can be observed that the velocity in the mixing chamber increases with increasing scale-up factor. Mixing does not seem to be affected by the scale-up, as can be concluded from the distribution of the tracer concentration which is relatively similar in all three cases.

The average mixing times as a function of the pressure drop across the mixer are plotted in Figure 4.32. The average mixing time is calculated as described in section 4.4.4. It can be observed that at fixed pressure drop the mixing time is increased approximately by the scale-up factor.

The pressure drops as a function of the jet Reynolds number are shown in Figure 4.33. The pressure drop depends quadratically on the velocity and has also a strong dependence on the jet diameter. It can be noted that for the desired flow rate range, i.e. 300 to 1300 kg/h, the pressure drops are below 20 bar and standard pumps can be employed.

Figure 4.31: Distribution of the velocity and the concentration of a passive tracer in the Roughton mixer for different sizes of the mixer (view from top). The average inlet velocity is 10.5 m/s in all three cases. The figure is not in scale.
4. Mixing characterization

Figure 4.32: Average mixing time $t_m$ based on the mean residence time in the mixing zone for different scale-up factors of the Roughton mixer.

Figure 4.33: Pressure drop across the Roughton mixer for different scale-up factors.
4.5.4 Mixing time correlation

Characteristic time scales for micro-mixing, such as engulfment or vortex lifetime, are often assumed to be proportional to the Kolmogorov time microscale \( \tau_K \) (Baldyga and Bourne, 1999; Johnson and Prud'homme, 2003a):

\[
\tau_K = \left( \frac{v}{\varepsilon} \right)^{0.5}.
\]  

(4.53)

Assuming that \( \varepsilon \propto u_j^{3}/d_j \) and that the absolute mixing time \( t_{ms} \) is proportional to the Kolmogorov time scale the following equation can be derived (Gillian and Kirwan, 2008; Johnson and Prud'homme, 2003a):

\[
t_{ms} = K \frac{d_j^{0.5} v^{0.5}}{u_j^{1.5}}
\]  

(4.54)

with \( K \) being a proportionality constant. The value of \( K \) can be determined by linear regression of the mixing times from the CFD simulations (section 4.4.4) when plotting them as a function of \( d_j^{0.5} v^{0.5}/u_j^{1.5} \), as shown in Figure 4.34. We have estimated \( K = 1.1 \times 10^3 \) for the Roughton mixer with a regression coefficient \( R^2 \) of 0.93 and \( K = 4.9 \times 10^3 \) for Y-mixer with a regression coefficient \( R^2 \) of 0.95. Thus, for the same value of \( d_j^{0.5} v^{0.5}/u_j^{1.5} \), mixing times being about 5 times shorter can be achieved in the Roughton mixer as compared to the Y-mixer.

The mixing times for the mixing of streams with different viscosities (section 4.5.1), for the mixing at different flow rate ratios (section 4.5.2) and for the upscaled mixers (section 4.5.3) are also plotted in Figure 4.34 and can be well approximated by Eq. (4.54). In these cases the values of the viscosity after complete mixing was used in Eq. (4.54).

Moreover, for flow rate ratios different from 1 an average velocity corresponding to a system with the same kinetic energy input but a flow rate ratio of 1 was used in Eq. (4.54):

\[
u_j = \left( \frac{u_1^3 + u_2^3}{2} \right)^{1/3},
\]  

(4.55)

The kinetic energy input into the system \( P \) is given by
\[ P = 0.5 \rho_1 A_1 u_1^3 + 0.5 \rho_2 A_2 u_2^3 \]  

(4.56)

with \( A \) being the cross-sectional area of the inlet tube (Johnson and Prud'homme, 2003a). The average velocity given by Eq. (4.55) can be calculated on the basis of Eq. (4.56) and assuming that \( \rho_1 = \rho_2 \) and \( A_1 = A_2 \).

The mixing times for a flow rate ratio of 30:1 and 50:1 are given as x-symbols in Figure 4.34 as well. It can be observed that under these conditions and at large flow rates, i.e. low values of \( d_{j}^{0.5} v_{j}^{0.5} / u_{j}^{1.5} \), there is a larger deviation from the straight line described by Eq. (4.54), and that the deviation increases with increasing flow rate ratio. This behavior might be explained by the completely changed flow field under these conditions (see Figure 4.30) and the corresponding increase of the mixing times.

Figure 4.34: Correlation between simulated mixing time (symbols) and mixing time given by Eq. (4.54) obtained by linear regression (lines).

4.6 Conclusions

Competitive-parallel chemical reactions were used to experimentally characterize mixing in static mixers. It has been shown that for a wide range of operating conditions the proposed Roughton mixer exhibits superior mixing behavior, expressed by a low DMP conversion, as compared to the Y-mixer also tested.
here and to the confined impinging jet mixer studied by others (Johnson and Prud'homme, 2003a).
The experimental data were compared with the results of CFD simulations and a remarkably good agreement was observed. It is noticeable that the CFD model is fully predictive, i.e. no additional parameters had to be fitted to match the experimental data. This indicates that the model presented here is very valuable for design and scale-up of mixers.

The influence of small-scale mixing on DMP conversion and reaction rate has been studied as well. The information about the local mixture structure was used to account for the effect of the concentration fluctuations on the reaction rate, i.e. to close the reaction rate term properly. It was shown that the influence of small-scale mixing on the reaction rate was more significant at low Reynolds numbers and that it was less pronounced at high Reynolds numbers. However, it can be concluded that a fully predictive model has to include a model for small-scale mixing.

The CFD model was used to obtain additional insight into the process, since the local concentrations, concentration variances and reaction rates were accessible. It was found that macro-mixing is very good in the Roughton mixer and that at higher Reynolds numbers the reaction zone stays within the mixing chamber. On the contrary, in the Y-mixer macro-mixing is relatively bad and the reaction zone is less well defined. It was found that mixing of fluids with different viscosities slightly decreases mixing efficiency in the Roughton mixer. In the Y-mixer, a larger viscosity ratio led to an increased mixing performance at large flow rates due to a symmetry breaking. It was shown that the mixing efficiency is affected by the flow rate ratio in the Roughton mixer for large flow rate ratios. Finally, it was found that the average mixing time can be well described for a wide range of flow rates, flow rate ratios, viscosities and jet diameters by

\[ t_{ms} = K d_{j}^{0.5} \nu^{0.5} / u_{j}^{1.5} \]

with \( K = 1.1 \times 10^3 \) for the Roughton and \( K = 4.9 \times 10^3 \) for the Y-mixer.
4.7 Nomenclature chapter 4

**Roman letters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>cross-sectional area of the inlet tube [m$^2$]</td>
</tr>
<tr>
<td>$A_i$</td>
<td>peak area of species $i$ [a.u.]</td>
</tr>
<tr>
<td>$c_i$</td>
<td>concentration of compound $i$ [mmol kg$^{-1}$]</td>
</tr>
<tr>
<td>$C$</td>
<td>normalized concentration of DMP [-]</td>
</tr>
<tr>
<td>$d$</td>
<td>diameter [m]</td>
</tr>
<tr>
<td>$D$</td>
<td>molecular diffusivity [m$^2$ s$^{-1}$]</td>
</tr>
<tr>
<td>$D_T$</td>
<td>turbulent diffusivity [m$^2$ s$^{-1}$]</td>
</tr>
<tr>
<td>$f'$</td>
<td>normalized tracer concentration [-]</td>
</tr>
<tr>
<td>$k$</td>
<td>turbulent kinetic energy [m$^2$ s$^{-2}$]</td>
</tr>
<tr>
<td>$k_i$</td>
<td>rate constant of reaction $i$ [m$^3$ mol$^{-1}$ s$^{-1}$]</td>
</tr>
<tr>
<td>$K$</td>
<td>proportionality constant [-]</td>
</tr>
<tr>
<td>$N_i$</td>
<td>molar flow rate of species $i$ [mol s$^{-1}$]</td>
</tr>
<tr>
<td>$P$</td>
<td>power input [W]</td>
</tr>
<tr>
<td>$r_i$</td>
<td>rate of reaction $i$ [mol m$^{-3}$ s$^{-1}$]</td>
</tr>
<tr>
<td>$R$</td>
<td>time scale ratio [-]</td>
</tr>
<tr>
<td>$Re_l$</td>
<td>local turbulent Reynolds number [-]</td>
</tr>
<tr>
<td>$Re_j$</td>
<td>jet Reynolds number [-]</td>
</tr>
<tr>
<td>$R_{Di}$</td>
<td>dissipation rate of variance component $i$ [s$^{-1}$]</td>
</tr>
<tr>
<td>$R_{Pi}$</td>
<td>production rate of variance component $i$ [s$^{-1}$]</td>
</tr>
<tr>
<td>$Sc$</td>
<td>Schmidt number $Sc = \nu / D$ [-]</td>
</tr>
<tr>
<td>$t$</td>
<td>time [s]</td>
</tr>
<tr>
<td>$t_m$</td>
<td>mixing time [s]</td>
</tr>
<tr>
<td>$t_r$</td>
<td>reaction time constant [s]</td>
</tr>
<tr>
<td>$T$</td>
<td>temperature [K]</td>
</tr>
<tr>
<td>$u$</td>
<td>velocity [m s$^{-1}$]</td>
</tr>
<tr>
<td>$w_i$</td>
<td>concentration of compound $i$ [wt.%]</td>
</tr>
<tr>
<td>$x$</td>
<td>space coordinate [m]</td>
</tr>
<tr>
<td>$X$</td>
<td>fraction of converted DMP [-]</td>
</tr>
<tr>
<td>$Y$</td>
<td>normalized concentration [-]</td>
</tr>
</tbody>
</table>
Greek letters

\(\beta\)  
ratio of initial concentrations \(\beta = \frac{c_{B0}}{c_{A0}}\)

\(\varepsilon\)  
energy dissipation rate [m^2 s^{-3}]

\(\phi\)  
beta-function [-]

\(\eta\)  
dynamic viscosity [mPas]

\(\nu\)  
kinematic viscosity [m^2 s^{-1}]

\(\rho\)  
density [kg m^{-3}]

\(\sigma_s^2, \sigma_i^2\)  
dimensionless concentration variances [-]
5 L-asparagine antisolvent precipitation*

In this chapter, an experimental setup based on a static micro-mixer is used to determine nucleation and growth kinetics of L-asparagine monohydrate precipitated via antisolvent addition. Mixing in static micro-mixers was characterized in chapter 4 using competitive-parallel reactions and computational fluid dynamics (CFD). The mixer setup is used in this chapter to determine nucleation and growth kinetics of L-asparagine at high supersaturations, i.e. true kinetics which are not affected by transport limitations. The method is based on measuring the particle size distribution obtained at different residence times. A population balance equation (PBE) model of the process is used for the design of a continuous precipitation process. An analysis of the characteristic time scales of nucleation, growth and mixing shows that, under the conditions in this study, mixing is much faster than precipitation and that the two processes can be decoupled.

A different approach for the production of small micron-sized particles is the application of specific additives to inhibit crystal growth and to stabilize particles by reducing agglomeration. The effect of additives on the precipitation is presented in the second part of this chapter.

5.1 Precipitation kinetics

5.1.1 Introduction

The attainment of fast mixing is a requirement to avoid transport limitations in processes with fast kinetics such as precipitation at high supersaturations. Precipitation is often conducted under these conditions to produce small particles with a narrow particle size distribution (PSD). Stahl and Rasmuson have developed a model combining meso- and micro-mixing with the population balance equation (PBE) to describe single-feed semi-batch reactive crystallization of

* Portions of this chapter appear in Lindenberg et al., AIChE Journal 2009.
benzoic acid (Stahl and Rasmuson, 2009). It was shown that feed position, feed pipe diameter, feeding time, feed concentration, stirring rate and reactor volume all had an effect on the final particle size. Similar results were found in several other studies (Baldyga et al., 2005; Baldyga et al., 2007; Vicum and Mazzotti, 2007; Woo et al., 2006), thus suggesting that reactive or antisolvent precipitations should rather be carried out in a different kind of setup, e.g. a static mixer with high mixing performance.

Confined impinging jet (CIJ), T- and Y-mixers are often applied to carry out precipitation processes at high supersaturations (see section 4.1). Peukert and co-workers have investigated the effect of mixing on nano-sized particles precipitated in a T-mixer (Schwarzer et al., 2006). They could clearly observe a decrease in particle size with increasing power input. Their model included direct numerical simulation of the flow, Lagrangian particle tracking and population balance modeling incorporating nucleation, growth and agglomeration kinetics. Braatz and co-workers have simulated the antisolvent precipitation of Lovastatin using a combined CFD-PBE model of a CIJ reactor (Woo et al., 2009) and could reproduce the same trends, i.e. decreasing particle size with increasing Reynolds number, as obtained experimentally by Kirwan and co-workers (Mahajan and Kirwan, 1996). In the last work, it was found that if the characteristic time scale for mixing is much smaller than the induction time, in this case about 3 times smaller, the precipitation process is not affected by the mixing conditions. As compared to T-, Y- or vortex mixers, the use of CIJ reactors is less beneficial in antisolvent precipitation since the momentums of the two streams should be equal (Liu et al., 2008).

CFD in combination with PBE models can be employed to predict the influence of mixing on the particle size distribution and thus they can be used for the design, optimization and scale-up of precipitation processes. The main problem to the routine use of CFD-PBE models is the identification of true kinetics, i.e. kinetics which are not affected by transport limitations. Static mixers have been used previously to determine nucleation and growth kinetics in antisolvent (Mahajan and Kirwan, 1993; Mahajan and Kirwan, 1994) or reactive precipitation processes (Blandin et al., 2001; Stahl et al., 2001). Kirwan and co-workers determined independently nucleation and growth rates of L-asparagine monohydrate using a grid mixer based on the measured PSDs at different residence times (Mahajan and Kirwan, 1993). Other studies use the measured PSDs at the
5.1 Precipitation kinetics

outlet of the mixer together with a population balance model and a nonlinear optimization algorithm to estimate simultaneously the parameters in the nucleation and growth rate expressions (Blandin et al., 2001; Stahl et al., 2001). In this work, different protocols for the determination of nucleation and growth kinetics in static mixers are compared for the antisolvent precipitation of L-asparagine monohydrate. Firstly, the nucleation and growth rates are determined independently by measuring the PSD at different time intervals, whereas the nucleation rate is calculated from the change of the particle concentration over time and the growth rate is determined based on the evolution of the average particle size. Secondly, the nucleation and growth kinetics are estimated simultaneously based on the experimental data by combination with a population balance model and an integral parameter estimation technique. These methods can only be applied if the time scales for mixing are much smaller than those for precipitation. Therefore, thirdly, a time scale analysis is carried out comparing the time scales for nucleation and growth of L-asparagine monohydrate with the mixing time scales determined earlier (chapter 4). Decoupling precipitation and mixing can be achieved by properly choosing the operating conditions, e.g. by increasing the flow rate or decreasing the supersaturation. Regarding the application in industry, this decoupling is beneficial since small changes in the flow rate or scaling of the reactor walls will not have an influence on the particle size in a continuous precipitation process. Moreover, the processes can be designed without using a CFD-PBE model, thus making the process design easier, as shown in section 5.1.3.4.

5.1.2 Experimental section

5.1.2.1 Materials and methods

The solute and the antisolvent stream are mixed in a Y-mixer using a custom-made setup, consisting of two pressure tanks, which allow for pulsation-free flows and high pressure drops. A schematic of the experimental setup and of the Y-mixer is given in Figure 4.1a and Figure 4.2b, respectively. The tanks are pressurized with nitrogen. The flow rate, pressure and temperature can be measured in both streams. The mixing efficiency of the Y-mixer has been characterized previously in chapter 4 using competitive-parallel chemical reactions and CFD.
L-asparagine monohydrate was precipitated at 25 °C from an aqueous solution by mixing it with 2-propanol as antisolvent. L-asparagine monohydrate (>99%, Sigma-Aldrich, Buchs, Switzerland), 2-propanol (>99.8%, Sigma-Aldrich, Buchs, Switzerland), and de ionized water were used in all experiments. The supersaturation was varied by changing the flow rate ratio of the two streams. The initial concentration of L-asparagine monohydrate in the aqueous solute stream was kept constant at 15 g/kg in all experiments. The supersaturation is defined as follows:

\[ S = \frac{c}{c^*(w)}, \]

with \( c \) and \( c^* \) being the concentration and solubility of L-asparagine monohydrate, respectively, and \( w \) being the antisolvent weight fraction. The measured solubility of L-asparagine monohydrate in water–2-propanol solutions is given in section 5.1.2.2. The flow rate ratio was changed from 1:1 to 1:20 (aqueous solute solution:antisolvent) yielding initial supersaturation from about 4 to 170. The pressure drop across the mixer was kept constant at 10 bar in all experiments, which corresponds to a mixing time of about 2 ms (chapter 4).

L-asparagine can precipitate as monohydrate or anhydrite. Both forms can be distinguished through their Raman spectra which exhibit distinct differences. In all experiments, only the monohydrate of L-asparagine was precipitated. The Raman spectra were measured using a RA 400 Raman spectrometer from Mettler-Toledo (Greifensee, Switzerland).

Particle size distributions were measured using a Multisizer 3 from Beckman Coulter (Nyon, Switzerland).

### 5.1.2.2 Solubility measurement

The solubility of L-asparagine monohydrate in aqueous solution at 25 °C was measured in the range of 50 to 90 wt% 2-propanol by HPLC analysis of saturated solutions. A HPLC system from Waters (Waters GmbH, Eschborn, Germany) with a 125 mm GROM-SIL 100 ODS-2 column (Alltech Grom GmbH, Rottenburg-Hailfingen, Germany), a variable wavelength UV detector and an aqueous mobile phase containing 0.1 wt% NaH₂PO₄ as a buffer were employed in all experiments. For each solvent composition at least 3 equilibrated samples were prepared. Each sample was injected 3 times into the HPLC system. The
measured solubility and the corresponding standard deviation are given in Table 5.1.

<table>
<thead>
<tr>
<th>( w ) [g/g]</th>
<th>( c^* ) [g/kg solvent]</th>
<th>stdv [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>2.18×10^0</td>
<td>0.65</td>
</tr>
<tr>
<td>0.6</td>
<td>9.77×10^-1</td>
<td>1.5</td>
</tr>
<tr>
<td>0.7</td>
<td>4.28×10^-1</td>
<td>1.7</td>
</tr>
<tr>
<td>0.8</td>
<td>9.43×10^-2</td>
<td>1.5</td>
</tr>
<tr>
<td>0.9</td>
<td>1.51×10^-2</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Table 5.1: Solubility of L-asparagine monohydrate at 25 °C in water-isopropanol solutions.

The measured solubilities are also plotted in Figure 5.1 together with data from literature (Orella and Kirwan, 1991). The differences between the experimental and the literature values are marginal for a 50 wt% solution, but are quite significant at higher 2-propanol concentrations. It can be observed that the experimental data of this study are always below the literature data.

For further analysis the polynomial given by Eq. (5.2) is used to describe the solubility as a function of antisolvent concentration. Note that the polynomial is only valid at 25 °C and in the range from 0 to 90 wt% 2-propanol and should not be extrapolated.

\[
\log_{10}(c^*) = -6.22 w^3 + 5.22 w^2 - 3.30 w + 1.46, \tag{5.2}
\]

where \( c^* \) is given in g L-asparagine monohydrate per kg of solvent and \( w \) is the solute-free weight fraction of 2-propanol.
5.1.3 Measurement of the precipitation kinetics

5.1.3.1 Nucleation kinetics

The nucleation rate is determined by measuring the PSD at different time intervals (Mahajan and Kirwan, 1993). Assuming agglomeration and breakage are negligible, the nucleation rate can be calculated from the change of the number of crystals over time as:

\[ J = \frac{dN}{dt}. \]  

(5.3)

Based on the inspection of many microscope pictures at different supersaturations and residence times, significant agglomeration and breakage could not be observed in the early stages of the precipitation processes, i.e. in the first 20 seconds.

In each experiment, the solution at the outlet of the mixer was quenched after a predefined residence time \( t_{\text{res}} \) using a saturated solution and applying a quench.
ratio $q$ of about 40. The exact quench ratio was determined by weighing the saturated solution before and after quenching. The residence time $t_{\text{res}}$ can be varied using outlet pipes of different lengths. The quenched solution was placed directly into the Coulter Multisizer. The constant volume mode, which measures the number of particles $N$ in a sampling volume $V_s$ (always 2 mL in our measurements), was employed. The nucleation rate can be calculated using the following equation:

$$J = \frac{N}{t_{\text{res}}} \left( \frac{q+1}{V_s} \right).$$

(5.4)

The measured nucleation rates are given in Table 5.2. It must be noted that only particles above a size of 1 μm could be measured and that some error was introduced thereby. Therefore, the nucleation rate was measured at the same supersaturation but different residence times. The comparison of these nucleation rates shows a reasonably good agreement, which is expressed by a relatively low variance $\sigma$, e.g. $\sigma = 16\%$ for $S = 9.1$ (runs 5 to 8), $\sigma = 21\%$ for $S = 18$ (runs 9 to 11), $\sigma = 19\%$ for $S = 52$ (runs 13 and 14), $\sigma = 7\%$ for $S = 81$ (runs 17 and 18), as calculated from the experimental data given in Table 5.2. The error introduced by the cut-off seems to be within the experimental error, i.e. the variance of repeated experiments at identical conditions, which is in the range of 3 to 53% as given in Table 5.2 for $S = 3.7$ (run 1), $S = 18$ (run 10), $S = 81$ (runs 17 and 18). The repeatability is relatively poor, i.e. the average standard deviation of the measured nucleation rate is about 19%, and is in the same order of magnitude as for L-glutamic acid (section 2.3). The relatively poor repeatability might be attributed to different amounts of microscopic dust, which is very difficult to control and might promote heterogeneous nucleation. In each experiment, the actual supersaturation was calculated through an overall mass balance. If the supersaturation did not change by more than 5 % across the mixer these experiments were used for the determination of the kinetics. The other experimental data, i.e. runs 12, 15, 16, 19, 20, 22 and 23, were discarded.
According to the classical nucleation theory, nucleation kinetics can be described using the following expression (Kashchiev and van Rosmalen, 2003):
5.1 Precipitation kinetics

\[ J = k_{J1}S \exp\left(-k_{J2} \frac{\ln^3 \frac{c_c}{c^*}}{\ln^2 S}\right), \quad (5.5) \]

where \( k_{J1} \) and \( k_{J2} \) are empirical parameters, \( c_c \) is given by \( \rho_c/M \) and \( c^* \) is the solubility in mol/m\(^3\). The crystal density of L-asparagine \( \rho_c \) equals 1568 g/L and the molecular mass \( M \) equals 150.14 g/mol.

The experimental nucleation rates divided by the supersaturation are plotted as a function of \( \ln^3(c_c/c^*)/\ln^2 S \) in Figure 5.2. The empirical parameters in Eq. (5.5) can be determined by linear least-squares regression of the experimental data:

\[ k_{J1} = 2.6 \times 10^{10} \text{ [m}^3\text{ s}^{-1}] \quad (5.6) \]
\[ k_{J2} = 2.7 \times 10^{-2} \text{ [-].} \quad (5.7) \]

The regression line has a regression coefficient of \( R^2 = 0.99 \) and is also plotted in Figure 5.2.

![Figure 5.2: Nucleation rate of L-asparagine monohydrate divided by the supersaturation at 25 °C. Circles: experimental data; solid line: regression line.](image-url)
The estimated value $k_{j2}$ can be used to calculate the experimental interfacial energy $\gamma_{\text{exp}}$ as described in section 2.3. The values of $\gamma_{\text{exp}}$ range from 11 to 19 mJ/m² for an antisolvent concentration from 50 to 90 wt%. These values can be compared with theoretical values for homogeneous nucleation (Kashchiev and van Rosmalen, 2003). The theoretical value of the interfacial energy is about 4 times larger than $\gamma_{\text{exp}}$. Moreover the estimated value for $k_{j1}$ is about 22 orders of magnitude lower than predicted theoretical values of the kinetic parameter for homogenous nucleation (Roelands et al., 2006). This analysis indicates a heterogeneous nucleation mechanism for L-asparagine. The same observation has already been made for L-glutamic acid precipitation (chapter 2) and several other organic compounds (Roelands et al., 2006).

5.1.3.2 Growth kinetics

The growth kinetics of L-asparagine monohydrate were determined using the same set of experimental data as for the nucleation kinetics, i.e. runs 1–11, 13, 14, 17 and 18 in Table 5.2. The other runs were discarded since the initial supersaturation decreased by more than 5 % across the mixer. Assuming agglomeration and breakage are negligible, the growth rate $G$ can be calculated from the change of the crystal size over time:

$$G = \frac{dL}{dt} \bigg|_{n=\text{const}}. \quad (5.8)$$

The $i$th moment $\mu_i$ of the PSD is defined as

$$\mu_i = \int_0^\infty L^i n \, dL. \quad (5.9)$$

Assuming agglomeration and breakage can be neglected, the time derivative of the moments can be calculated as

$$\frac{d\mu_0}{dt} = J, \quad (5.10)$$

$$\frac{d\mu_i}{dt} = iG\mu_{i-1} \quad i = 1, 2, \ldots. \quad (5.11)$$

At constant supersaturation Eqs. (5.10) and (5.11) yield the following expressions for the moments of the PSD (Vollmer and Raisch, 2003):
Thus, the change of the average crystal size $d_{10}$, which is defined as the first moment divided by the zeroth moment of the PSD, can be calculated as

$$\frac{d}{dt} \left( \frac{d_{10}}{d_{10}} \right) = \frac{d}{dt} \left( \frac{\mu_i}{\mu_0} \right) = \frac{d}{dt} \left( \frac{Gt}{2} \right) = \frac{G}{2}. \quad (5.14)$$

At each level of supersaturation the PSD was measured at different residence times; a plot of the experimental average crystal size $d_{10}$ over time, similar to the one given in Figure 5.3 for a supersaturation of $S = 9$, was used to calculate the average growth rate of the crystals. According to Eq. (5.14), the growth rate is equal to twice the slope of a straight line fitted through these data points using linear least-squares regression. The experimental growth rate as a function of the supersaturation is shown in Figure 5.4.

Figure 5.3: Average particle size $d_{10}$ as a function of residence time and for different initial supersaturations. Symbols: experimental data; lines: simulation results.
The following empirical expression for the growth kinetics was used to fit the experimental data by applying linear least-squares regression:

\[ G = 3.82 \times 10^{-8} c^* (S - 1)^{1.74}, \]

where \( G \) is given in m/s and \( c^* \) in g/kg. The regression coefficient \( R^2 \) is 0.998. The value of 1.74 for the exponent in Eq. (5.15) is very reasonable as typical values are in the range of 1 to 2 (Mersmann, 2001). The estimated growth rate (Eq. (5.15)) is plotted in Figure 5.4 as well.

![Figure 5.4: Growth rate of L-asparagine monohydrate at 25 °C. Circles: experimental data; solid line: fit of the experimental data described by Eq. (5.15).](image)

### 5.1.3.3 Comparison with literature data

The nucleation and growth kinetics of L-asparagine were measured previously by Kirwan and co-workers (Mahajan and Kirwan, 1994). They used a similar approach for the determination of the kinetics. Induction times, nucleation and growth kinetics were measured at a constant solvent composition of 50 vol\% of 2-propanol and by employing a grid mixer. Since only equal volume flow rates could be realized in their setup the maximum achievable supersaturation was about \( S_0 = 4 \). However, even at these low supersaturations, induction times as
low as 1 second were measured. We could not reproduce these data in our laboratory; our induction times were about two orders of magnitude longer.

At a supersaturation of 4, the nucleation kinetics found in the literature are about 15 times larger than the kinetics measured here. Accordingly, the interfacial energies are also quite different: 6.1 mJ/m² for the literature data as opposed to 10.3 mJ/m² for our kinetics. A comparison of the growth rates shows also significant differences, though the growth rates are in the same order of magnitude. At a supersaturation of 4 the literature value is about 4 times larger than our data.

The differences between our results and the data from the literature cannot be explained convincingly. We assume that both the purity of the substances and the experimental procedure may have an effect on the measured kinetics. In the procedure described in the literature the flow is delivered using syringe pumps. Thus, the maximum experimental time is limited and conditions might not be stationary. Moreover, to achieve residence times longer than 360 ms the sample was held in the aging hose before quenching (Mahajan, 1993). In our experiments, samples were taken at stationary conditions, i.e. after the flow rates had become constant, which was validated by measuring the flow rates of both inlet streams.

### 5.1.3.4 Precipitation experiments

The precipitation of L-asparagine monohydrate in the Y-mixer is modeled assuming plug flow through the mixer and using the population balance framework. The evolution of the PSD as a function of the position in the mixer is then converted to a temporal evolution. Thus, the following PBE model can be applied (Randolph and Larson, 1988):

\[
\frac{\partial n}{\partial t} + G \frac{\partial n}{\partial L} = 0 ,
\]

(5.16)

where \( n \) is the number density of particles, \( t \) is the time and \( G \) is the size-independent growth rate. The concentration \( c \) of the solute can be obtained by the material balance and is given by the following equation:

\[
\frac{dc}{dt} = -3k_c \rho c G \int_{L_o}^{\infty} n L^2 dL ,
\]

(5.17)
with \( k_v \) being the volume shape factor. In this work we have used a value of \( k_v = \pi/6 \). The following initial and boundary conditions apply for the PBE and the material balance:

\[
    n(L_0, t) = \frac{J}{G} \tag{5.18}
\]

\[
    n(L, 0) = 0 \tag{5.19}
\]

\[
    c(0) = c_0, \tag{5.20}
\]

where \( c_0 \) is the initial solute concentration. The PBE is solved using the method developed by Kumar and Ramkrishna (Kumar and Ramkrishna, 1997) as described in chapter 2.

The plug flow model is only a reasonable simplification if the time scales for mixing are much smaller than those for precipitation, i.e. the course of the precipitation process is not affected by the mixing conditions. In the following, the model results for the precipitation experiments in the Y-mixer (sections 5.1.3.1 and 5.1.3.2) are presented. The model employs the nucleation and growth kinetics given by Eqs. (5.5) and (5.15), respectively, together with the solubility given by Eq. (5.2).

Figure 5.5: Simulated final average particle size \( d_{10} \) as a function of the initial supersaturation. The initial concentration of L-asparagine in the inlet stream is always 15 g/kg.
The evolution of the average particle size $d_{10}$ is shown in Figure 5.3 for different initial supersaturations, i.e. $S = 9$ (runs 5 – 8), $S = 18$ (runs 9 – 12), and $S = 52$ (runs 13 – 16). The initial concentration in the solute stream was constant at 15 g/kg and the supersaturation was varied by changing the flow rate ratio between the solute and the antisolvent stream. The agreement between model and experiment is good in a rather broad supersaturation range. It can be observed that at fixed (residence) time the particle size increases with increasing supersaturation. However, the final particle size decreases with increasing initial supersaturation as shown in Figure 5.5.

The particle size can be controlled either by quenching after a certain residence time or by adjusting the initial supersaturation and consuming the supersaturation. The first method has the disadvantage that large amounts of solvent are necessary, which might make this option unattractive for industrial applications. On the other hand, the second method does not allow for producing every desired particle size. In fact, the final particle size depends on the intrinsic ratio of nucleation and growth, and on the dependence of this ratio on supersaturation. It is plotted as a function of the supersaturation in Figure 5.5; in the supersaturation range studied here the particle size can be varied between 5 and 50 μm. Moreover, also secondary effects such as agglomeration and breakage are sometimes important, e.g. agglomeration often becomes the dominant mechanism for very small particles.

### 5.1.3.5 Simultaneous kinetics estimation

Most particle size measurement techniques, e.g. the widely used laser diffraction methods, measure only the normalized particle size distribution and the number concentration cannot be determined. Therefore, we want to check if the kinetics can also be determined based on the evolution of the average particle size along the mixer. In total, experimental data at 5 different initial supersaturation levels, namely 9, 18, 52, 81 and 169, and in a range of residence times between 0 and 20 seconds were used for the parameter estimation (runs 5 – 23 in Table 5.2). Some of the experimental data that was used for the kinetics estimation is shown in Figure 5.3. The parameters in the kinetic expressions for nucleation and growth are estimated simultaneously on the basis of these precipitation experiments using a nonlinear optimization algorithm that minimizes
the sum of square residuals, $SSR$, between the experimental and simulated values of the average particle size:

$$SSR = \sum_{i=1}^{N_e} \sum_{j=1}^{N_{d,i}} (d_{10,i,j}^{\text{exp}} - d_{10,i,j}^{\text{sim}})^2,$$  \hspace{1cm} (5.21)

where $N_e$ is the number of experiments at different initial supersaturations, $N_{d,i}$ is the number of data points at different residence times per experiment $i$, and $d_{10}^{\text{exp}}$ and $d_{10}^{\text{sim}}$ are the experimental and simulated average particle sizes, respectively. The PBE model given by Eqs. (5.16) to (5.20) was applied for the parameter estimation. The optimization problem was solved using the \textit{lsqnonlin} algorithm of the MATLAB optimization toolbox. Changing the initial values of the estimated parameters in the optimization procedure over several orders of magnitude always produced the same results, thus indicating a global optimum. Approximate confidence intervals of the model parameters $b$ can be determined as described in chapter 2.

As a result of the parameter estimation we have obtained the following kinetics:

$$J = (6.3 \pm 1.6) \times 10^{10} S \exp \left( -3.9 \pm 0.5 \times 10^{-2} \frac{\ln^3 C_c}{\ln^2 S} \right),$$  \hspace{1cm} (5.22)

$$G = (3.9 \pm 0.3) \times 10^{-8} c^* (S - 1)^{(1.73 \pm 0.02)}. \hspace{1cm} (5.23)$$

The approximate correlation matrix can be obtained using the covariance matrix of the estimated parameters as described elsewhere (Beck and Arnold, 1977). The off-diagonal elements of the correlation matrix relating the nucleation and the growth rate parameters are in the range between 0.11 and 0.37. Thus, it can be concluded that the nucleation and growth kinetics are only slightly correlated (Beck and Arnold, 1977). A comparison of the growth rates given by Eqs. (5.15) and (5.23) shows a very good agreement between the two different techniques for the determination of growth rates. In fact, the independently measured growth rate Eq. (5.15) is within the (rather narrow) confidence interval of the simultaneously estimated growth rate Eq. (5.23). However, the two nucleation rates given by Eqs. (5.5) to (5.7) and (5.22) differ significantly. It must be noted that the confidence intervals of the nucleation rate parameters are much larger than those for the growth rate, i.e. the estimation of
the nucleation rate is less accurate. A comparison of the simulated time evolution of \( d_{10} \) shows that the curves for the model employing the independently measured kinetics and for the model employing the simultaneously estimated kinetics coincide for all precipitation experiments. It can be concluded that the method for the simultaneous estimation of nucleation and growth kinetics based on measurements of the average particle size yields very similar results as compared to the independent determination. However, this might not be true in all cases and the correlation matrix should always be calculated to check whether or not the kinetics are highly correlated.

5.1.4 Time scale analysis

The mixer setup is used to determine true kinetics, i.e. kinetics that are not affected by mixing. Obviously, the precipitation time scales are not known before measuring the kinetics. Therefore, a time scale analysis should be conducted by hindsight to validate if there were actually no mixing limitations during the experiments used for the determination of the kinetics. Moreover, the plug flow model employed above is also valid only if the time scales for mixing are much smaller than those for precipitation.

Average mixing times in the Y-mixer have been determined previously (chapter 4) and are used here as characteristic time scale for mixing. For the flow rate, flow rate ratio and viscosity ratio applied here mixing time scales are always below 20 ms.

The characteristic time scale for nucleation \( \tau_N \) is the induction time, which can be estimated as follows (Kashchiev et al., 1991):

\[
\tau_N = \left( \frac{4 \alpha_v}{k_v J G^3} \right)^{1/4},
\]

(5.24)

with \( \alpha_v \) being the detectable volume fraction. A value of 0.1% of the maximum solid concentration is chosen arbitrarily for \( \alpha_v \):

\[
\alpha_v = 0.001 \left( c_0 - c^* \right),
\]

(5.25)

where \( c_0 \) and \( c^* \) are the initial and equilibrium concentration, respectively, both given in m\(^3\)/m\(^3\).
The characteristic time scale for growth $\tau_G$ describes the rate of concentration decrease resulting from crystal growth and can be calculated as follows (Baldyga and Bourne, 1999):

$$\tau_G = c/(\rho_c a_c G),$$

(5.26)

with $a_c$ being the specific surface of the crystals in the reactor. A typical value for L-asparagine and the conditions studied here is $a_c = 100 \text{ m}^2/\text{m}^3$.

![Figure 5.6](image_url)

Figure 5.6: Characteristic nucleation, growth and mixing time scales as a function of supersaturation. The initial concentration of L-asparagine in the inlet stream is always 15 g/kg.

The characteristic time scales as a function of the supersaturation are shown in Figure 5.6. It can be readily observed that the precipitation time scales are at least one order of magnitude larger than the mixing time scale. Thus, the precipitation process is not affected by the mixing conditions. It should also be noted that mixing time scales in static micro-mixers can be as low as 0.1 ms (see chapter 4), i.e. three orders of magnitude lower than the precipitation time scales.
In order to validate the aforementioned analysis, the particle size of L-asparagine monohydrate crystals was measured at different flow rates and fixed supersaturation and residence time. The initial concentration of L-asparagine monohydrate was 15 g/kg in the solute stream, the flow rate ratio was 1:8 (solute:antisolvent) and the corresponding initial supersaturation was 88. The residence time was 11 s and was adjusted to the flow rate by changing the length of the outlet tube. The experimental average particle size $d_{10}$ is plotted in Figure 5.7 as a function of the flow rate of the larger stream. It can be observed that the particle size is independent of the flow rate, thus supporting the result of the time scale analysis, namely that mixing is much faster than precipitation.

![Figure 5.7: Measured average particle size $d_{10}$ for different flow rates (symbols) and corresponding simulation result (line). The residence time is 11 s and the initial supersaturation is $S_0 = 88$ in each experiment. The inset shows the PSD at a flow rate of 200 g/min (symbols: experiment; line: simulation).](image)

The corresponding simulation results are plotted in Figure 5.7 as well and a good agreement with the experimental data can be observed. In this case the model is used in a fully predictive manner. It must be noted that the plug flow
model does not account for mixing effects. Thus, at fixed residence time the final particle size does not dependent on the flow rate.
A comparison of the simulated and the measured PSD at a flow rate of 200 g/min is shown in the inset of Figure 5.7. It can be observed that the experimental PSD is slightly broader and shifted towards larger particle sizes as compared to the simulated PSD. The broadening of the PSD might be attributed to agglomeration, growth rate dispersion, hydrodynamic backmixing or the sampling procedure (Stahl et al., 2001). However, studying the effect of these parameters on the PSD was beyond the scope of this work.

5.2 Effect of additives
Micron-sized particles are required in the pharmaceutical industry to administer a drug in pulmonary or oral dosage forms. As outlined in section 5.1.3.4 the minimum particle size of L-asparagine monohydrate which can be obtained in precipitation experiment is about 5 μm.
In a recent study by Rasenack and co-workers, the effect of different additives on several drug substances was investigated (Rasenack and Muller, 2002; Rasenack et al., 2004). The focus of that work was on dissolution rate enhancement by in-situ micronization of poorly water-soluble drugs. It was shown that among the additives being tested hydroxypropyl methylcellulose (HPMC) was the most effective one, i.e. it caused the largest change in particle size. The antisolvent precipitations were carried out in a beaker and the particles were obtained by spray-drying.
In this section, the effect of different additives on the precipitation of L-asparagine monohydrate is studied.

5.2.1 Precipitation in the Y-mixer
We have studied the effect of HPMC on the precipitation of L-asparagine monohydrate in the Y-mixer. A solution of 15 g/kg L-asparagine and 1 wt% HPMC was mixed with 2-propanol to create a supersaturated solution. The level of supersaturation was varied by changing the flow rate ratio of the two streams. The solution was quenched after a certain residence time and the PSD was measured using the Coulter Multisizer as described in section 5.1.3. The average particle size $d_{10}$ as a function of the residence time is shown in Figure 5.8 for different initial supersaturations. We assume that the solubility is not
affected by the presence of HPMC. It can be observed that the particle size increases with increasing residence time similar to the experiments without HPMC (Figure 5.3). However, at high supersaturations, e.g. $S_0 = 169$, the particle size has reached a constant value already after 2.5 seconds. The final particle size is about 1.5 $\mu$m and much smaller than for precipitation without additive (Figure 5.5). Thus, HPMC can be used effectively to reduce the particle size.

Simulation results are shown in Figure 5.8 as well. The same model as in section 5.1.3.4 was used, i.e. a model being valid for the precipitation of L-asparagine monohydrate without additives. It can be observed that for moderate supersaturations the agreement between model and experiment is good, while the deviation increases with increasing supersaturation. This means that the effect of the additive is more prominent at high supersaturation levels.

![Figure 5.8: Average particle size $d_{10}$ as a function of residence time and for different initial supersaturations. Symbols: experimental data; lines: simulation results. The experiments are carried out with 1 wt% HPMC in the L-asparagine inlet stream.](image)
### 5.2.2 Additive screening

The effect of different additives, pH and supersaturation on the final particle size of L-asparagine monohydrate precipitated in a beaker is studied in this section. An aqueous solution containing 15 g/kg L-asparagine monohydrate and the additive is mixed with 2-propanol. The supersaturation is varied by changing the ratio of aqueous solution and antisolvent. The PSD is measured using the Coulter Multisizer. The experimental conditions and measured average particle sizes are given in Table 5.3.

<table>
<thead>
<tr>
<th>Run</th>
<th>$S_0$ [-]</th>
<th>$c_{\text{polymer}}$ [wt%]</th>
<th>pH value [-]</th>
<th>$c_{\text{salt}}$ [g/kg]</th>
<th>$d_{43}$ [μm]</th>
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<td>n/a</td>
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<td>n/a</td>
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<td>n/a</td>
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<td>n/a</td>
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<td>n/a</td>
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</tr>
<tr>
<td>7</td>
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<td>n/a</td>
<td>17.2</td>
</tr>
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<td>n/a</td>
<td>17.1</td>
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<td>n/a</td>
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<tr>
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<td>n/a</td>
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</tr>
<tr>
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</tr>
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<tr>
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<td>3.5</td>
<td>1.2 g/kg AlCl$_3$</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Table 5.3: Experimental conditions of the L-asparagine monohydrate precipitation experiments using additives and corresponding final average particle size $d_{43}$.
5.2 Effect of additives

**HPMC concentration**

The HPMC concentration was varied from 0 to 4 wt% with respect to the L-asparagine solution (runs 1 – 4 in Table 5.3). The measured PSDs are plotted in Figure 5.9. The particle size decreases with increasing amount of HPMC from 36.7 μm at 0 % HPMC to 13.6 μm at 4 % HPMC. The HPMC concentration could not be increased more than 4 % due to the high viscosity.

Microscope pictures of the L-asparagine monohydrate crystals are depicted in Figure 5.10. It can be observed that with increasing HPMC concentration the shape of the crystals changes from regular platelets at low HPMC concentration to irregular X-shaped particles at high concentrations.

**Supersaturation**

Runs 5 to 8 in Table 5.3 demonstrate the effect of supersaturation on particle size at a HPMC concentration of 1 wt%. The particle size decreases from $S_0 = 5.7$ to $S_0 = 59.0$ (runs 5 to 7), but stays constant a higher supersaturations. This effect might be attributed to mixing limitations at high supersaturations since smaller particles have been observed under similar conditions in the Y-mixer (section 5.2.1).

**Type of additive**

Runs 7, 9 and 10 in Table 5.3 show the effect of HPMC, sodium dodecyl sulfate (SDS) and Pluronic on the final particle size. Supersaturation and additive concentration were the same in all three experiments. SDS has been used effectively by Prud‘homme and co-workers to stabilize hydrophilic and hydrophobic substances using a confined impinging jet mixer (Chiou et al., 2008). Pluronic is a surface-active block copolymer used as emulsifier in chemical industry. Block copolymers have also been used by the group of Prud'homme to stabilize nano-particles (Johnson and Prud'homme, 2003b; Zhu et al., 2007). In Table 5.3 it can be observed that HPMC is more effective than SDS and Pluronic. Therefore, this substance is used for the subsequent experiments.

**pH value**

The surface charge of particles is affected by the pH value of the solution. As a consequence the particles can be stabilized by adjusting the pH, i.e. agglomeration is reduced and smaller particles are obtained.
5. L-asparagine antisolvent precipitation

The pH has also an effect on the species of L-asparagine in solution. At low to neutral pH L-asparagine exists as neutral and protonated form. The speciation of L-asparagine can be determined as a function of pH by solving a system of equations consisting of dissociation equilibrium, autoprotonation of water, elec-

Figure 5.9: Experimental PSDs of L-asparagine monohydrate for different concentrations of HPMC and an initial supersaturation of $S_0 = 18$.

![Figure 5.9: Experimental PSDs of L-asparagine monohydrate for different concentrations of HPMC and an initial supersaturation of $S_0 = 18$.](image)

Figure 5.10: Microscope pictures of L-asparagine crystals for a HPMC concentration of 1 wt% (left) and 4 wt% (right), respectively. The initial supersaturation was $S_0 = 59$.

![Figure 5.10: Microscope pictures of L-asparagine crystals for a HPMC concentration of 1 wt% (left) and 4 wt% (right), respectively. The initial supersaturation was $S_0 = 59$.](image)
troneutrality and mass balance as described for L-glutamic acid by Schöll and co-workers (Schöll et al., 2006b). The $pK_a$ value for the protonation of the amino group is 2.1 (Lide, 2004). The concentration of the protonated and the neutral form of L-asparagine as a function of the pH value is shown in Figure 5.11.

![Figure 5.11: Concentration of the species of L-asparagine as a function of the pH value, at a concentration of 0.1 mol/L.](image)

Runs 11 to 13 in Table 5.3 show the effect of pH on the final particle size. The nominal supersaturation, i.e. the supersaturation neglecting the speciation of L-asparagine, was 59.0 and the HPMC concentration 1 wt% in all three experiments. The pH was varied by adding different amounts of HCl to the L-asparagine solution. The pH of the initial solution before mixing with 2-propanol is reported in Table 5.3. The actual supersaturation decreases with decreasing pH. It must be noted that the dissociation of L-asparagine might also be affected by the presence of 2-propanol. Nevertheless, the measured pH can be used to explain qualitatively the effect of $H^+$ ions on the PSD as depicted below.
Figure 5.12: Effect of pH on the final PSD of L-asparagine monohydrate. The concentration of HPMC is 1 wt% and the initial nominal supersaturation is $S_0 = 59$.

The final PSDs corresponding to the precipitation experiments at different pH values are shown in Figure 5.12. It can be observed that the particle size decreases with decreasing pH owing to a reduced degree of agglomeration as observed on microscope pictures. However, no particles could be detected for a pH below 1.5 due to the low concentration of the neutral form of L-asparagine (Figure 5.11).

It can be concluded that the pH can be used to stabilize the particles, most likely by increasing the surface charge and thereby increasing the repulsive forces between the particles. The lower the pH the more prominent is this effect. However, at a pH below 1.5 no precipitation can occur due to the speciation of L-asparagine. The same effect of decreasing particle size with decreasing pH was also observed for experiments without HPMC as additive (runs 14 to 16 in Table 5.3).

**Salt concentration**

Electrolyte salts are also very effective in changing the surface charge of particles. We have tested salts of different valence to check their potential to de-
crease the particle size by stabilizing the particles. In runs 17 to 19 in Table 5.3 we have tested 1:1 (NaCl), 1:2 (Na$_2$SO$_4$) and 3:1 (AlCl$_3$) electrolytes in the presence of 1 wt% HPMC. All additive concentrations are given with respect to the L-asparagine solution. The corresponding PSDs are shown in Figure 5.13. It can be observed that AlCl$_3$ is most effective, even at low concentrations. In run 21 it was tested if AlCl$_3$ is also effective without HPMC. It can be observed that the particle size is much lower than the corresponding run without AlCl$_3$ but it is also much larger than employing both AlCl$_3$ and HPMC.

![Figure 5.13: Effect of different salts on the final PSD of L-asparagine monohydrate in the presence of 1 wt% HPMC. The initial nominal supersaturation is $S_0 = 59.$](image)

It must be noted that the speciation of L-asparagine is affected by the presence of a salt, i.e. the pH changes as shown in Table 5.3, and that only the nominal supersaturation, i.e. the supersaturation neglecting the speciation, is reported. A SEM picture of L-asparagine monohydrate crystals precipitated in the presence of HPMC and AlCl$_3$ (run 19) is depicted in Figure 5.14. It can be observed that the surface is rough and that the crystals form agglomerates where all single crystals appear to grow from the center.
5. L-asparagine antisolvent precipitation

Figure 5.14: SEM picture of L-asparagine monohydrate crystals. The initial nominal supersaturation was $S_0 = 59$. The concentrations of HPMC and AlCl$_3$ were 1 wt% and 1.2 g/kg, respectively.

A comparison of the crystals of run 19 and 21, i.e. with the same AlCl$_3$ concentration but once with and once without HPMC, is shown in Figure 5.15. Although the two runs exhibit different particle sizes of the single crystals in the agglomerate, they have the centered structure of the agglomerate in common. However, the crystals without HPMC seem to be much more agglomerated and form loosely bound aggregates.

Figure 5.15: Microscope pictures of L-asparagine crystals for a HPMC concentration of 0 wt% (left) and 1 wt% (right), respectively. The initial nominal supersaturation was $S_0 = 59$ and the AlCl$_3$ concentration was 1.2 g/kg.
In run 20 an even higher AlCl$_3$ concentration was applied and the particle size could be further reduced to about 0.7 \( \mu \)m. The PSD in this case had to be measured using a Sympatec Helos (Clausthal-Zellerfeld, Germany) applying laser diffraction. The PSDs of the experiments at \( S_0 = 59 \) without additive (run 14), with 1 \% HPMC (run 7), with 1\% HPMC and 1.2 g/kg AlCl$_3$ (run 19), and with 1\% HPMC and 5 g/kg AlCl$_3$ (run 20) are shown in Figure 5.16. It can be observed that the particle size can be changed by almost two orders of magnitude by employing different additives.

![Figure 5.16: Comparison of the experimental PSDs of L-asparagine monohydrate precipitated using different additives.](image-url)

**5.3 Conclusions**

In this chapter, two techniques for the production of small micron-sized crystalline particles was presented. The first is based on a precipitation process carried out at high supersaturation levels and in a static mixer to avoid transport limitations. Nucleation and growth kinetics of L-asparagine monohydrate precipitated by antisolvent addition were determined for a wide range of supersaturations, i.e. from about 4 to 170. Two different methods for the kinetics estimation were compared. In the first method, nucleation and growth kinetics were measured
independently, whereas the nucleation rate was calculated from the change of particle concentration over time, and the growth rate was calculated based on the change of the particle size over time. In the second method, nucleation and growth kinetics were estimated simultaneously based on the time evolution of the particle size by a combination with a population balance model and an integral parameter estimation technique. It was found that both methods yield similar kinetics; however, it should always be checked if the kinetics parameters are highly correlated. The precipitation of L-asparagine monohydrate in the Y-mixer was modeled assuming plug flow through the mixer and using the population balance framework. The model was in good agreement with the experimental data and was used to design a continuous precipitation process. A time scale analysis showed that mixing is much faster than precipitation and therefore the two processes could be decoupled.

The second technique employs additives which are used to inhibit crystal growth and to stabilize particles by reducing agglomeration. Different additives, salts and operating conditions were tested. It was found that the addition of HPMC and AlCl₃ was most effective in decreasing the particle size, even down to the nanometer range.
5.4 Nomenclature chapter 5

**Roman letters**

- $a_c$: specific surface area [m$^2$ m$^{-3}$]
- $c$: concentration [mol m$^{-3}$]
- $c^*$: solubility [g per kg of solvent]
- $d_{ij}$: average particle size: $i$th divided by $j$th moment of PSD [m]
- $G$: growth rate [m s$^{-1}$]
- $J$: nucleation rate [m$^{-3}$ s$^{-1}$]
- $k$: empirical parameter [-]
- $k_v$: volume shape factor [-]
- $L$: particle size [m]
- $n$: number density [m$^{-4}$]
- $N$: number of particles [m$^{-3}$]
- $M$: molecular mass [g mol$^{-1}$]
- $q$: quench ratio [g g$^{-1}$]
- $R^2$: regression coefficient [-]
- $S$: supersaturation [-]
- $t$: time [s]
- $t_i$: induction time [s]
- $V_s$: sampling volume [m$^3$]
- $w$: antisolvent concentration [g g$^{-1}$]

**Greek letters**

- $\alpha_v$: detectable volume fraction [m$^3$ m$^{-3}$]
- $\gamma$: interfacial energy [J m$^{-2}$]
- $\mu_i$: $i$th moment of the PSD [m$^i$ m$^{-3}$]
- $\rho_c$: crystal density [kg m$^{-3}$]
- $\tau$: time scale [s]
6 Concluding remarks

In the pharmaceutical and chemical industry precipitation and crystallization processes are employed to produce crystalline particles with specific properties, e.g. particle size, polymorphic form and purity. Model-based design and optimization of crystallization processes requires the knowledge of the key mechanisms of particle formation and growth. Therefore, the goal of this thesis was to devise protocols for the determination of all relevant kinetics and to develop tools to simulate precipitation and crystallization processes.

6.1 Summary

In chapter 2, methods for the fast and robust measurement of crystallization kinetics are presented. They are based on in-situ process analytical technologies, namely FBRM, ATR-FTIR and Raman spectroscopy, to monitor the solid and the liquid phase during the precipitation of L-glutamic acid. The work shows how key mechanisms of particle formation, such as nucleation, growth, agglomeration and polymorph transformation, can be determined from batch experiments carried out in the same setup but applying different measurement protocols if the process is not affected by mixing. A timescale analysis was employed to check that this condition was fulfilled, i.e. that the characteristic timescales for mixing are much smaller than those for particle formation. Firstly, growth kinetics of α L-glutamic acid were determined based on seeded batch desupersaturation experiments in a broad range of temperature and supersaturation. The experimental requirements for an independent growth kinetics determination, i.e., the absence of other mechanisms such as nucleation, agglomeration and breakage, were checked using the Coulter particle analyzer and scanning electron microscopy. It could be shown, that the presented characterization method was robust also in case of occurring agglomeration. Secondly, induction times of α L-glutamic acid were measured as a function of supersaturation and temperature. It was shown that the induction times decrease with increasing supersaturation and temperature. A scale effect has also been investigated by comparing induction times measured in a 0.5 and a 2L reactor,
respectively. The induction times measured in the two reactors agree relatively well and no significant difference was observed. Combined with independently measured growth kinetics the nucleation rates were determined at 25, 35 and 45 °C and in a supersaturation range between 1 and 8. The estimated kinetic parameters and calculated interfacial energies were much lower than predicted theoretical values for homogeneous nucleation, thus indicating a heterogeneous nucleation mechanism.

Thirdly, a method for the determination of agglomeration kinetics was presented and applied to α L-glutamic acid pH-shift precipitation. The method is based on a population balance model and an optimization routine in order to estimate empirical parameters in the agglomeration kernel. An agglomeration kernel was devised to model accurately the agglomeration process in a wide range of operating conditions, i.e. initial supersaturation, stirring rate, seed size and seed mass. A model that accounts for the dependence of the agglomeration rate on the heterogeneously distributed shear rate in stirred reactors has also been presented. Computational fluid dynamics (CFD) was used to calculate the shear rate distribution. Alternatively, the mean shear rate was also estimated using a power number correlation. Both approaches gave similar results in this study, but it is believed that the proposed use of CFD is applicable under more general conditions, especially if the mean energy dissipation rate is not accessible, and can be used to account for scale-up effects.

Fourthly, it was shown that the quantitative use of in-situ Raman monitoring enables new insights in fundamental mechanisms of polymorph transformations. The solvent mediated polymorph transformation of L-glutamic acid is governed by nucleation, growth and dissolution of the metastable α polymorph and the nucleation and growth of the stable β polymorph. Raman spectroscopy was used to determine the secondary nucleation rate of the stable β polymorph of L-glutamic acid at various operating conditions. From the experimental observations it was concluded that an attrition-based nucleation mechanism governs the transformation of the metastable α to the stable β polymorph. The effect of stirring on the course of the polymorph transformation was investigated experimentally and was also modeled using a population balance model and implementing the relevant kinetics. The proposed model allowed calculating the course of a polymorph transformation in a fully predictive manner for
seeded as well as for unseeded conditions under a wide range of operating conditions.

Chapter 3 is devoted to the design and optimization of crystallization processes. The combined cooling/antisolvent crystallization process of acetylsalicylic acid from ethanol-water solutions was designed and optimized. The model-based optimization required the knowledge of solubility, nucleation and growth kinetics of acetylsalicylic acid, which were measured using process analytical technologies, such as ATR-FTIR and FBRM, and by applying previously development experimental protocols. A process model based on a population balance equation was used for a multiobjective process optimization. More specifically, the resulting Pareto-optimal solutions showed that the two objectives are conflicting, i.e. short process time results in a larger nucleation rate and vice versa, and yielded the corresponding optimal cooling and antisolvent flow rate profiles. The process performance of the optimized process was improved as compared to conventional process alternatives which are commonly applied in industry, i.e. the addition of the antisolvent either at the beginning or at the end of the cooling process. In particular, a unimodal particle size distribution at a minimum process time has been obtained. The advantage of the combined process was shown through both modeling and experiments.

Chapter 4 describes the use of competitive-parallel chemical reactions to characterize mixing in static micro-mixers. These mixers should be applied to avoid transport limitations in precipitation processes carried out at high supersaturations to produce smaller particles. Two different mixer geometries were compared and it was shown that for a wide range of operating conditions the proposed Roughton mixer exhibits superior mixing behavior, expressed by a low DMP conversion, as compared to the Y-mixer also tested here and to the confined impinging jet mixer studied by others (Johnson and Prud'homme, 2003a). The experimental data were compared with the results of CFD simulations and a remarkably good agreement was observed. It is noticeable that the CFD model is fully predictive, i.e. no additional parameters had to be fitted to match the experimental data. This indicates that the model presented here is very valuable for design and scale-up of mixers. The CFD model was used to obtain
additional insight into the process, since the local concentrations, concentration variances and reaction rates were accessible.

The effect of jet velocity $u_j$, flow rate ratio, viscosity $\nu$ and jet diameter $d_j$ on mixing efficiency was studied and it was found that the average mixing time $t_m$ can be well described by $t_m = K d_j^{0.5} \nu^{0.5} / u_j^{1.5}$ with $K = 1.07 \times 10^3$ for the Rough-ton and $K = 4.91 \times 10^3$ for the Y-mixer.

In chapter 5, two techniques for the production of small micron-sized particles of L-asparagine monohydrate precipitated by antisolvent addition were presented. The first is based on a precipitation process carried out at high supersaturation levels and in a static mixer to avoid transport limitations. Protocols for determining nucleation and growth rates under these conditions were presented. The estimated kinetics were used in a population balance model of the plug flow reactor. The model was in good agreement with the experimental data and was used to design a continuous precipitation process. A timescale analysis showed that mixing is much faster than precipitation and therefore the two processes can be decoupled.

The second technique employs additives which are used to inhibit crystal growth and to stabilize particles by reducing agglomeration. Different additives, salts and operating conditions were tested. It was found that the addition of HPMC and AlCl$_3$ were most effective in decreasing the particle size, even down to the nanometer range.

Thus summarizing, this thesis presents experimental methods and simulation tools for the model-based design and optimization of precipitation and crystallization processes. Depending on the specific goal regarding the particle size and on the intrinsic kinetics of the compound, different methods for the measurement of nucleation, growth and agglomeration kinetics should be used. In this context, it has to be decided first which type of equipment, i.e. a stirred tank or a micro-mixer, should be applied. It is suggested that the decision should be based on an analysis of the characteristic mixing and precipitation time scales. For both the stirred tank and the micro-mixer, this thesis provides suitable tools for the determination of the kinetics and for the process modeling.
6.2 Outlook

One area of future work regarding the measurement of crystallization kinetics is the effect of additives. The growth rates of crystal faces can be retarded by adsorption of additives on the crystals surface. Since the molecules have a different orientation at the different crystal faces, the additives will have a different effect on the growth rate of different faces. Hence, by choosing properly the additives or by using tailor-made additives the growth rates can be affected in such a way that the morphology of the crystal changes. Furthermore, the dissolution rates can be affected by changing the shape of the crystals and by using suitable additives that enhance the wettability through hydrophilization of the crystal surface.

Another possible application of additives is the complete inhibition of crystal growth during precipitation in order to produce nano or micron-sized particles. The suppression of growth should result in a relatively higher nucleation rate with respect to the growth rate and therefore the number of particles should increase while the particle size should decrease. Other possible effects of additives could be to increase directly the nucleation rate by changing the surface tension or to stabilize the produced particles by inhibiting particle agglomeration.

A critical issue in this context is the monitoring of particle size and shape. The development of tools for in-situ measuring of particle size distributions as well as for quantifying particle shape should be scope of future research activities.

Another area of future work is the development and application of multi-dimensional population balance models. In many practical application, e.g. breakage of needle-like crystals, both size and shape of the crystals change during crystallization. Thus, a multi-dimensional or at least a 2D-PSD is needed, where each crystal is described by more than one characteristic dimension.

Another critical issue is the modeling of precipitation processes being affected by the mixing conditions, e.g. antisolvent precipitation in a stirred tank. Possible research activities in this area are the development and improvement of predictive CFD-PBE models and the efficient solution of these models.
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List of own publications


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