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Master Thesis

Continuous Crystallization of Pharmaceuticals in a Tubular Reactor

Created for

RCPE (Research Center Pharmaceutical Engineering)

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Kurzfassung

Kontinuierliche Kristallisation pharmazeutischer Wirkstoffe in einem Schlauchreaktor

Die Kristallisation ist ein Kernprozess für Trennungs- und Reinigungsprozesse. Speziell in der pharmazeutischen Industrie ist die Qualität der erzeugten Kristalle bezüglich der Reinheit, Breite der Partikelgrößenverteilung und der mittleren Kristallgröße von großer Bedeutung. Diese Eigenschaften sind ausschlaggebend für die weitere Prozessierbarkeit der Kristalle sowie auch ihrer Wirkung im menschlichen Körper. Durch eine enge Korngrößenverteilung können in weiterer Folge Kosten hinsichtlich der Trennprozesse eingespart werden. Der Hauptfokus dieser Arbeit liegt in der Entwicklung eines Systems um den Mehrphasenfluss zu regulieren und an der Produktion einsatzfähiger Seeds (Kristalle mit denen ein Kristallisationsprozess gestartet werden kann) für die eigentliche Kristallisation im Schlauch. Neben diesen wird auch die Probenahme kritisch untersucht und die temperaturabhängige Löslichkeit der zu kristallisierenden Substanz im verwendeten Lösungsmittel bestimmt.

Abstract

Continuous Crystallization of Pharmaceuticals in a Tubular Reactor

Crystallization is a key process for separation and purification. Especially in the pharmaceutical industry the quality of the developed crystals concerning purity, crystal size distribution and mean particle size is of great importance. The particle size influences further handling and determines the solubility of the particle in the human body. If a narrow particle size can be achieved, costs can be reduced in the separation process. In this thesis the continuous crystallization process in a tubular reactor is developed and improved. The main focus lies on the realization of a system to control the multiphase flow in the system and on the production of suitable seeds (Crystals that can induce the process of crystallization) to run the continuous crystallization process in the tubular reactor. Further attention is given to the procedure of sampling and the solubility of the crystals in the solvent, depending on the temperature is analyzed.

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1 Introduction

Crystallization is commonly used in the pharmaceutical field. The quality of the crystallization process itself determines the crystals outcome and further processing procedures. A lot of research has been conducted on crystallization in a batch reactor and less attention has been focused on crystallization in a continuous flowing tube reactor. Advantages of crystallizing in a tube reactor are for instance the narrow residence time distribution and the continuous operation. Also cooling can be achieved in a series of steps. Beside the continuous operation mode advantages of crystallizing in a tubular reactor can be for instance achievement of narrow residence time distribution of the crystals and the generation of well defined process conditions. Especially of the temperature profile due to a high surface to volume ratio which enables fast heat transport through the reactor wall. The ambition of this thesis is to analyze crystals based on various methods. Optimal process parameters are to be determined and a suitable procedure for the production of the seeds shall be established. At the same time the whole process of crystallization is to be developed and analyzed.

1.1 Problem Definition

A major concern in pharmaceutical crystallization processes is the broadness of the product crystal's particle size distribution. The particle size influences further handling and determines the solubility of the particle in the human body. This is why analyzing growth of the crystals concerning size, particle size distribution and their formation is of importance. Also the purity of crystals is essential for further handling. Crystal growth determines the purity of the product. In this thesis methods for controlling and regulating the growth of the crystals shall be found and implemented.

1.2 Aim

The aim of this thesis is to be able to control and optimize the growth of the crystals in order to obtain a certain particle size distribution. Not only the distribution but also the structure of the crystals is to be analyzed. Whilst working on the thesis, the experimental procedure is to be optimized and defined. In summary the following steps should be included in the thesis.

- Determination and evaluation of an optimized process for the production of the seeds.
- Establishing a solubility curve
- Long term analysis and monitoring of the process to determine critical process parameters.
- General analysis of problems concerning sampling procedure and measurement of the particle size distribution and seed preparation

- Process development concerning flow rates, slug flow and tubing

2 Theory

2.1 Crystallization

First of all it is important to explain and define certain terms that are used in the following chapters.

The process of crystallization is determined by two steps, nucleation and crystal growth. Crystallization begins with a phase transition for the formation of the nuclei. [1] To achieve phase transition, a number of solute molecules have to form a cluster of critical size. Then the phase transition may take place. The necessary time required for clusters to reach the critical size is called nucleation time. Nucleation time can be reduced by several factors which will be described in detail later on in this chapter. [2]

A further requirement for the development of nuclei is that the free Gibbs enthalpy ΔG for the phase transition between the solution and the crystal is negative. This correlation is shown in the Gibbs Helmholtz equation (1): [3]

$$\Delta G = \Delta H - T\Delta S \qquad (1)$$

S…Entropy [J/K]

H…Enthalpy [J]

G…Free Gibbs enthalpy [J]

During the transition the entropy ΔS is reduced because the disorder of the system is decreased, hence the term –TΔS becomes positive. The term ΔH has to compensate this change by becoming negative. ΔH can be described as the interaction energy between the particles. If the interactions of particles increase, the term ΔH becomes negative and the chance of developing a stable crystal is increased. [4] The decisive factor is the total energy of the system. A certain amount of energy is necessary for the formation. This total energy can be divided into the enthalpy ΔG_V that is set free during the formation and the surface energy ΔG_S for the formation of the new surface. [4] This correlation can be seen in Equation (2). [5]

$$\Delta G = \Delta G_V + \Delta G_S \qquad (2)$$

ΔG_S...Surface Gibbs free energy [J]

ΔG_V…Volume Gibbs free energy [J]

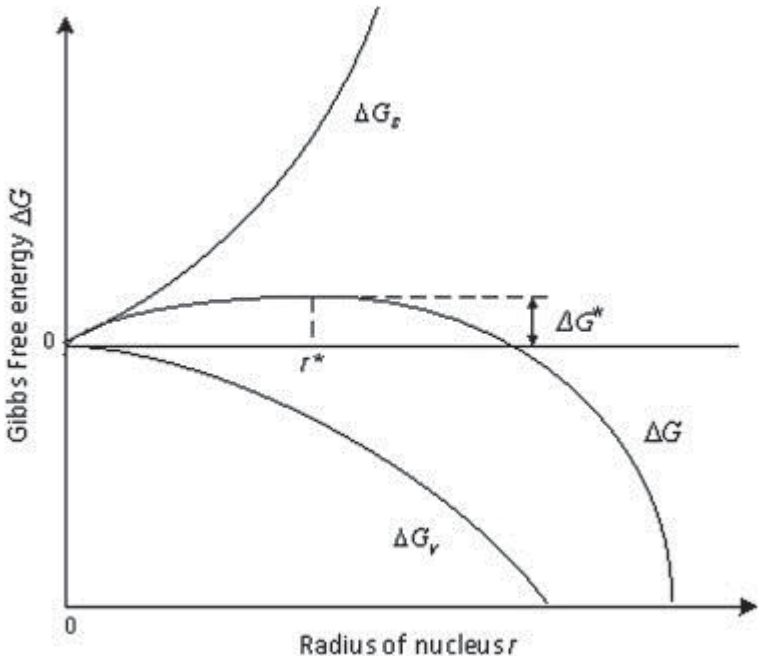

Figure 1: Gibbs free energy as a function of the nuclei radius [5]

ΔG_S...Surface Gibbs free energy [J]

ΔG_V…Volume Gibbs free energy [J]

r^*…critical nucleus radius [µm]

Figure 1 shows ΔG as a function of the particle radius for a subsaturated and supersaturated system. In the subsaturated section an increase of the radius results in an increase of the Gibbs free energy and dissolution of the particle, on the contrary the increase in radius in the supersaturated environment can lead to nucleation if the critical radius r^* is reached. [6]The critical radius is where the slope is defined as d(ΔG)/dr = 0. [5] At this point the nucleus is in balance with the supersaturated solution and the possibilities of the nucleus dissolving or growing are equivalent. An aggregate on the left hand side of the maximum is likely to lose a component and on the right hand side it is likely to grow or develop. [4]

The basic concept of crystallization is that the solids, referred to as crystals, develop out of a molten bath or suspension. Here the crystals are developed in a suspension. For the development of crystals in the suspension, the system has to be brought out of equilibrium into a supersaturated state using a driving force. [7] [8]

The degree of supersaturation often determines the rate of crystallization and can be described by the difference in concentration of the solution and its equilibrium concentration: [9] [10]

$$\Delta c = c - c^* \tag{3}$$

Or as the relative supersaturation ratio:

$$S = \frac{c}{c^*} \tag{4}$$

Or as the relative supersaturation:

$$\sigma = \frac{\Delta c}{c^*} \tag{5}$$

c…concentration

Δc…concentration difference (concentration driving force)

c^*…concentration of the saturation concentration (equilibrium concentration).

σ…relative supersaturation

In the supersaturated state crystals will develop in order to balance the system. This state can be reached by changing pressure, temperature or by applying vacuum, salting out or evaporation. It can also be achieved means a chemical reaction. For the growth of the crystals the system has to be kept in the state of supersaturation. [7] [8] The dependence of the solubility in accordance with the temperature is shown in Figure 2.

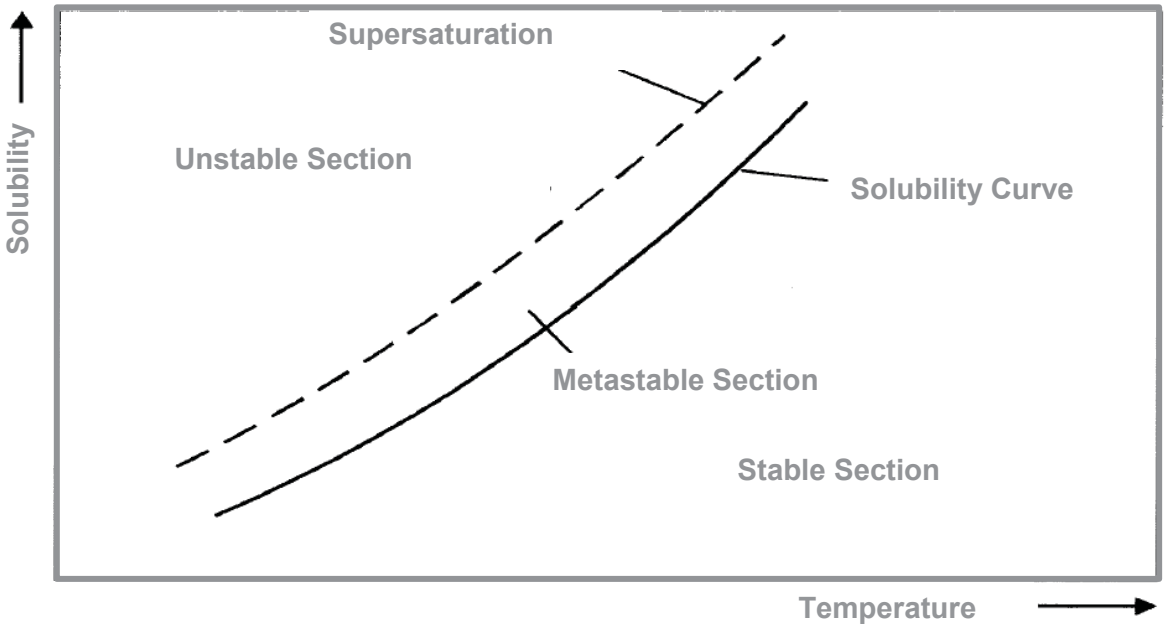

Figure 2: Solubility – temperature diagram [11]

The solubilty of a certain substance depending on the temperature is shown in Figure 2. Three areas are visible in the figure. The stable, metastable and unstable section which are divided by the solubility and supersaturation curve. Below the solubilty curve the solution is unsaturated and all particles are dissolved. Crystallisation is not possible in this section.

Above the supersaturation curve the system is supersaturated and unstable. In this area, the unstable section, the concentration of the substance in the system is the highest and nuclei will develop spontaneously. Further crystal growth of already existing crystals is also possible. Between the solubility curve and the supersaturation curve lies the metastable zone. The supersaturation curve is dashed due to the fact that it varies strongly and is thermodynamically and kinetically not well defined. [7] [12] [1] Spontaneous nucleation does not occur here, but crystals may grow if the crystallisation is induced by the addition of seeds or if a surface for nucleation is created. [3]

The process of seed development influences the size of the metastable section. For example a lot of energy is necessary for primary nucleation which possibly increases the metastable section. [7] [12] Some other influencing parameters are the temperature level, the rate of generating the supersaturation, the solution history, impurities and fluid dynamics. [1] Nucleation may take place anywhere in the metastable zone leading to different results concerning particle size distribution, formation of crystals, agglomeration etc. For example, if the crystals are developed close to the saturation limit they will grow slowly but will have a high purity. Otherwise the crystals contain a high amount of liquids. Optimal crystallisation should be achieved at approximately half of the metastable zone. [7] [12] [1]

Nucleation can be divided into the primary and secondary nucleation (Figure 3).

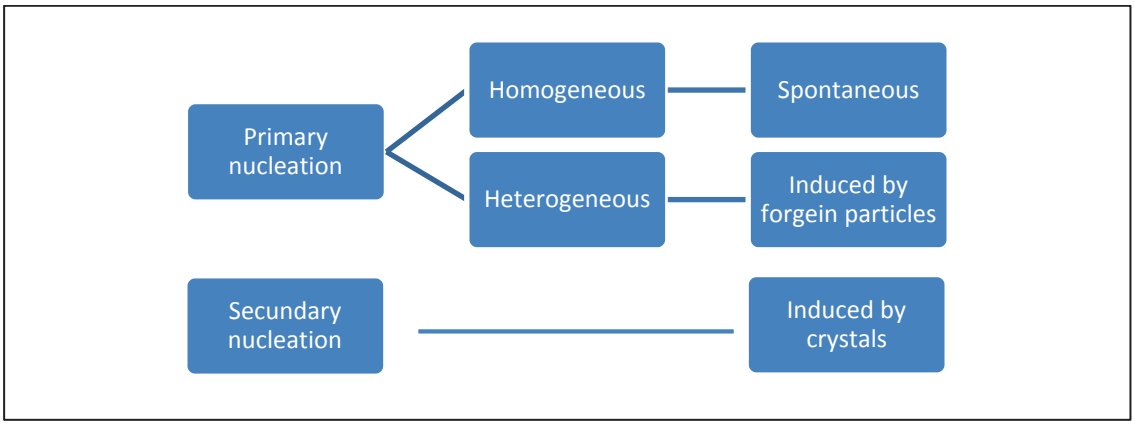

Figure 3: Types of nucleation [13] [4]

Provided the nuclei develop in supersaturated systems without unwanted substances it is homogenous nucleation. However if impurities are taken up, the reaction is catalyzed leading to heterogeneous nucleation. Secondary seeds are formed in supersaturated solutions with already developed crystals. [4] [11]

Primary nucleation can be prevented by keeping the saturation level as low as possible and within the metastable section. The secondary nucleation can be limited by keeping the turbulences in the solution low and by minimizing fittings. Following influences may lead to formation of secondary seeds: [4] [11]

- Collision between crystals

- Collision on walls
- Collision on fittings (pumps, stirrer etc.)
- Hydrodynamic transactions
- Supersaturation
- Crystal size
- Hardness of the crystal
- Surface hardness
- Density of the solution

The **collision** between the crystals results in small particle fragments that grow if the solution stays supersaturated. The probability of a collision increases with the **size of the crystal** but its influence is low if the particles are smaller than 100µm. [4] Collisions on fittings and walls have the same effect. Whether the particle breaks during the collision depends on its **hardness** and on the **surface hardness** of the collision object. Assuming the solution is **supersaturated,** there is a larger possibility of particles colliding. [11] In this thesis the crystal growth takes place in a tube reactor. This limits secondary nucleation which is a major influence factor according to the following ratio: [4]

$\eta_{Kristall\text{-}Rührer} : \eta_{Kristall\text{-}Wand} : \eta_{Kristall\text{-}kristall} = 1000:10:1$

In the formula above η is the effectiveness of the formation of secondary nuclei due to collision. The effectiveness depends on the amount of energy that is set free during collision. [4]

In this case crystal growth takes place in the tube and the major influence factor for secondary nucleation is ruled out.

If there is a nuclei in the solution, crystal growth begins when the system is slightly saturation. For the growth of the crystals, already existing seeds have to be in the solution, otherwise primary nucleation will take place and will result in a large particle size distribution. Crystal growth starts as soon as a stable nucleus is formed. There are several theories concerning crystal growth. The surface energy model, adsorption layer model, diffusions theory model, Burton-Cabrera-Frank model, birth and spread model. [11] It would be too extensive to describe these models in detail. Further information can be taken from [11]. Principally it is believed that crystals may grow faster in a solution with higher saturation but will not necessarily have the wanted size.

2.1.1 Ageing of Crystals

When all the crystals have been formed out of the liquid phase, aging of the particles takes place. In this stage the single particle is in thermodynamic equilibrium with the medium and it is assumed that the solid phase stays quasi constant. This regime is also called Ostwald ripening. During this stage large particles with a certain mass will keep growing and smaller particles will slowly decrease in size and are resorbed when they reach a sub-critical size. In summary the total number of particles decreases along with the particle total surface area [14]

2.1.2 Cooling

As mentioned at the beginning, supersaturation can be created by cooling the solution. Cooling crystallization is the most common crystallization method and is the main method of crystallization in this paper. [15] Cooling means that supersaturation is reached and the crystals are forced to grow to reestablish equilibrium. There are many possibilities of cooling a solution each influencing the size and shape of the crystals and it is difficult to find the optimal cooling profiles. An example for a cooling profile is shown in Figure 4. [16]

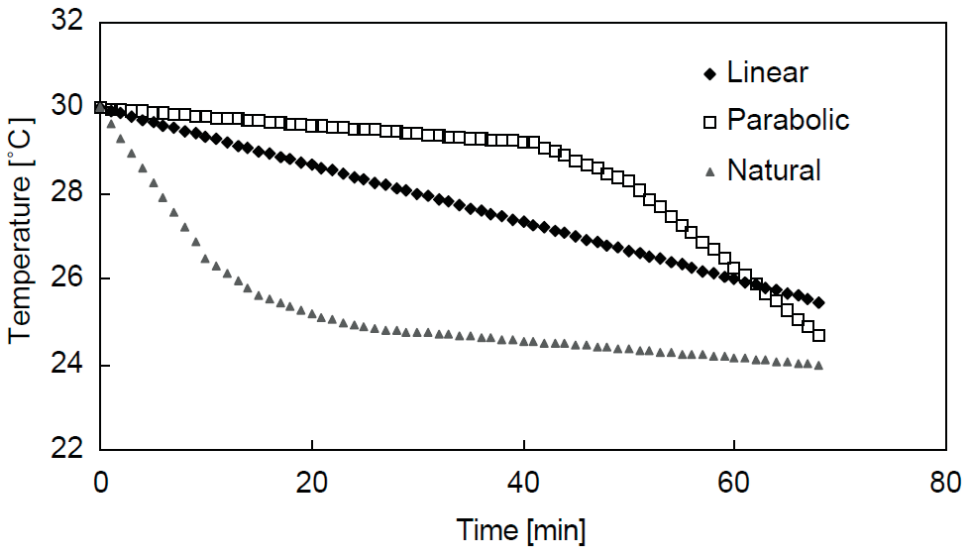

Figure 4: Controlled and natural cooling curves [1]

As visible in the figure above, cooling can be performed in form of a natural, linear or parabolic profile. Through natural cooling the cooling curve first drops rapidly and then more slowly near the end. Possibly secondary nucleation can be suppressed if the cooling is controlled, cooling slowly at the beginning and letting the temperature drop quickly near the end as shown in the parabolic cooling profile. [16] Often the linear cooling profile is used because it is easy to control and only the temperature of the system has to be measured. In order to create parabolic cooling profiles, the supersaturation or the width of the metastable zone has to be known. In summary, the starting point of nucleation depends on the cooling

rate which expands with increasing cooling rates and the degree of supercooling which influences the number of nuclei and growth rate. There is no profile which can be declared as optimum for all systems because nucleation conditions are also depending on several other factors like hydrodynamics. [1]

2.1.3 Seeded Crystallization

Seeding is a further method of realizing, stabilizing and controlling crystallization. It is mostly combined with other crystallization methods like cooling. Means seeding the crystal growth can be regulated, spontaneous nucleation is inhibited and the growth of crystals can be regulated by adding seeding crystals to the solution. [11] If seeds are added to the solution during cooling, the developed supersaturation is consumed by the added crystals and secondary nucleation can be avoided due to low supersaturation. This process depends on the quantity of seeds added, which has to be found out via trial and error and can only be accomplished through slow cooling. Depending on the amount of seeds added, the crystal size distribution varies. [16] Advantages of seeding are a narrow particle size distribution and a reduced amount of fine particles. [11]

Influencing variables for seeding: [17]

- Particle size distribution of seeding crystals
- Mass of seeding crystals
- Growth rate of seeding crystals
- Morphology of seeding crystals
- Purity of seeding crystals
- Treatment and storage of seeding crystals
- Temperature of seeding crystals
- State of crystallization unit during seeding
- Place of addition

2.1.4 Ultrasound Crystallization

Seeding is a popular technique to control the nucleation of crystals but for some applications in the pharmaceutical field, seeding is not an option due to high standards concerning the purity of the product and because it can cause additional regularity efforts. Therefore ultrasound is an alternative option to nucleate at low supersaturation and to have an optimized particle size distribution. Ultrasound crystallization is used to get uniform particles with a narrow particle size distribution even though its mechanism is not completely clear. [12]

Nucleation is presumably promoted by the higher pressure and temperature or possibly the cavitation bubble-gas surface itself enables nucleation. The proceeding mechanism, nucleation, occurs when cavitation bubbles collapse; the critical nuclei radius is reduced and nucleation can be initiated. These bubbles consist of vapor and dissolved gas and are able to grow fast when local pressure is below the vapor pressure of the liquid. Ultrasound could also cause nucleation due to the fact that when the solvent evaporates into the cavitation bubble, local cooling and superstation occurs. Another possibility, as always when crystallizing, is that nucleation takes place due to impurities in form of particles in the liquid. Recent studies believe that the nucleation due to ultrasound could also be due to the modification of the wetting angle. [18] Wetting angles are contact angles greater than zero between the adhesive and surface promoting nucleation. A smaller wetting angle leads to a lower nucleation barrier. [19], [20]

In [12] the influences on the crystallization by ultrasound were tested. Results showed that solvent properties such as vapor pressure and surface tension are not influenced by ultrasound. Mainly the particle size distribution is influenced by ultrasonic parameters like power output and frequency and in the supersaturation ratio at which the ultrasound is applied. [12] Power output and frequency are both adjustable parameters on the ultrasound generator. [18]

To realize crystallization, a certain amount of energy has to be induced into the system. For the crystallization with ultrasound, a certain amount of irradiation is needed, otherwise the crystals can withstand nucleation. In summary, the experiments have shown the following results: [12], [21]

- Average crystal size decreases with increasing insonation time
- Single-burst ultrasound creates well shaped but large crystals
- Continuous insonation results in small crystals
- Pulsed ultrasound has the narrowest particle size distribution
- Generally crystals are smaller and the particle size is smaller through ultrasound
- Local cooling and agitation have only a slight impact on the nuclei formation

- Agglomeration is inhibited by ultrasound
- Ultrasound leads to modification of polymorphism. According to [3] a substance capable of crystallizing into different, but chemically identical crystalline forms is said to exhibit polymorphism. Different polymorphs of a given substance are chemically identical but will exhibit different physical properties
- Smaller particles are obtained through longer periods of radiation
- There are certain areas where radiation inhibits crystallization

The results listed above do not necessarily apply for all substances. These effects may vary depending on the substance, ultrasound conditions and pre-treatment of the substance. [21] In this thesis ultrasound was applied in an ultrasound basin.

2.1.5 Aggregation/Agglomeration

Aggregation/agglomeration occurs when two particles collide with each other and create a new and larger particle. This process is part of the secondary nucleation and happens regardless of the supersaturation. The difference between agglomeration and aggregation is that the former occurs in a supersaturated system because bridges can be formed between the particles due to particles dissolving out of the solution. Aggregation on the other hand is the cohesion of particles solely due to Van der Waals forces. [22]

Agglomeration is a complicated process that depends on many parameters. Some of the influencing parameters for agglomeration are [11]:

- Half-life of the agglomeration
- Particle density
- Supersaturation
- Stir intensity
- Particle size

Small, fine particles are more likely to aggregate than larger ones. The superstation and stir intensity increase the development of agglomerations. Due to high stir intensities, the particles are smaller and more likely to agglomerate. In general, particle collision will lead to smaller particles, increasing the probability of aggregation. [11]

2.1.6 Industrial Crystallization Process

Crystallization is used in a large number of fields such as the purification or separation of crystals and can be run as a batch or a continuous process. It is often used for products of a high purity. The size and characteristics of the crystals determine its flow ability and bulk density for further procedures in the down process. [23] Due to its complexity and dynamic nature, crystallization is difficult to control. It is highly non-linear along with consisting of a liquid and solid phase. On the one hand the optimal operation of a crystallization unit with constant growth rates is important for the overall process; on the other hand a compromise has to be found concerning the economic efficiency. [15] [1] The process can either be run with long retention times near the saturation zone to produce small crystals of a high purity or to have fast growing crystals with liquid enclosures and dendritic growth. [1]

As mentioned above it can be run as a batch or as a continuous process. Advantages of running a batch crystallization are: [11]

- Producing smaller amounts
- Product changes are easily possible
- Higher levels of purity possible – quality control

Advantages of running a continuous process are that the process parameters are easier to adjust and crystals can be produced at a larger scale. It is also easier to trim the process to optimal conditions and it has less down time. Disadvantages are that the system is not as flexible for adjustment, takes longer to reach a steady state, can easily be thrown out of balance and lead to incrustation problems. [23], [13]

To quantify the industrial process of crystallization, crystal size, suspension density and liquid concentration are the key parameters. During the process the liquid phase should be monitored to stay inside the metastable zone and prevent spontaneous nucleation. If the crystallization is constantly monitored, the crystal growth can be optimized. Additionally the suspension density and the crystals themselves also have to be monitored to get information on the progress of the crystallization. There are many techniques available for measuring and monitoring parameters, such as the conductivity, density, turbidity, ultrasonic, in-line microscopy, laser backscattering and the laser diffraction measurement. [24]

Optimal control of the particles and correct information has to be collected and measured under the same conditions as in the process vessel itself, referring to temperature and liquid characteristic to prevent further changes to the crystals. The standard measurement method is laser diffraction which can only measure diluted suspensions, expect for the Focused Beam Reflectance Method (FBRM) which can operate in dense suspensions. Disadvantages of this measurement technique are the errors caused by particle shadowing, and particle masking. Results are localized and not representable for the whole bulk. Ultrasonic measuring devices are also used for online measuring. However, these instruments have to

be extensively calibrated for a particular system and are dependent on the particle size distribution. [25]

In this thesis continuous crystallization is accomplished in a long tube with cooling of the solution to achieve a narrow crystal size distribution and an even growth of crystals. Process parameters are taken through samples which cannot be analyzed by online measurement. After running the process, the samples are analyzed by microscopy (Chapter 2.3.3), QICPIC (Chapter 2.3.1) or high speed camera (chapter 2.3.4).

2.1.6.1 Industrial Crystallizers

Standard continuous crystallization procedures are the Mixed Suspension Mixed Product Removal (MSMPR) Forced Circulation (FC) crystallizer, the Draft Tube Baffle (DTB) and Oslo crystallizer. [23]

FC Crystallizer

Figure 5 shows a scheme of a FC crystallizer in form of vacuum cooled crystallization. These are classified as Mixed Suspension, Mixed Product Removal (MSMPR) crystallizers.

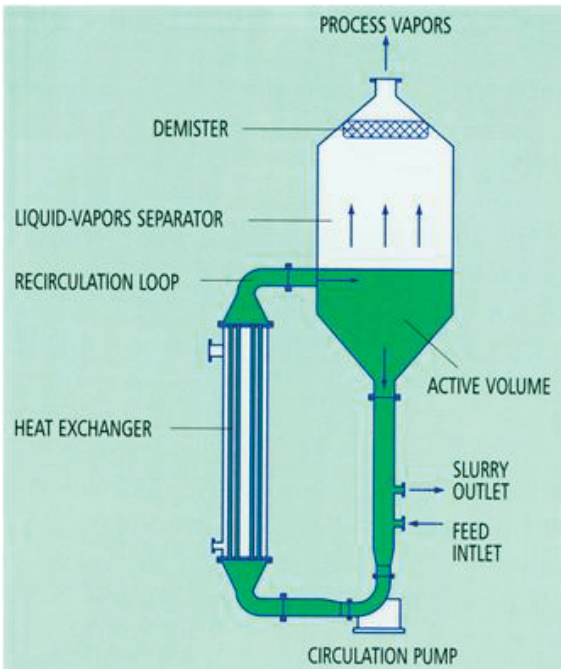

Figure 5: Forced Circulation Crystallizer (FC) [26]

The feed is mixed with the suspension in the tube and pumped into the vapor/liquid separator. In front of the mixing area, the feed has a higher mass fraction and is hotter than the suspension. In the separator the mixture is heated to the boiling point and due to evaporation the temperature drops and a supersaturated state is reached. As a result the crystals are able to grow and a steady state is regained. The level of supersaturation

generated can be controlled through circulation. The nucleation is also controlled and spontaneous nucleation is avoided by recirculation. The vaporized solvent is condensed and recirculated. [26], [27]

Table 1: Advantages and disadvantages of a FC crystallizer [28], [26], [29]

Advantages	Disadvantages
• Most simple construction • Slurry is perfectly mixed • Large range of sizes possible • Through circulation the particles do not accumulate on the walls of the vessel • Simple operation	• Not suitable for the production of large crystals • Crystal size is difficult to control • Fines destruction not possible • Product classification not possible

DTB Crystallizer

In Figure 15 the scheme of a DTB crystallizer is visible in Figure 6.

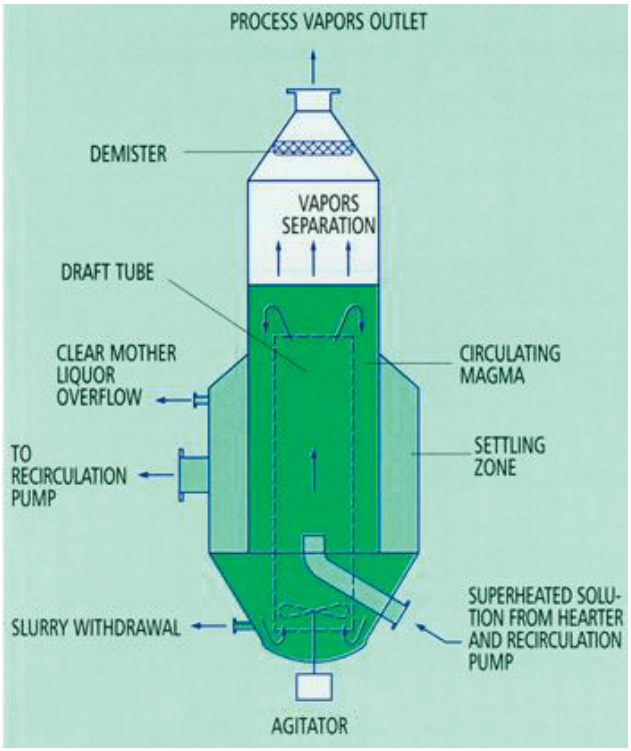

Figure 6: DTB crystallizer [26]

The unit is separated into a draft tube and a settling area. Due to stirring the mixture is pushed up through the draft tube and into the settling area. In the settling area the exhaust solution slowly moves upwards, allowing large crystals to settle and recirculate. Therefore

only the fines are extracted and are destroyed by heating to create additional supersaturation. The DTB crystallizer has two discharge points. One of them contains the slurry with the product crystals and the other for the mother liquor with a small amount of fines. [26], [30],

Table 2: Advantages and Disadvantages of a DTB crystallizer [28], [26], [29]

Advantages	Disadvantages
• For the production of coarse crystals • Less nuclei are created and therefore larger crystals result • It has distinct growth zones and kinetic parameters can easily be determined. • Good operation control can be achieved • For excessive nucleation • Maximal crystal recovery due to recirculation • More efficient than FC crystallizers • Economic because fines are recyclable • Long operation cycles	• Frequent flushing necessary to prevent deposits on the vessel walls • Problems handling high density slurry • Higher investment costs

Oslo Crystallizer

The Oslo crystallizer, also known as classified suspension crystallizer in Figure 7 is the oldest design of a crystallizer for the production of large crystals.

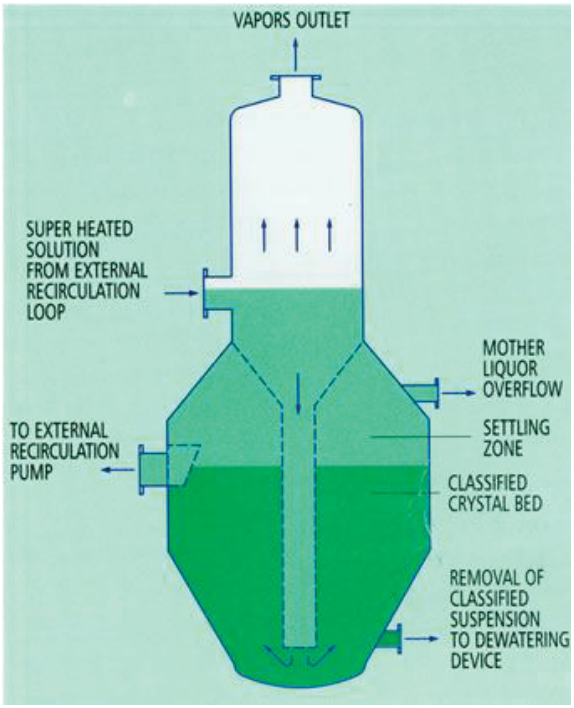

Figure 7: Oslo type crystallizer [26]

Crystallization takes place in the lower part of the unit and the supersaturation is created in the upper part where the solvent is separated and circulated where it is mixed with fresh feed solution. Slightly supersaturated solution from the circulation flows down to the crystal bed through a pipe. Crystals of the desired size are collected at the bottom of the vessel and discharged at regular intervals. [26], [3]

Table 3: Advantages and disadvantages of the Oslo type crystallizer [26], [31]

Advantages	Disadvantages
• Crystal growth in a fluidized bed • Larger crystals can be grown compared to the other systems • Well established design	• Shorter operating cycles than DTB crystallizer • Operation often unpredictable • Accumulation of crystals on wall

As shown in Figure 8, there are several further steps necessary, after the actual crystallization in the unit before the final product crystals can be collected. Figure 8 schematically describes a possible setup for the units required to retrieve the crystals. After the crystallization in the crystallizer, the slurry is pumped into the prethickener or hydrocyclone and then into a centrifuge to separate the suspension from the crystals. For

small crystals it is also possible to use filters instead of the centrifuge. The last step is the drying of the crystals in the drier. Several forms of driers are available. Most commonly used are the fluid bed and flash drier. [26]

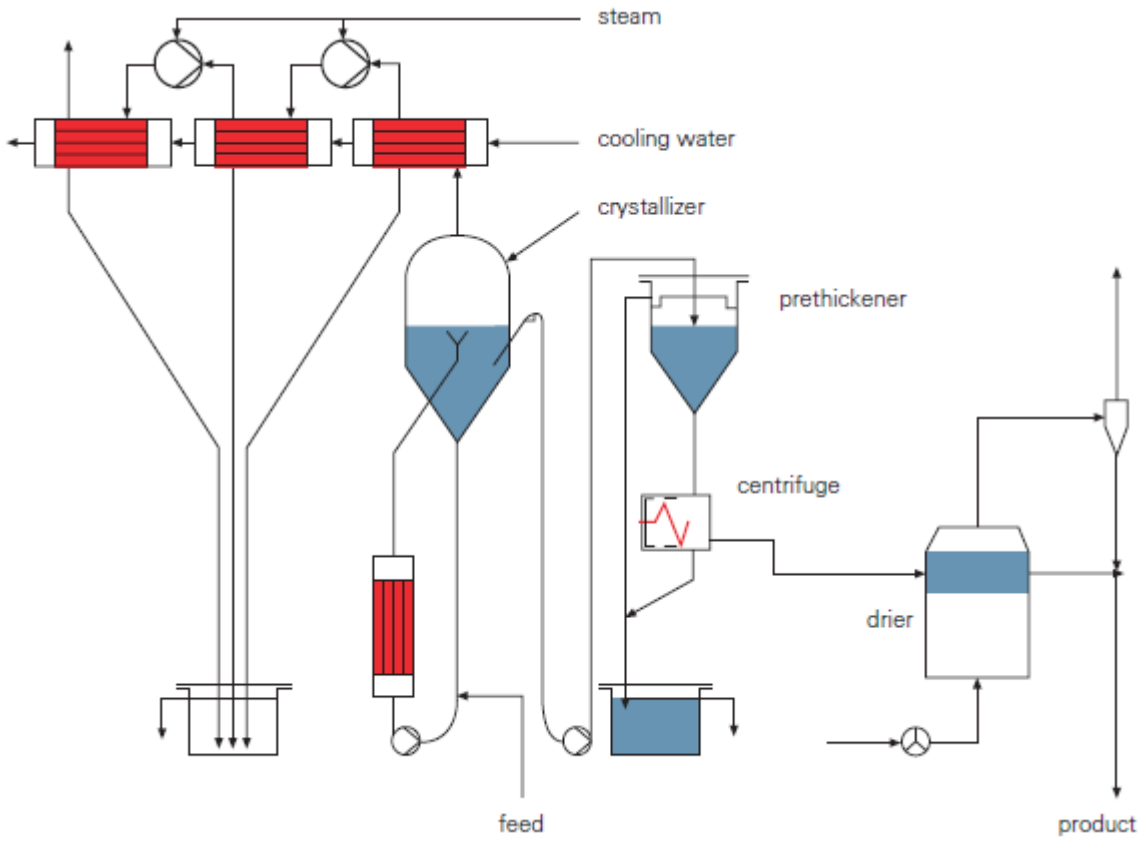

Figure 8: Simplified flow sheet of a complete crystallization plant [32]

2.2 Multiphase Flow – Slug Flow

The crystallization process can be regulated by running the system with slug flow. A slug flow can be established by feeding air bubbles into the process tube and forming an alternating air and liquid flow

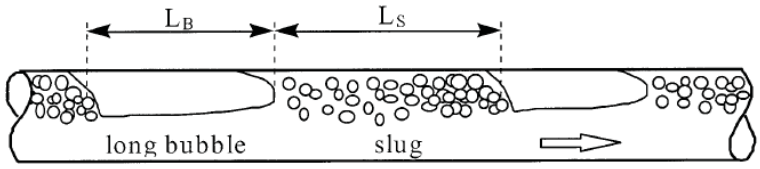

Figure 9: Gas-liquid horizontal slug flow [33]

Advantages of having a slug flow are that all the particles in the tube have the same retention time. Same retention time means that all particles have the same time to grow leading to a narrow particle size distribution. Therefore the growth of the particles is easier to control and to simulate. Slug flow also increases the transverse mass and heat transfer due to particle recirculation in the liquid slug. [34] Multiphase flow in microchannels has not yet been fully understood. Nevertheless different types of two-phase gas-liquid flow can occur. In order to distinguish different types of multiphase flow, these can roughly be divided into [35]:

- Bubbly
- Slug
- Annular
- Stratified flow

At low gas flow rates **bubbly** flow patterns are likely to occur. These bubbles that are distributed within the liquid abd vary in size but will not fill out the whole channel. When the gas flow rates are accelerated, the bubble size increases until they reach almost the same cross-section as the channel. These are the desired air bubbles, referred to as Taylor bubbles or air **slugs**. In this case the term “slug” was used throughout the work. Air slugs are separated by the liquid phase, the so called liquid slugs. In the liquid phase other types of bubbles can also occur additionally. For an **annular flow** pattern the gas flows in form of a gas continuum along with the liquid flow. By increasing the gas flow rate even more **annular** flow rates are created. **Stratified** flow is the complete opposite, occurring when both the gas and liquid flow have a low velocity. Here the two phases are completely separated. Gas stays at the top and the liquid flows at the bottom of the channel. [35] All these types of multiphase flow patterns and derivatives are visible in Figure 10.

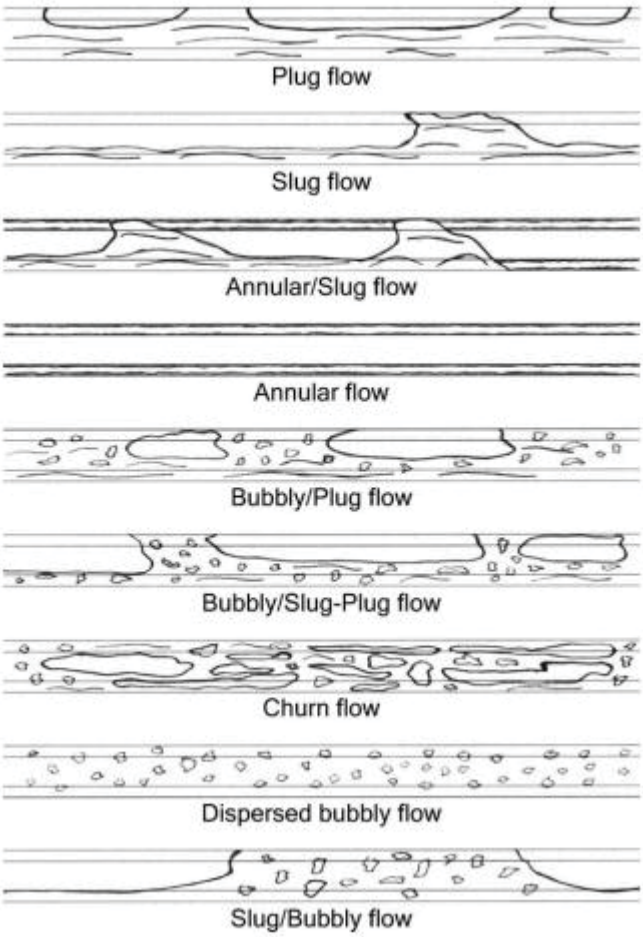

Figure 10: Two-phase flow patterns [36]

All these types of flow patterns are difficult to distinguish. Pure Taylor flow is dominated by surface tension and for the slug flow and slug-annular flows the internal forces play a larger role. Often different types of flow patterns can occur all at once or can change during the flow. For example the surface tension increases in small passageways creating other flow patterns. Taylor flow is characterized by long bubbles separated through a liquid phase, also referred to as liquid slug, from each other and by a liquid film from the wall. More complex are annular flows which develop at higher gas velocities. Advantages of these flow patterns are that they occur naturally and a higher throughput can be realized. [35]

Case studies have been performed on the length and size of the slugs. One of the case studies was carried out in form of simulations. Here the slug flow in small microchannels with T and Y-fittings was analyzed. In comparison to other case studies this one was carried out with curved microchannel whereas other studies have only considered straight channels. Following conclusions were given for this study: [35]

- Gas slug length increases with gas flow velocity
- Slug length increases with curvature ratio
- Increase of flow rates leads to a higher non-uniformity of slugs

A continuous slug flow is very important for the transportation of the seeds. [33] Slug flow can change over the course of the channel. When air slugs are formed they continue to grow in length. Especially the initial slugs can carry on growing until the end of the tube. The reason for the growth is that the fronts of the air slugs travel faster than their tails. Particularly at the entrance of the tube, the formation, growth and decay of slugs is very complicated. [37]

2.3 Analytical Devices

2.3.1 QICPIC and HELOS

QICPIC

One of the used analyzing methods is the QICPIC from the company Sympatec GmbH (System Particle Technik), combing particle size and shape analysis. This measuring device can measure the particle size distribution. As visible in Figure 11, the sample is put into the cone shaped feeder from which the sample is conveyed to the intake.

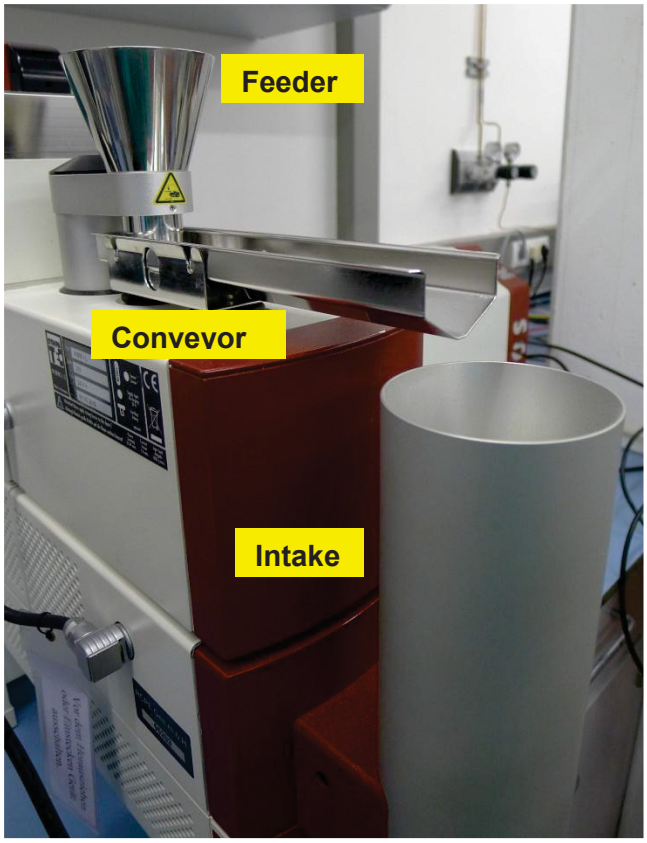

Figure 11: QICPIC measuring device

The sample drops into the intake to the dispersion unit. Here the particles are dispersed and sucked into the machine through the analyzing chamber. While the particles run through the analyzing chamber, 450 pictures per second are taken and analyzed automatically. According to the producer this device can measure particle sizes between 1 µm and 30 mm. This was however treated with a lot of sceptic during the course of the thesis and the microscope was preferably used for analysis. Also taking into account that aggregation, which is a crucial factor, can be better determined with the microscope. Even though the QICPIC measurement device can supply information on the contour of the particle it cannot determine if the particle is an aggregate or a single particle. [38]

HELOS

The Helium Neon Laser Optical System (HELOS) is another method of measuring the particle distribution. For the most part the HELOS measurement is similar to the QICPIC but is equipped with a laser analyzer instead of a photo analyzer. The advantage of a laser diffraction sensor laser is that smaller particles can be measured more accurately but the sampling amount has to be large enough to receive substantive results. [38]

2.3.2 Density and Sound Velocity Meter

Producer of the meter is Anton Paar GmbH and the used density and sound velocity meter is the model DSA 5000M. Figure 12 shows the used meter.

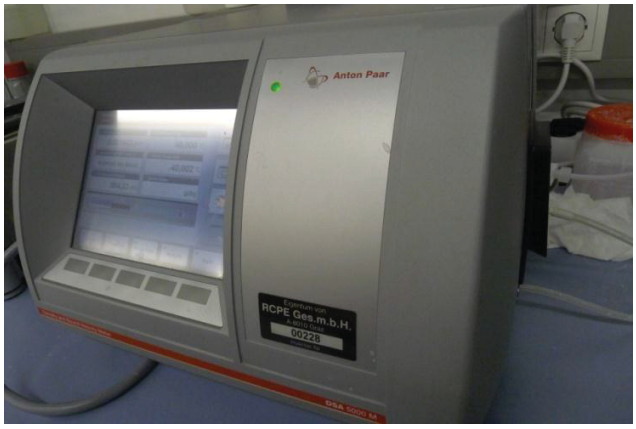

Figure 12: Anton Paar – Density and Sound Velocity Meter

The density measurement was used for the solubility experiments. Generally the usage of this device is simple. The sample is injected into the sampling chamber with a syringe. The sampling chamber is a small u-shaped tube which is automatically vibrated. Depending on the density of the sample its resonance frequency differs. Taking into consideration that the density changes with temperature, the sampling chamber can be heated or cooled to the desired temperature. Samples measured for this thesis were measured at 40°C. One of the problems with this device is that sometimes it is difficult to insert the liquid without creating bubbles and if they reach the analyzing chamber the density cannot be measured correctly. Either bubbles are inserted into the chamber or bubbles build up inside the chamber during the heating period. To prevent false measurement the display will show a warning sign when bubbles are inside the tube and additionally the chamber is shown on the screen so that bubbles can be seen and removed. A picture of the screen is shown in Figure 13. Another difficulty is the cooling of the solution. Often, if the sample is injected at a high temperature the chamber will not cool down to the wanted temperature. To solve this problem the wanted temperature has to be set lower.

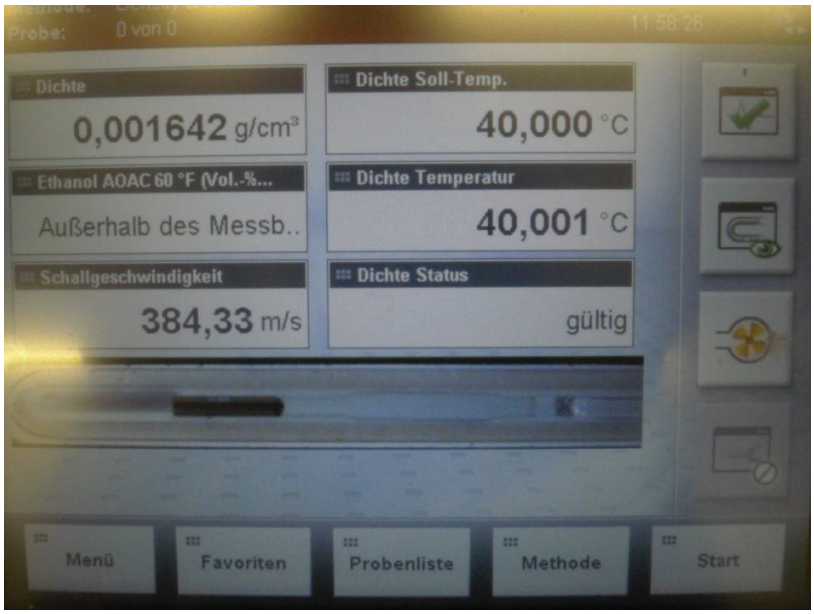

Figure 13: Screen of density and sound velocity meter

2.3.3 Microscope

Most of the samples were analyzed with microscope or additionally looked at with the microscope. For microscoping the sample is dispersed on a small glass plate. Pictures of the sample are saved by a computer which is attached to the microscope. The program used to control the microscope is the leica application suite.

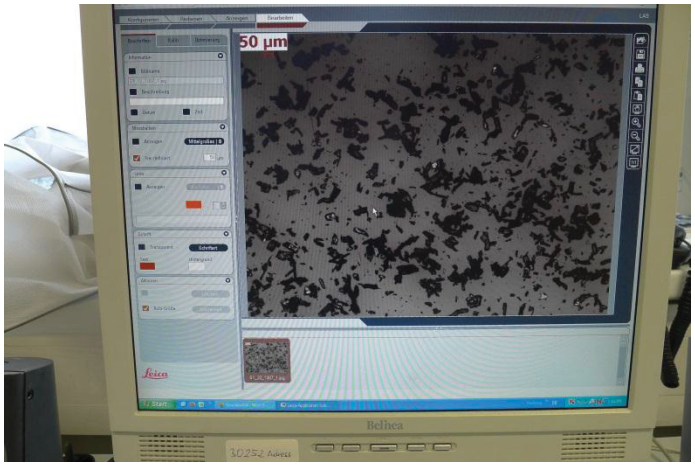

Figure 14: Monitor screen of microscope

The microscope is a microscope from Leica Microsystems type DM4000M. Microscope is a very suitable method for analyzing the seed. Unfortunately only a small portion of the sample can be analyzed. It is impossible to conclude on the basis of one sample the characteristics of all seeds. It is better to use the microscope as an addition to another measuring device.

2.3.4 High Speed Camera

The analysis of the experiments in chapter 3.3.1 was carried out with the high speed camera and some of the crystallization processes. The IDT-M3 high speed camera is equipped with a 12X objective from the company Invitar. The advantages of using the camera are that the process can be viewed in real time and other influencing factors due to the method of sampling can be ruled out.

3 Experimental Procedure

Many different types of experiments were conducted during the thesis. The main experiment is the crystallization which is going to be improved and developed during the course of this thesis. The principle of the continuous crystallization is that a seed suspension containing already formed crystals is mixed with a saturated solution in a tube. Through cooling in various steps along the tube, supersaturation is created and the already existing crystals are able to grow.

For the improvement of the crystallization process, further smaller experiments had to be carried out and analyzed. Chapter 3.1 shows the setup of the crystallization itself and the following chapters describe the smaller experiments and tests. The results of all experiments are listed in chapter 4 and the conclusion and summary can be found in chapter 5 and chapter 6.

3.1 Crystallization in a Tubular Reactor

Figure 15 shows the experimental setup for crystallization at the beginning and the major part of the thesis.

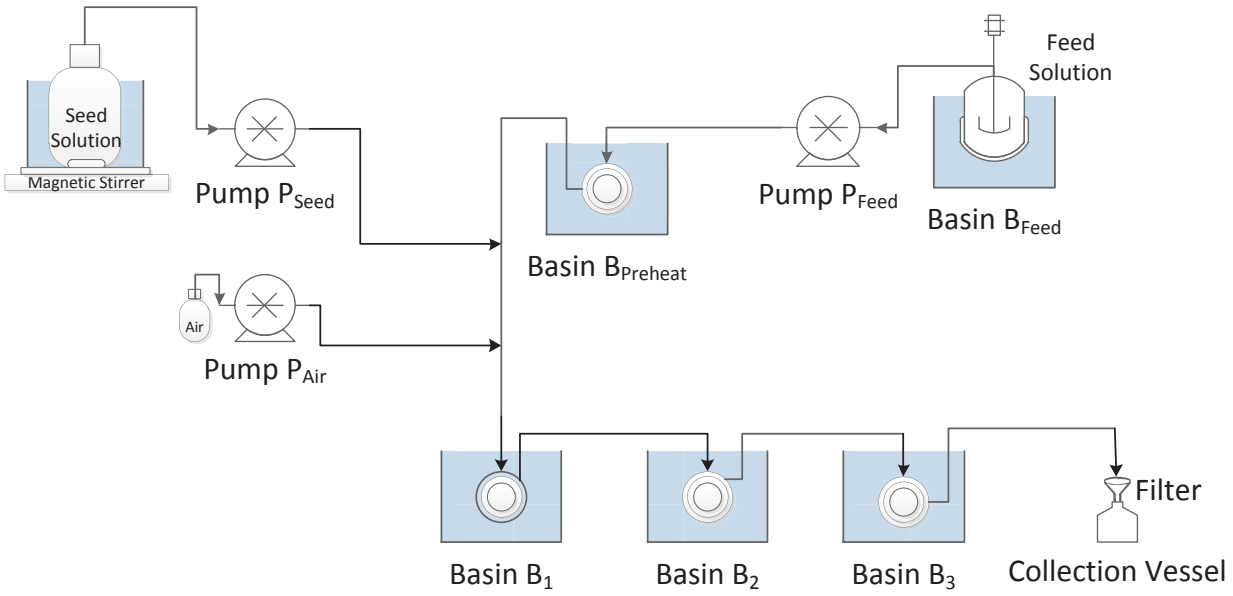

Figure 15: Experimental setup – crystallization

Setup and execution:

Setting up the crystallization takes up a lot of room. All the coils are placed in separate temperature basins. Each coil has 5 meters of tube wrapped around it, resulting in a total length of 15 meters starting from basin B_1. In basin $B_{Preheat}$ only 2 meters of tube are wrapped around the coil. The feed solution is placed in the water basin B_{Feed} and the seed solution is placed in a beaker placed on a magnetic stirrer.

A number of stages explain the process. These include suspension preparation, execution, sampling and analyzing.

1. Suspension preparation: The seed solution is prepared as described later on in chapter 3.2. Less complicated is the preparation of the feed solution for which the ASA and Ethanol (EtOH) is filled into a large piston. A two-pedaled stirrer is attached to the flask and the whole setup is lowered into the water basin B_{Feed}. In this water basin the suspension is heated and stirred until all the particles are dissolved. Once all the particles are totally dissolved, the solution can be used for crystallization.

2. Execution: First of all, the pump P_{Air} is turned on and EtOH is pumped through the pump P_{Seed} and pump P_{Feed} to adjust the pump settings for an even slug flow. Subsequently the seed solution is fed into the coils before the feed solution is turned on. If the feed solution is turned on first, the crystals nucleate in the tube and this can lead to clogging. As soon as the feed is mixed with the seeds and the solution is cooled, the seeds will grow and ideally no new nuclei are formed.

3. Sampling: Sampling was performed as shown in Figure 16 .

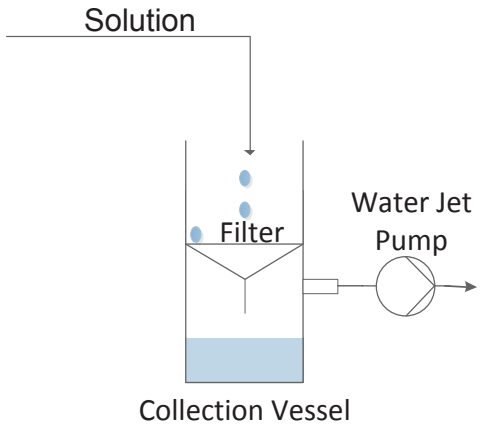

Figure 16: Sampling procedure

After turning on the water jet pump the filter was rinsed with EtOH and then the filter paper was placed on it and secured. The wanted solution was then dripped evenly onto the filter for a certain amount of time. In most cases sampling took between one or two minutes. Then the filter paper was removed and placed in a disposable sample dish. This was put into the desiccator and put under vacuum for drying. Thereafter the samples were scraped carefully off the paper filter into a small closed glass jar. In this jar the sample is kept until taken for analyzing.

4. Analysis: The analysis was carried out with either QICPIC measuring device or microscope. These analyzing devices are described in chapter 2.3.

3.2 Seed Preparation

Seed experiments were conducted to control and regulate the seeds that are used for the crystallization process. It may be possible that the purchased ASA has a large particle size distribution. If this ASA is used for crystallization agglomeration and nucleation is likely to occur. Keeping this in mind, the seeds should always have the same narrow particle size distribution. In order to receive optimal crystals with crystallization the seeds used should not be too large and have no aggregates. Large particles will grow in the tubes and cause blockages. Aggregates are not wanted as an end product and should therefore be avoided from the beginning. It can only be determined if aggregates are build up in the tube if it can be ruled out that aggregates are going in.

3.2.1 Setup 1

This experiment was conducted to find out what can be done to achieve an optimal seed size without aggregates. An improved method of producing the seeds was developed by these experiments.

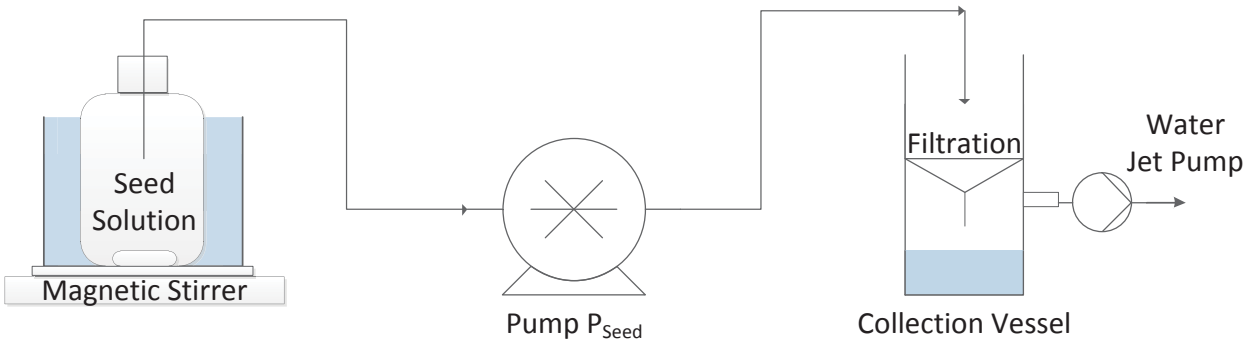

Figure 17: Experimental setup 1 – seed experiments

Setup and execution

Figure 17 shows the experimental setup for the seed experiments including sampling. This setup was used for the most part of this thesis and later optimized to the setup described as setup 2 and setup 3. The experiment can easily be described in a number of stages. These include suspension preparation, crystal dissolving, cooling, tempering, temperature cycles and sampling.

1. Suspension Preparation: For the seed solution a certain amount of ASA and EtOH are mixed together in the desired ratio. At the beginning of the thesis the used ratio was 1 ASA : 2 EtOH. During the thesis this ratio was changed first to 0.8 ASA : 2 EtOH and then finally to 0.6 ASA : 2 EtOH due to blockage in the tube. The high amount of seed concentration and their growth in the tube caused them to block the tube. In this

experiment a bottle was filled according to the wanted ratio with ASA and EtOH. Enough solution was added to fill the bottle up to the neck.

2. Crystal Dissolving: The created seed solution in the bottle is put in a beaker and placed on the magnetic stirrer. A magnet stir bar is put into the bottle with a stir speed of 200 ppm or 300 ppm depending on the bar size and experiment. The beaker is filled with 33°C water up to the 1500 ml mark and the water is changed a number of times until the crystals are totally dissolved. This takes about 10 minutes.

3. Cooling: When all the seed are dissolved the solution is cooled. A number of these experiments were carried out with cooling temperatures ranging from 0°C (Ice) to 20°C. Cooling is done by exchanging the 33°C water with water that has the appropriate cooling temperature. The water is filled up to the 1500 ml mark.

4. Tempering: The cooled solution is reheated to a temperature of 25°C. This is achieved by exchanging the cooling water for water that has 25°C and filling the beaker to the 1500 ml mark. The water has to be exchanged a few times until the solution has reached the wanted 25°C.

5. Temperature Cycles: Temperature cycles were carried out with the expectation of creating seeds with a smaller particle size distribution. When the solution has a constant temperature of 25°C the sample is warmed up for a short period of time so that the smaller crystals dissolve. However this has to be done carefully to prevent total dissolving of the particles. Then the solution is cooled with 25°C water and the temperature cycle is finished. Depending on the experiment this temperature cycle can be undertaken a number of times. Temperature cycles should have as a result, larger particles and a smaller particle size distribution because during the cooling the dissolved particles should not nucleate but cause the existing particles to grow. Often the large particles will not grow with this method and aggregates build up instead.

6. Sampling: Sampling was carried out as described in chapter 3.1.

7. Analysis: The analysis was carried out with either QICPIC measuring device or microscope. These analyzing devices are described in chapter 2.3.

3.2.2 Setup 2

The results from the experiments shown in setup 1 were neither satisfying nor reproducible. To eliminate some of the problems the experimental setup was changed. Setup 2 was installed primarily due to room temperature changes which were a big issue in setup 1. The improved setup is visible in Figure 18.

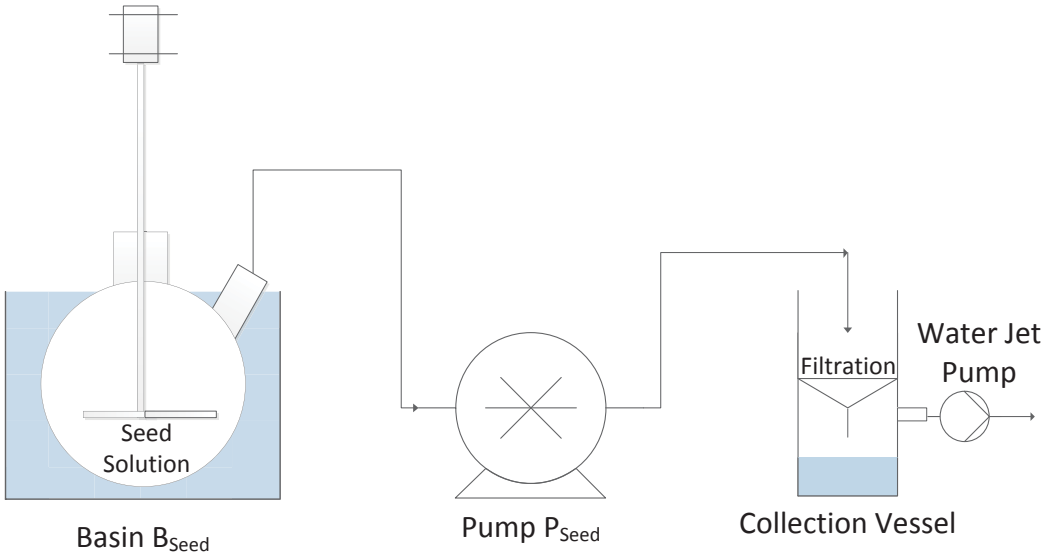

Figure 18: Experimental setup 2 – seed experiments

Setup and execution

For this setup the flask is placed in a temperature regulated water basin B_{Seed} and a sealed precision glass (KPG®) teflon (PTFE) two-paddled stirrer is placed in the sample. Due to difficulties with the correct placement of the stirrer, it is put into the 1000 ml empty three necked flask, the solution is mixed in the usual bottle as described in setup 1, the seeds are dissolved with the magnetic stirrer and then poured into the flask through a preheated funnel. It was decided, based on the results that a higher mass fraction of seed solution is to be used because more even crystals with less fines and aggregates are produced. As a consequence, a new method was tried out in which the seeds are produced at high concentrations and then diluted with EtOH. For the generation of the seeds a concentration of 1 ASA : 2 EtOH which was then diluted with a certain amount of EtOH was used. The amount of ETOH that was added was the amount to reach the total concentration of 0.6 ASA : 2 EtOH as used in Setup 2. Dilution with EtOH was carried out at varying speeds.

3.2.3 Setup 3

New seed experiments were undertaken with seeds using an ultrasound basin due to the fact that the results from the other experiments were not satisfying. Expectations for the ultrasound experiments were to reach smaller particle sizes than in the other experiments.

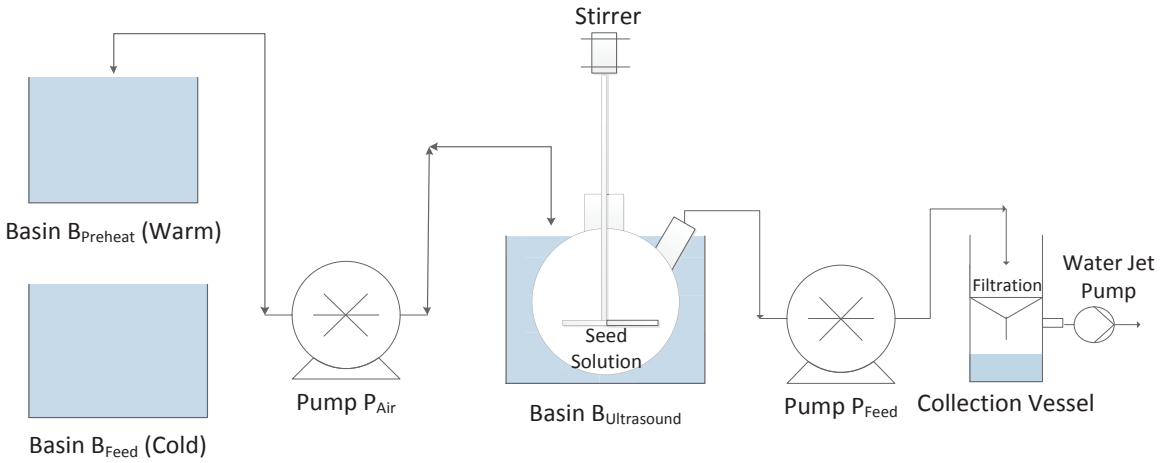

Figure 19: Experimental setup 3 – seed experiments

Setup and execution

As shown in the scheme, the flask is placed in the basin $B_{Ultrasound}$ and stirred with a KPG® PTFE two-paddled stirrer. This basin is not temperature regulated, so the water temperature is controlled by circulating water from basin B_{Feed} and basin $B_{Preheat}$. First the water in the basin is heated, depending on the experiment type and then cooled. The seed solution is filled into a 500 ml flask and placed in $B_{Ultrasound}$. Through circulation of heated water the seeds are dissolved and then cooled with cool water from B_{Feed}. Ultrasound was turned on and off at differing intervals for each experiment to see how it influences the size of the particles after and before nucleation.

3.3 Solubility Measurements – Solubility Curve

Solubility experiments were conducted to determine the right temperatures in the water basins for crystallization. For the determination of the solubility, two types of experiments had to be conducted. One experiment was executed in order to determine the calibration curve with already known concentrations and the other to measure the solubility of ASA/EtOH solutions at varying temperatures with unknown concentrations. Based on the calibration curve the concentrations of the solutions can be determined.

Calibration Curve

These experiments were carried out to gather information on the density of various samples of EtOH and ASA at different concentrations. A calibration curve was finally established using the results of the various tests as described.

Setup and execution

The wanted concentrations are mixed into 80 ml bottles. These are put into a 200 ml beaker filled with 40°C water to dissolve the particles. As soon as the crystals are dissolved the solution is injected into the density analyzing device as described in chapter 2.3.2.

Density Curve

The second set of experiments was carried out for the determination of the density of a supersaturated solution at varying temperatures. For this experiment the concentration of the solution was unknown and enough ASA was added to the EtOH to create supersaturation. The setup of the experiment is visible in Figure 20. Two samples can be tested simultaneously.

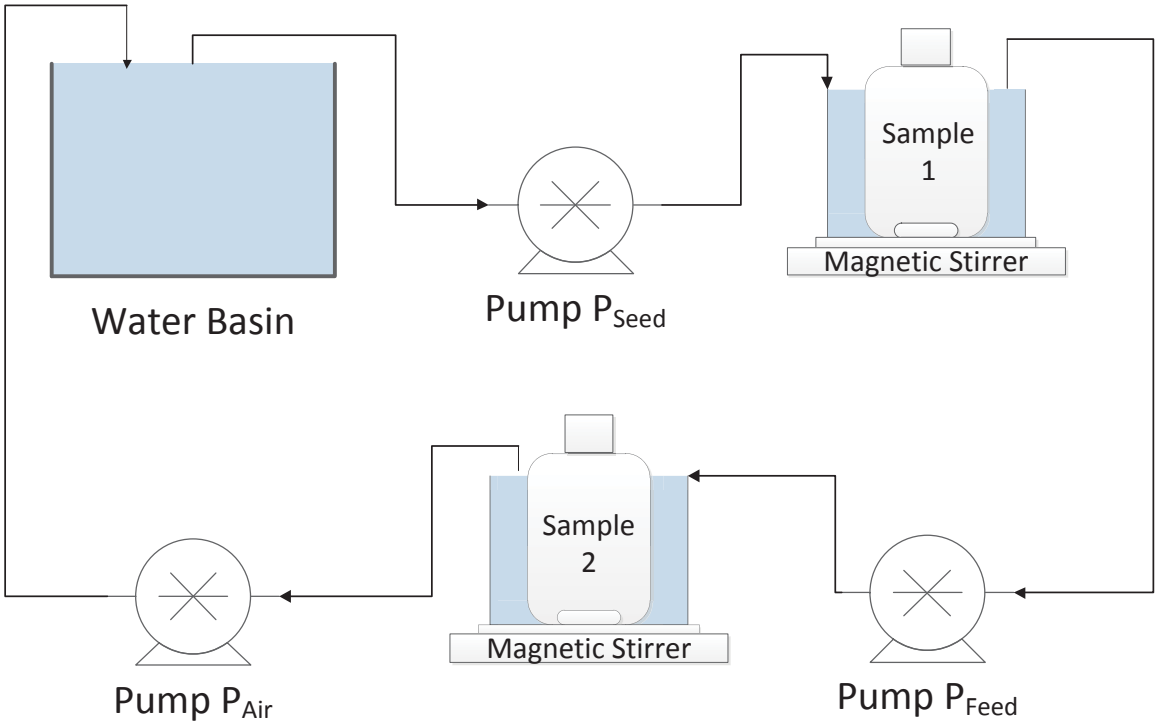

Figure 20: Experimental setup for the solubility experiments

Setup and execution:

For this experiment two 80 ml bottles were filled with EtOH and enough ASA to have a supersaturated solution. A small magnetic stir bar was placed in each bottle and but into a 200 ml beaker which was placed on a magnetic stirrer. The stirrers were turned on and the bars rotated as fast as possible to dissolve all possible ASA. The temperature of the water basin was regulated at a certain temperature and the pumps turned on to circulate the water. The water was circulated in order to ensure even temperatures in the water beakers. For half an hour the solution was stirred at the same water temperature and then the stir bars were turned off to let the undissolved particles settle. During this procedure the measurement device was adjusted to 40°C and the syringe for taking the sample was warmed up by holding it in the hand. After letting the solution settle for ten minutes a sample was taken with a syringe and injected into the measuring device. In the measurement device the sample was heated up to 40°C and the density was automatically measured. Each density was noted for subsequent analysis. In Figure 21 the experimental setup of the experiment is visible. The pumps and water basin are marked in yellow.

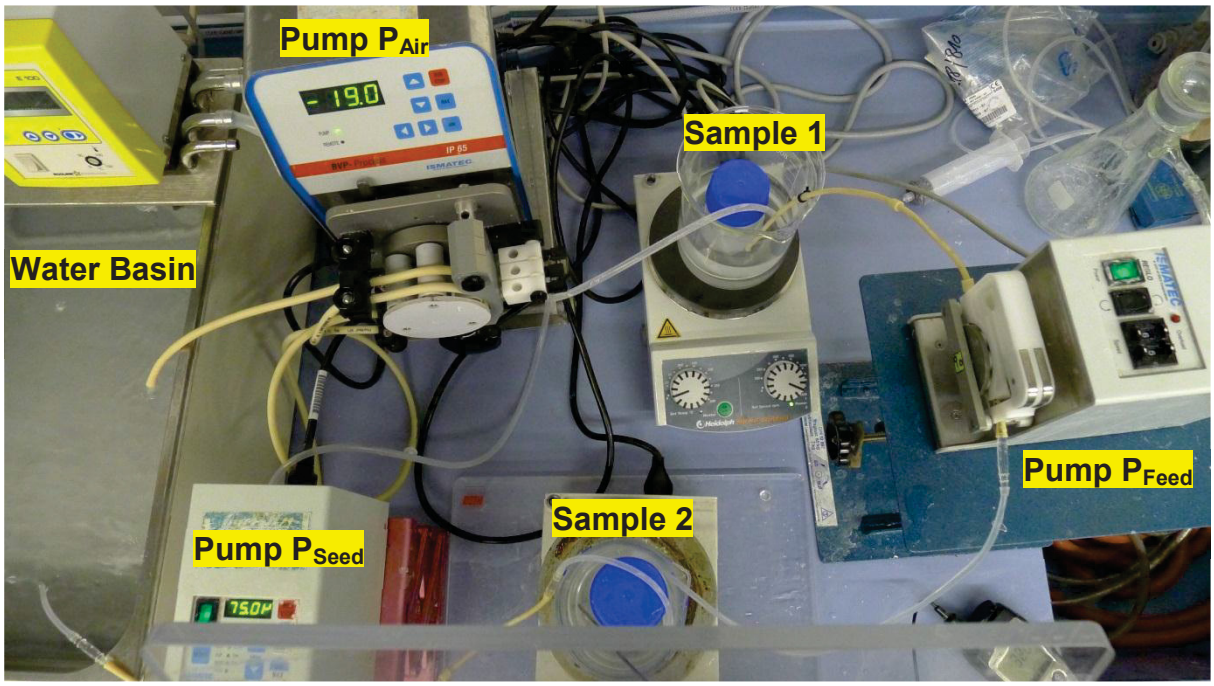

Figure 21: Experimental setup – solubility experiments

One of the problems during this experiment was that a number of times it was not possible to draw a sample without bubbles; especially with samples of high concentrations which had to be dissolved at high temperatures. Another issue was that the used bottles were so small that it was not possible to place a magnetic stirrer into them. Dissolving of the particles takes much longer if the solution is not stirred continuously especially at higher temperatures. To reduce the dissolution time the sample was shaken occasionally. A further problem was that the samples taken at high temperatures, (above 37 °C) started to crystallize immediately when drawn into the syringe. Particles should not be injected into the analyzing device. They influence the results negatively. Therefore the syringe was heated up before the sample was taken and then shortly heated again with the sample to ensure that no crystallization of the sample occurs. Opening of the bottle also leads to an error because some of the EtOH evaporates. Depending on the temperature of the solution more or less EOTH will be released. Other difficulties are device related and are mentioned in chapter 2.3.2 along with the description and function. In addition to the experiments for the solubility curve, it was difficult to keep the water baths at the same temperature at all times. A temperature change of 1°C might have taken place at some point during the sampling. For taking the temperature the thermometer was placed in the water bath and was left there for the entire experiment to keep control of the temperature. When changing the thermometer's position in the water bath the temperature also changed, displaying another error. Bearing this in mind, the thermometer was kept as close to the wall of the bottle as possible because the temperature of the solution in the bottle is the wanted temperature. This error could be eliminated by measuring the temperature inside the bottle instead but for a various number of reasons it was not possible to organize the necessary equipment.

3.3.1 High Speed Camera Analysis

Video analysis was carried out to observe the crystals directly during their growth. Presumably the crystals undergo a change with the sampling techniques used and therefore it is important to have a direct view of the crystals in the tube. The setup for the observation is shown in Figure 22.

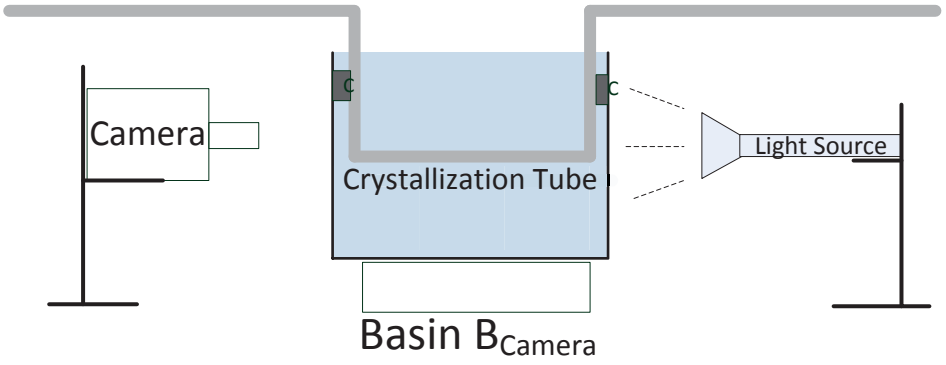

Figure 22: Experimental setup – video analysis

Setup and execution

The setup is quite simple. Crystals flow through the crystallization tube which is attached to the wall inside of a small basin B_{Camera} filled with water. The basin is made of transparent plastic. On one side of the basin the camera is installed and on the other the light source. The camera is connected a computer in order to monitor the crystallization online during the experiment. It is also possible to take video and picture sequences of the process.

3.3.2 Basin Temperature Experiments

Basin temperature experiments were carried out to determine the correct temperatures for the basin B_{Feed} and basin B_1. They were carried out because the temperatures, according to the model were too high. High temperatures in the basins caused the seeds to dissolve after being mixed with the feed solution.

Mass Increase/Decrease Determination

An experiment was carried out in which the mass difference between the seed input and output after basin B_1 was determined. Following figures (Figure 23 and Figure 24) show schematically the setup of this experiment.

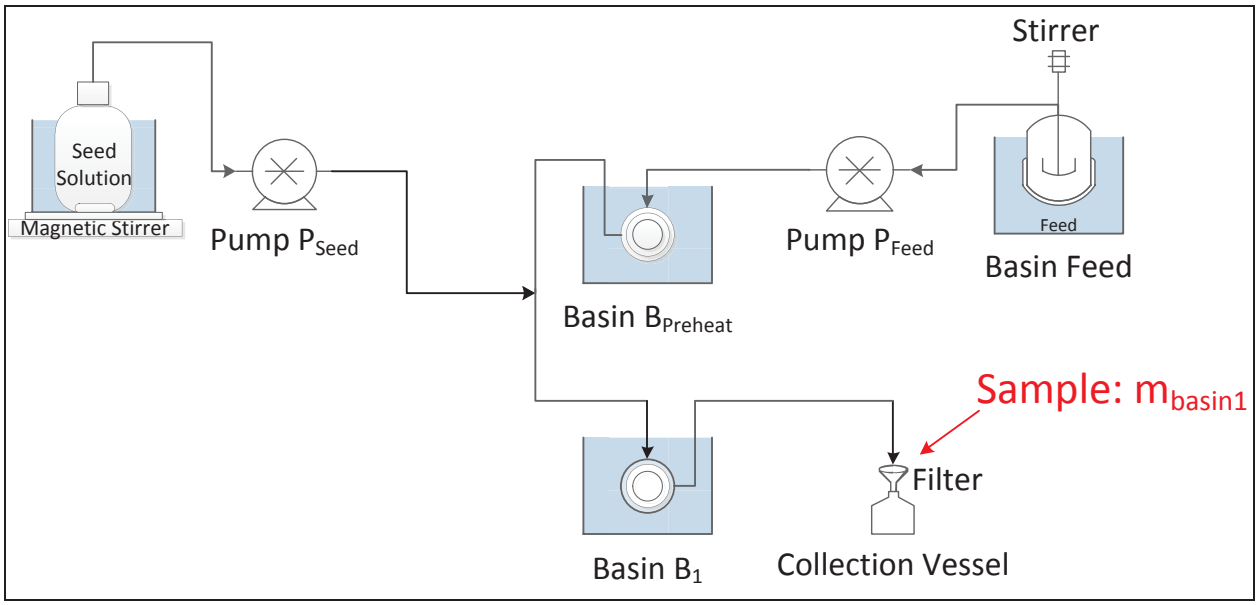

Figure 23: Experimental setup 1 – sampling mass flow in basin B_1

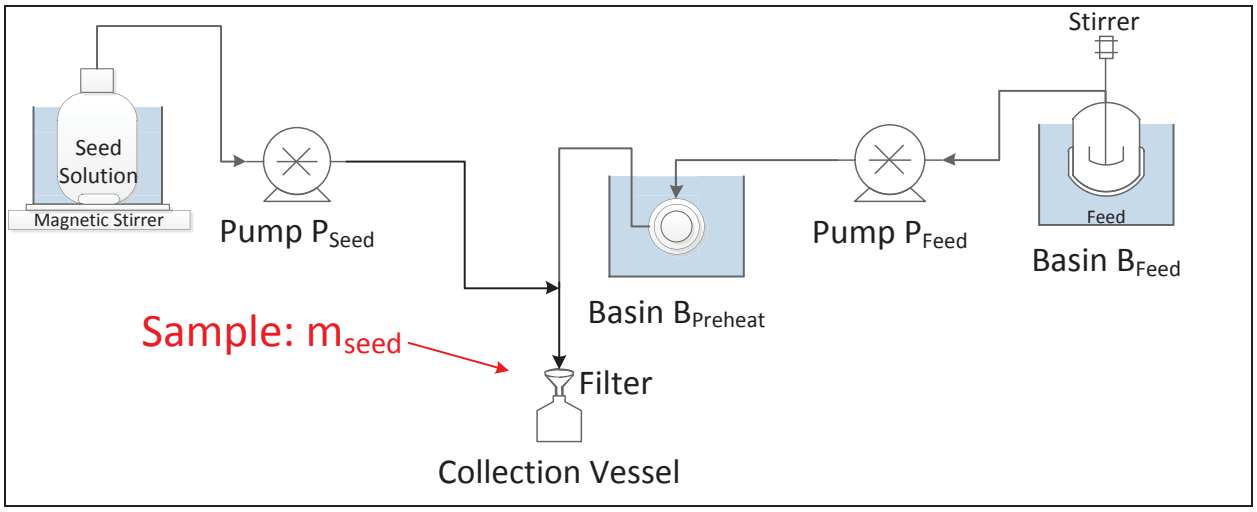

Figure 24: Experimental setup 2 – sampling mass flow in basin B_1

Setup and execution:

The setup taken was the same as for the crystallization (chapter 3.1) but a few changes were made. Only two basins were used and the pump P_{Air} was branched off, leaving only pump P_{Seed} and pump P_{Feed}. Sample m_{Basin1} was taken as shown in Figure 23 after basin B_1. For the experiment the seed and feed were fed and mixed as usual for the crystallization and run through basin B_1. The experiment was run without slug flow. Sample m_{Seed} was taken before basin B_1 as demonstrated in Figure 24. The setup was the same as for sampling m_{Basin1} except that the sample was taken before basin B_1. For running the experiment the feed and seed solution were fed into the tube, mixed and either sampled immediately or run through basin B_1.

Visual Mass Increase/Decrease Monitoring

To confirm the results of the prior experiment shown above, the seeds dissolution was additionally analyzed with the high speed camera. With the setup as shown in Figure 25 the ideal temperatures were determined.

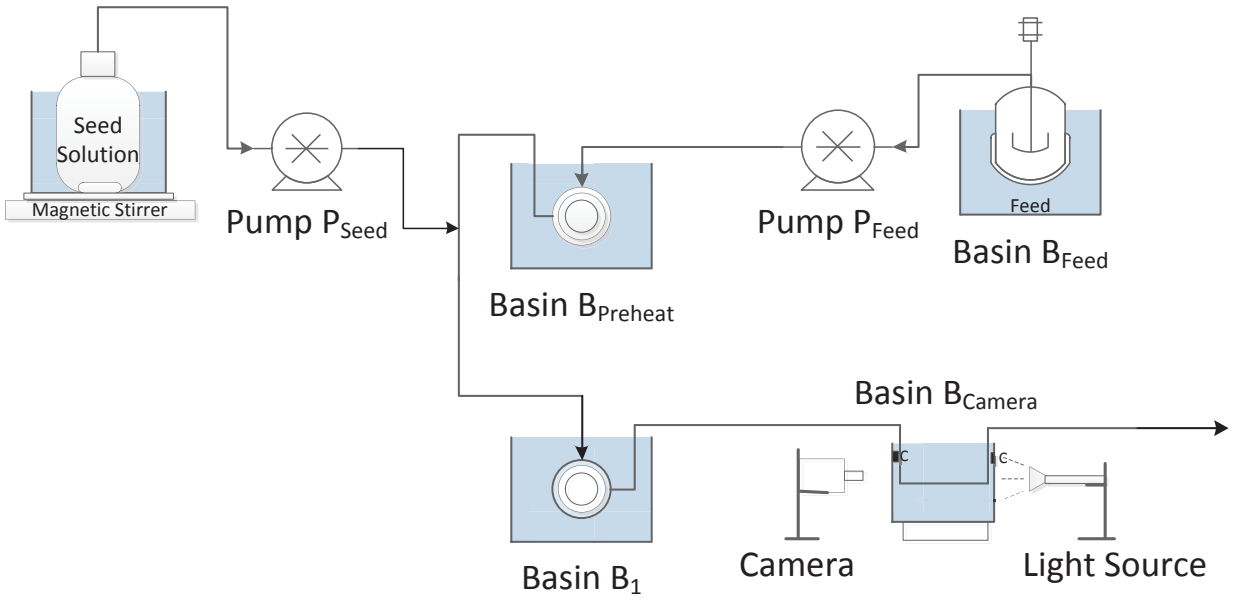

Figure 25: Setup basin temperature experiments – video camera

Setup and execution:

For this experiment the same setup as for the setup in Figure 23 and Figure 24was taken, except that a sample was drawn with pipette instead of surveying it with the high speed camera. After basin B_1 the camera was installed as previously shown in Figure 22. Execution was quite simple. As usual first of all the flow rates of the pumps had to be regulated. They were regulated to 6 ml/min for the pump seed and 25 ml/min for the other. Then feed and seed solution were fed into the tubes, mixed together and pumped through basin B_1 and basin B_{camera}. As the solution went through the tube it was analyzed in real time. The temperature in basin B_1 was changed according to basin B_{Feed}. Its temperature was calculated using the following formula which calculates the temperature of the slurry after mixing, assuming equal heat capacities.

$$T_{B1} = T_{seed} * \frac{V_{seed}}{V_{seed}+V_{sol}} + T_{sol} * \frac{V_{sol}}{V_{sol}+V_{seed}} = 25 * \frac{6}{6+35} + 35 = \mathbf{33,1} \quad (6)$$

T_{B1}… Temperature of basin B_1 [°C]

T_{sol}… Temperature of the feed solution [°C]

T_{seed}… Temperature of seed solution [°C]

V_{seed}… Volume flow of seed solution [ml/min]

V_{sol}… Volume flow of feed solution [ml/min]

As shown above the high speed camera was installed after basin B_1. The crystallization process was run as usual but with varying temperatures in the basins. With the camera it was possible to determine whether the seeds had dissolved up to that point.

3.4 Sampling Analysis

There are many critical factors when taking a sample. Some of these are:

- Transportation
- Room temperature
- Possible aggregation on filter paper
- Scraping off filter paper

As the seeds are transported along the tube into the sampling device the surrounding temperature change possibly leads to a change in particle size or aggregation.

For all these reasons the sampling procedure was tested. Two different types of tests were performed. Testing with high speed camera and testing of the sample with pipette.

Sampling Analysis with High Speed Camera

Testing with the high speed camera was done in front of and after the pump P_{Seed}. This was carried out to see if the structure of the seeds changes due to compression of the tube in the pump. The setup was very simple. The camera set up as shown in chapter 3.3.1 in front of the pump, solution was pumped through the tube and pictures of the particles were taken. Afterwards the camera was set up after the pump and the seed solution was pumped through again and pictures were taken.

Sampling Analysis with Pipette

By pipetting the sample instead of pumping it into the filter, the influence of the pump on the sample was tested. For the analysis a sample was taken with the pump and straight afterwards with the pipette and dripped into the filter.

3.5 Slug Flow Experiments

The slug flow also had to be analyzed because it influences the speed of the seeds passing through the tube. Figure 26 shows the experimental setup of the slug flow experiment.

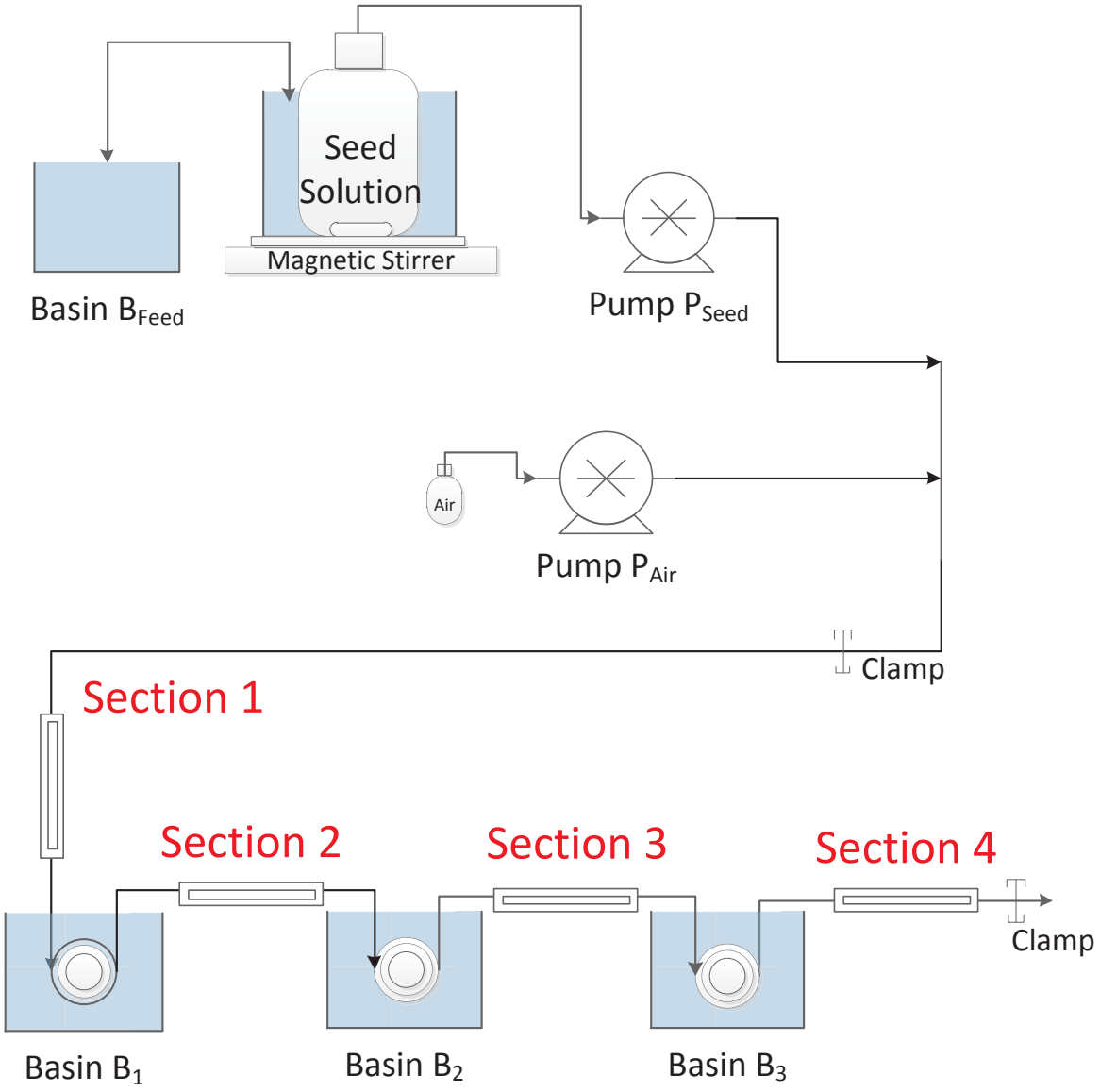

Figure 26: Experimental setup – slug flow

Setup and execution

For this setup, the seed solution was placed in a tempered water basin and stirred by a magnetic stirrer. The used seed solution was a 0.6 ASA : 2 EtOH solution which was dissolved with 33°C water and then cooled to 23°C. Nucleation was induced by applying ultrasound as described in chapter 3.2.3. By circulating water from basin B_{Feed} the temperature of the seeds was kept at 23°C during the whole experimental procedure. Before running the experiment the pump P_{seed} was calibrated manually each time to the according flow rate. For the experiment the seed solution is pumped through the tube and mixed with the saturated EtOH air means a Y-fitting. Here the Y-fitting is placed so that the two angular openings take in the air and solution and both exit at the straight opening (Figure 27).

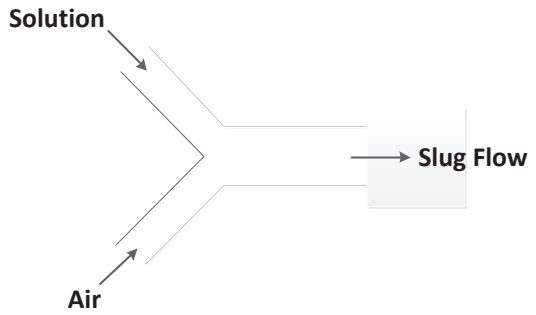

Figure 27: Y-fitting

The produced slug flow then passes through the coils in the water basins with each a length of 5 meters. Over the whole length, four test sections, each having a length of 20 cm, were set up. These were principally made of a piece of wood on which the tube was attached along with a ruler, as can be seen in Figure 28. Measuring of the slugs was carried out at each section and section 1 and 4 were also used for measuring the speed.

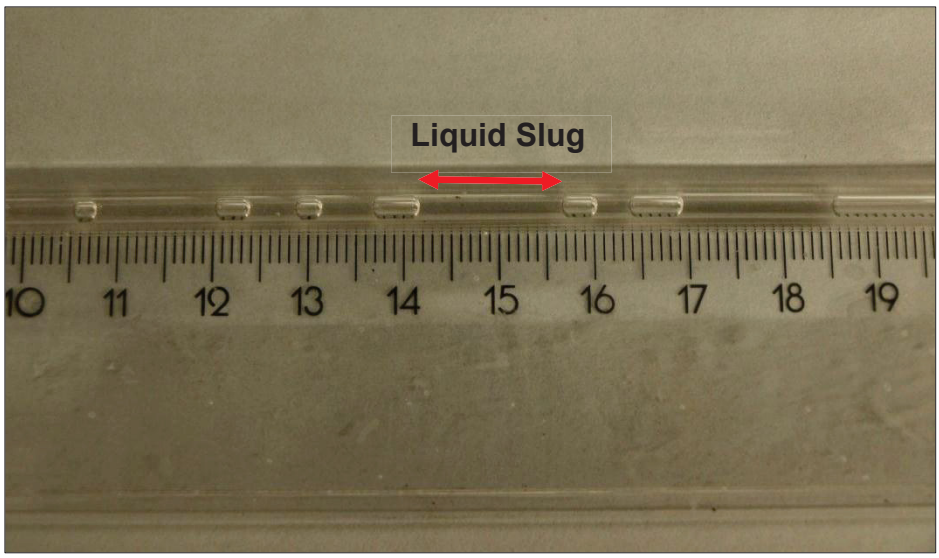

Figure 28: Liquid slug length measuring section

The process was run at certain air flow and seed solution flow rates. For each flow rate the trial was run until the slug flow seemed stable. During that, the time for a bubble to pass through the test section 1 and 4 was measured with a stop watch. Then the process was turned off and the tube was blocked with a clamp at both ends as shown in the setup. This was necessary to keep the slugs in the tube stable for measuring. The length of each liquid slug at each section was measured and noted. The same procedure was carried out for various pump settings and for three different types of tubes. Following tubes were used:

Tube 1) Versilic® silicone tube with an inner diameter of 2 mm and an outer diameter of 4 mm resulting in a total wall thickness of 1 mm

Tube 2) Rotilabo® tube with an inner diameter of 2 mm and an outer diameter of 4 mm resulting in a total wall thickness of 1 mm

Tube 3) Tygon® tube with an inner diameter of 1.6 mm and an outer diameter of 4.8 resulting in a total wall thickness of 1.6 mm.

Unfortunately it was difficult to take the time with the stop watch because at high pump settings the speeds were too high to receive accurate results. Therefore the results were compared to each other according to the pump settings. This may have a small influence on the accuracy of the results because the flow rate is not always the same for each tube. Nevertheless the results can be compared relatively to each other and certain characteristic in their flow behavior analyzed. Another small impact on the accuracy has the measurement of the length of the liquid slugs. As seen in the setup, the liquid slug lengths are read off a ruler placed beside the tube. It is possible that small errors of 1-2 mm occur when determining the slug length, also because two different people were taking the results.

3.6 Equipment and Materials

Pumps

- P_{seed}: Ismatec Reglo Hose Pump Modell MS-2/6V1 13C
- P_{Feed}: Ismatec Reglo Hose Pump
- P_{Air}: Ismatec IP65 BVP-Process Hose pump
- Vacuum Pump: VACUUBRAND PC510

Temperature basins

- Basin B_{Feed}: P Selecta Ultraterm
- Basin B_{Seed}: Lauda Alpha
- Basin $B_{Preheat}$: Grant
- Basin B_1:Lauda Alpha A24
- Basin B_2: Lauda Alpha A24
- Basin B_3: Lauda Alpha with Lauda Ecoline thermostat E100
- Basin B_{Camera}: Self made

Ultrasound basin:

- T460, HF 35 kw, 230 V, 0,38 A

Hot plate

- ICAMG RCT
- Heidolph MR 3001 K

Scales

- Mettler AE 200

Fittings:

- Y-fitting
- T-fitting

Tubes:

- P_{seed}: 3-stop Ismatec PharMed BPT tube. ID: 2.79 mm. Wall: 0.9 mm
- P_{Feed}: 3-stop Ismatec PharMed BPT tube. ID: 2.79 mm. Wall: 0.9 mm
- P_{Air}: PharMed® BPt

Agitator

- CAT. M.Zipperer GmbH: Type R50 with a two paddled KPG®, PTFE stirrer

Temperature Measurement

- Testo AG 110

Materials

- In this thesis ASA (Acetylsalicylacid, 2-Acetoxybenzoesäure), commonly known as Asprin, is used as the model substance. D ASA (Rhodine 3020, pharmaceutical grade 100%, monoclinic) was provided from GL-Pharma. EtOH (99.8% denaturized with 1% metyl ethyl ketone) was purchases from Roth (Lactan)
- Polysiloxane tubing with an inner diameter (din) of 2.0 mm and an outer diameter (dout) of 4.0 mm

4 Results

4.1 Improvements and Development

All major improvements that were made to the process during the course of this paper are listed below. They will be discussed thoroughly on the basis of the results during this chapter.

- Tubes
- Tube roles
- Method of mixing
- Seed and feed concentration
- Seed size
- Seed cooling

At the beginning of the thesis the tubes for crystallization were rolled up around a mesh wiring. A picture is shown in Figure 29.

Figure 29: Mesh wiring

One of the problems with this wiring was that the mesh wiring has edges and is not perfectly round. This caused the occasional build up of seeds in the tube along the edges. It was also assumed that the edges negatively influence the slug flow leading to an unequal flow. A continuous slug flow is essential for crystallization and to prevent clogging. Figure 30 shows the unevenness of the mesh wiring.

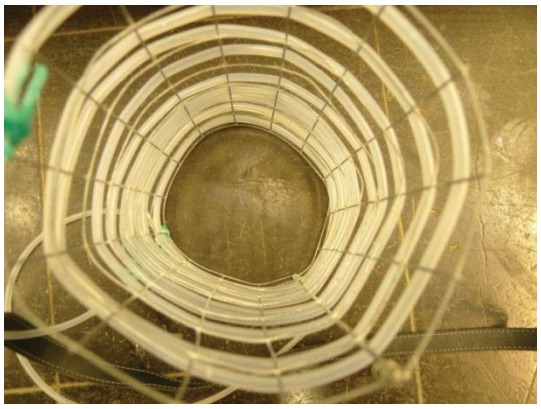

Figure 30: Uneven mesh wiring

To prevent further difficulties with the tubes, new roles made of plastic were used. These were covered with aluminum foil and the crystallization tubes were wrapped around them. They were attached through holes bored into the plastic.

Even though the process was improved with this technique it had not reached perfection. One of the major problems is the heat conduction of plastic, which is low and the tubes are not surrounded by the media, water. Another issue is created by turbulences in water that cause the roles to swim on the surface, causing the crystallization tubes to slip off. Therefore new roles out of stainless steel were installed (Figure 31).

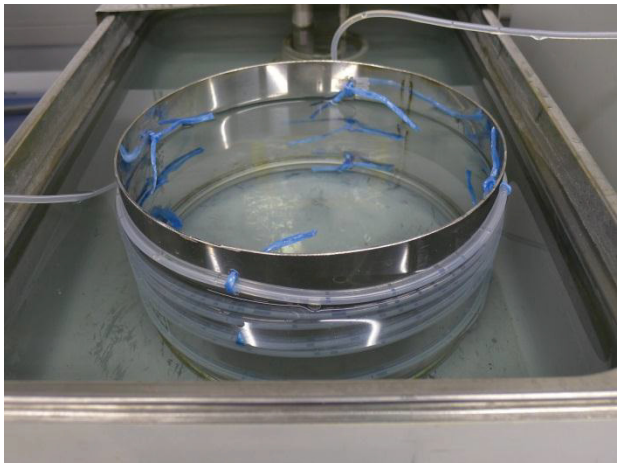

Figure 31: Stainless steel role

These roles have a larger diameter and are placed in the water basin in the upright position. Holes were bored to attach the tubes to the role.

For the crystallization to run stable, it is essential to have a continuous slug flow. The slug flow in the crystallization tube is shown in Figure 32. Air bubbles push the crystals through the tubes enabling the same retention time for all particles as mentioned in chapter 2.2.

Figure 32: Slug flow in crystallization tube

In theory this sounds simple but it is challenging to achieve continuous slug flow. Nevertheless the flow was improved with various improvements. First of all it was necessary to find out what type of flow is needed. There are many variations ranging from small bubbles and large spaces between the bubbles to small bubbles with small spaces. It was not possible to find out the correct slug flow because it was difficult to analyze the behavior of the seeds in the flow, solely by looking at it. Air bubbles are added via a Y-fitting. T-fittings were also tested but no major change in the flow behavior was observed. Even though according to the theory in chapter 2.2, change in the bubble length should be recognized, depending on the inlet geometry.

Some of the difficulties that arise when adjusting the slug flow were:

- Hose pump
- Edges in mesh wire
- Tubes
- Inlet
- Flow rates
- Turning on

Hose pumps are not designed for a continuous flow. It was tried nevertheless with various ideas to achieve it anyhow.

At the beginning of the thesis the roles for the crystallization tubes in the water basins were made of **mesh wire**. This was not perfectly circular and altered the formation of the slugs as

described at the beginning of this chapter. The roles were replaced over the course of this thesis.

It was decided to try regulating the slug flow, by using **tubes** made out of a harder material or higher wall thickness. To try the mentioned theory two different tubes were ordered. One tube made out of a more durable material and the other with a higher wall thickness. The tubes used up to this date were Versilic® silicone tubes with an inner diameter of 2 mm and an outer diameter of 4 mm resulting in a total wall thickness of 1 mm. One of the new tubes is a Rotilabo® tube with the same measurements and the other is a Tygon® tube with an inner diameter of 1.6 mm and an outer diameter of 4.8 resulting in a total wall thickness of 1.6 mm.

The geometry of the **inlet** also influences the length and mean distance of the bubbles. Some tests were done trying to use a Y-fitting or a T-fitting in different positions but it was not possible to analyze the formed bubbles because the high speed camera was not available. Another problem was that, water, pure EtOH and EtOH with ASA all have a different density on which the formation of the slug flow depends. Due to costs, it was not possible to run these trials with EtOH or EtOH with ASA. Some ideas that were gathered by running some tests with water were refuted when using EtOH. Some trials were performed nevertheless. One of the methods was by adding a narrower tube piece into the Y-fitting as shown in Figure 33. Results were reasonably good with small flowing bubbles but the problem was that it led to clogging of seeds at the entrance of the air bubbles.

Figure 33: Y-fitting with narrowing at the inlet

Even though the slug flow was improved with this method the narrowing clogged up within a short time due to particles from the seed stream coming around the bend. Consequently this method was abandoned.

The regulation of the **flow rates** of the pumps can be challenging because they change frequently. Not only does the slug flow depend on the flow rate of the pump P_{Air} but also on the flow rates of the pump P_{Seed} and pump P_{Feed}. After running the pumps for some time the flow rate changes, due to the tubes in the pumps being constantly pressed together and released. Due to problems with delivery, it was not possible to measure the flow rates during the process until the end of the thesis and therefore it was difficult to assess the slug flow beforehand. For

measuring the flow rate the whole process would have had to be stopped and measured manually.

Turning on the process is a tricky matter. It makes a difference to the slug flow whether one or the other pump is turned on first. Generally it seems the slug flow works best if the pump P_{Seed} and P_{Feed} are turned on before the pump P_{Air} is started. The reason for this is that otherwise air will be pumped into the liquid tubing.

The experimental setup for producing the seeds is problematic and it is difficult to accomplish reproductive results. Several uncertain factors are listed below. Many of them were improved in the course of the thesis. They are described more detailed in chapter 4.3.

- Room temperature
- Magnetic stir bar
- Refilling/changing of water
- Ice/water mixture
- Fill volume

The **room temperature** in the lab is not always the same. During the experiments the room temperature varied between 19 and 27°C. If the room temperature is warmer, the water in the beaker for cooling the solution will warm up quickly and so will the solution, resulting in slow crystallization. So when the room temperature varies, the size of the particle changes because they are cooled slowly or fast or heated up too quickly. Due to the temperature changes the setup was changed to setup 2 and finally to setup 3 to have even more control over the process by inducing ultrasound.

The magnetic **stir bar** is difficult to handle. If turned on at high speed it does not always circulate correctly. Especially after changing the water it takes a while for the stir bar to regain balance. Sometimes the stir bar had to be turned slower during the experiment which influences the heat conduction and the particle size. These problems due to the stir bar were resolved by using a KPG® stirrer for setup 1 and 2.

Another large influencing factor is the **changing and refilling of the water**. When the water is refilled it is not possible to refill it at the same speed each time. Sometimes the distance to the water basin is larger or smaller depending on the desired water temperature. If the water is filled up slowly the solution will be cooled more slowly and nucleation is delayed. This problem was also resolved in setup 1 and 2 by using a tempered water bath or water circulation.

An **Ice/water mixture** is one of the methods for cooling the particles. Problematic is that the mixture does not always have the same ice water ratio. If it has more ice and larger particles of ice the solution is likely to cool slower than with a higher water ratio.

After taking a sample, the **fill volume** of the solution sinks. Further, the cooling and heating processes as used for temperature cycles are changed because less amount of solution cools and heats up faster.

At the beginning of the thesis many of the crystallization experiments in the tubular reactor did not work and no samples were taken. These problems were resolved during the thesis. First crystallization experiments were carried out with high seed and feed concentrations. This was at first 1 ASA : 2 EtOH. The high amount of seeds caused blockage in the tubes. Later this concentration was changed to 0.8 ASA : 2 EtOH , improving the process and allowing crystallization for a short period of time before clogging. Consequently the concentration was lowered even more to 0.6 ASA : 2 EtOH for the seed and 0.8 ASA : 2 EtOH for the feed solution. With this concentration the crystallization ran more smoothly and was kept at this concentration for the rest of the thesis. Another problem was the length of the crystallization tube. At the beginning, the crystallization was realized along 20 meters of tube (4 water baths with each 5 meters of tube). Due to the length of the tubes the crystals grew too much and caused blockage in the tubes. To resolve this problem the tube length was reduced to 15 meters by taking away one of the water basins.

4.2 Crystallization in a Tubular Reactor

The crystallization experiments were carried out according to the setup in chapter 3.1 and the samples analyzed with the analyzing devices described in chapter 2.3, depending on the desired measuring parameters.

Initial results of the products displayed the necessity of collecting more information on the seeds and to develop suitable seeds without aggregates, before proceeding with crystallization in the tubular reactor because the process did not run and if a sample was taken, it had too many aggregates. Due to these findings, more experiments concerning the seeds were carried out and these results are shown in chapter 4.3.

Overall the results showed that crystallization has to be carried out with a lower mass fraction and with smaller seed particles. With lower seed and feed concentrations it was possible to run the process for a longer period of time.

4.3 Seed Preparation

Seed experiments were performed as described in chapter 3.2, either according to setup 1, 2 or 3. Other changes in the preparation were made concerning the concentration, cooling temperatures, and the stir speed. At the beginning the seed experiments were carried out with higher concentrations 1 ASA : 2 EtOH and during the thesis the concentration was lowered to 0.6 ASA : 2 EtOH.

Setup 1

The goal of one of the first sets of experiments was to see if temperature cycles have an influence on the particle size and aggregation and to test the **reproducibility** by taking three samples at the same conditions. Table 4 gives information on how the slugs, shown in the following microscope pictures, were developed.

Table 4: Seed development parameters – comparison of seeds

Sample	Mass Ratio	$T_{Dissolve}$	Cooling		Sampling
-	g_{EtOH}:g_{ASA}	°C	°C	min	°C
Sample 1, 2,3	1:2	50	25	45	25

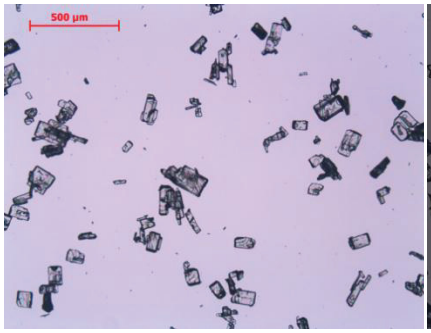

Figure 34: Sample 1

Figure 35: Sample 2

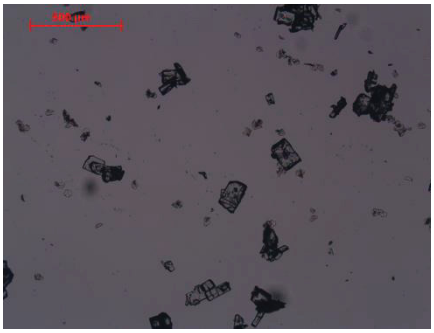

Figure 36: Sample 3

Three of the samples (Figure 34, Figure 35, Figure 36) were treated the same way and all of them show similar results, especially sample 1 and sample 2. According to these samples it is possible to reproduce results using the same settings. Later on during the thesis a lower mass fraction was used and it was more difficult to reproduce the same results.

The influence **of temperature cycles** was tested next. The process settings for the generation of the seeds are shown in Table 5.

Table 5: Seed generation process – temperature cycles

Sample	Ratio	$T_{Dissolve}$	Cooling		TC 1		TC 2		TC 3		Sampling
-	g_{ASA}:g_{EtOH}	°C	°C	min	°C	min	°C	min	°C	min	°C
Without TC	1 : 2	50	25	45							25
One TC	1 : 2	50	25	45	50	10					25
Two TC	1 : 2	50	25	45	50	10	50	10			25
Three TC	1 : 2	50	25	45	50	10	50	10	50	10	25

TC…Temperature Cycle

Before taking the samples, it was assumed that by using temperature cycles the fines will dissolve and larger particles will grow. As visible in the results, shown in the figures below (Figure 37, Figure 38, Figure 39, Figure 40), this theory has been proven right.

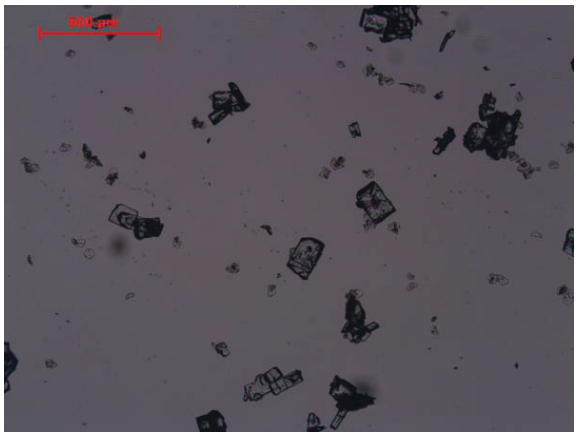

Figure 37: Without temperature cycle

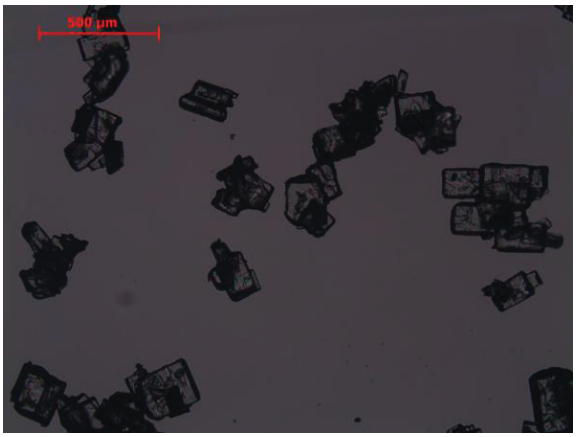

Figure 38: One temperature cycle

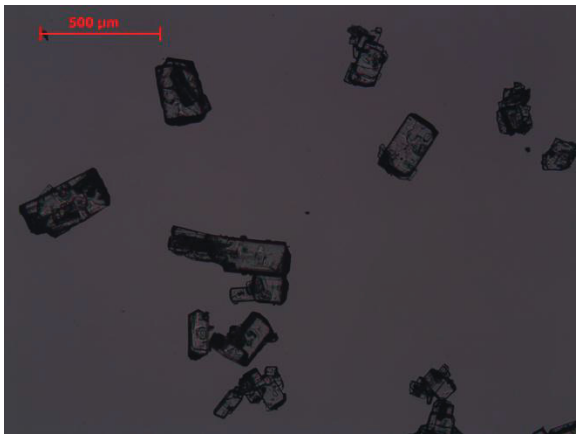

Figure 39: Two temperature cycles

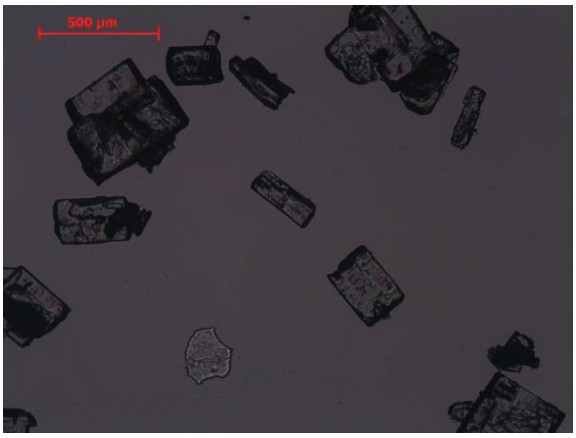

Figure 40: Three temperature cycles

Clearly the sample with the most temperature cycles has the largest particles with the least amount of fines. Due to the agreeable results with the temperature cycles, crystallization was carried out with the seed which had undergone two temperature cycles. Problems with running the crystallization process with these seeds were that the seeds became too large and kept continuously growing in the tube, until it resulted in the blocking of the tube. Consequently the mass fraction of ASA was lowered in the following experiments.

Following this conclusion, temperature cycle experiments were carried out with the new concentration to see if smaller seeds with less fines can be produced. A concentration of 0.6 ASA : 2 EtOH was used. The process parameters are shown in Table 6 and Table 7. The samples were analyzed with the QICPIC device and the obtained data evaluated in Matlab®. Following figures show the particle size distribution of all samples (Figure 41). Three graphs were drawn, each one showing a possible consequence of seeds without temperature cycle (green, dashed line), seeds with one temperature cycle (black, dotted line) and seeds with two temperature cycles (red, straight line). Figure 41 and Figure 42 clearly confirm that the particles grow during temperature cycles.

Table 6: Seed generation paramters – temperature cycles 1

Sample	Mass Ratio	$T_{dissolvin}$	Cooling	TC 1		TC 2		Sampling
-	g_{ASA}:g_{EtOH}	°C	°C	°C	min	°C	min	°C
Without TC	0.6 : 2	40	13					13
One TC	0.6 : 2	40	13	40	2			13
Two TC	0.6 : 2	40	13	40	2	40	2	13

TC…Temperature Cycle

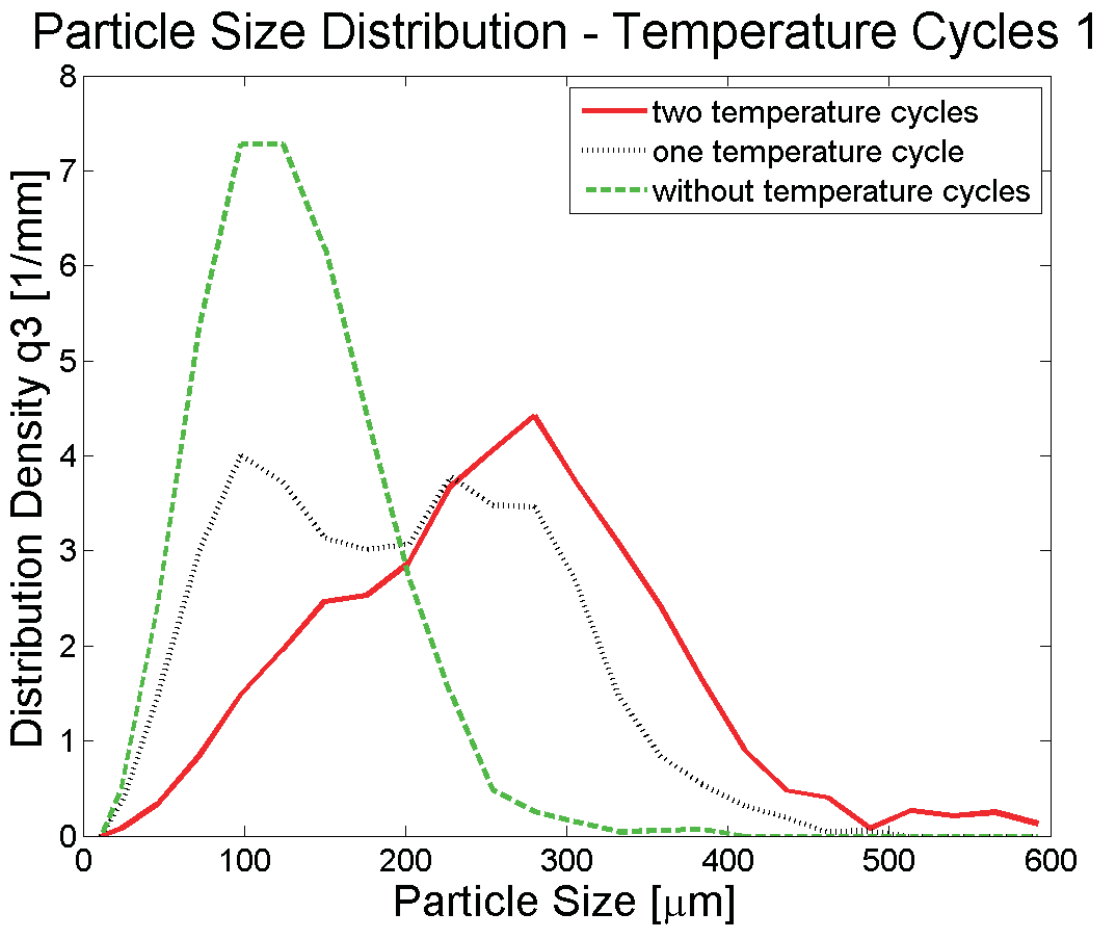

Figure 41: Particle size distribution 1 – temperature cycles

Table 7: Seed generation parameters – temperature cycles 2

Sample	Mass Ratio	$T_{dissolve}$	Cooling	TC 1		TC 2		Sampling
-	g_{ASA}:g_{EtOH}	°C	°C	°C	min	°C	min	°C
Without TC	0.6 : 2	40	13					25
One TC	0.6 : 2	40	25	36	1			25
Two TC	0.6 : 2	40	25	36	1	36	1	25

TC…Temperature Cycles

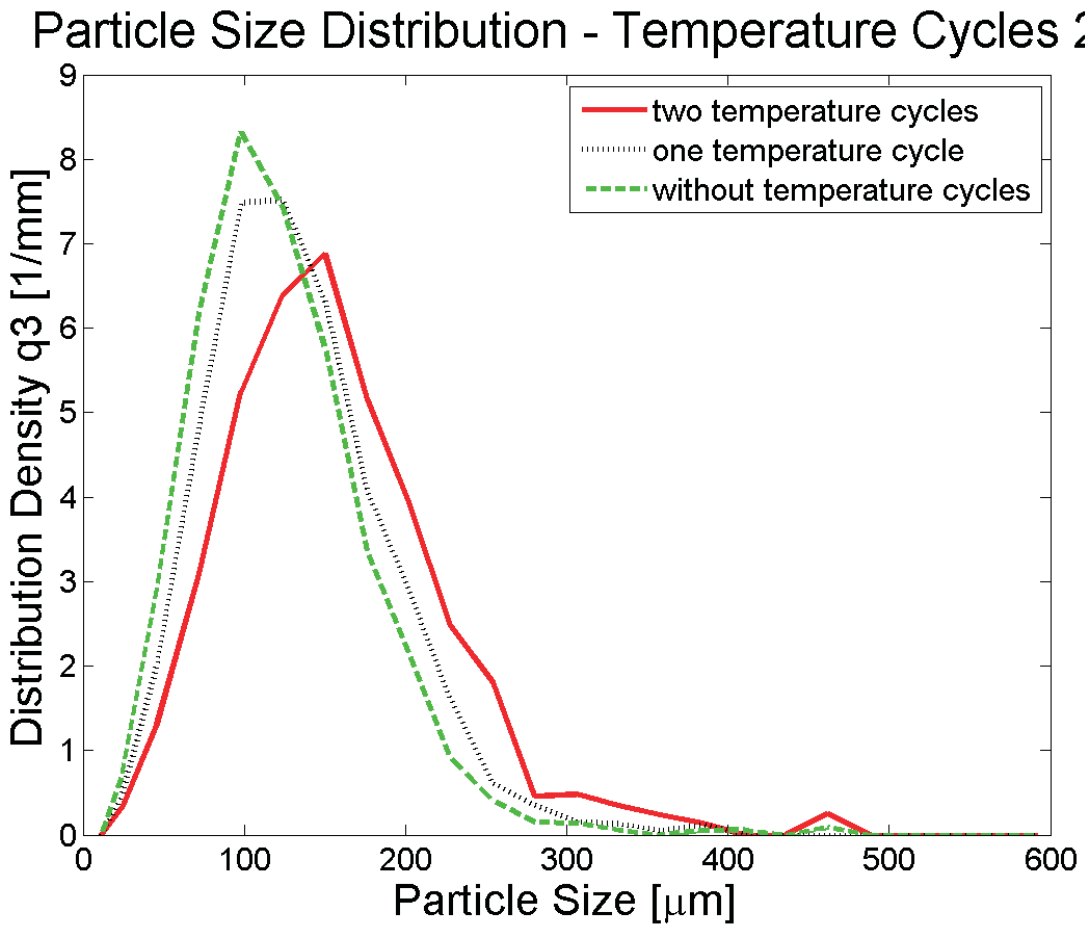

Figure 42: Particle size distribution 2 - temperature cycles

As clearly displayed in the diagrams above (Figure 41 and Figure 42), the particle size of the seeds increases with the number of temperature cycles, regardless of the temperature and duration of the process. Starting from the left side of the diagram, the green dashed line is the distribution of the seed without temperature cycle. Next follows the dotted, black line showing the seeds with one temperature cycle. The last line is the solid line, showing the distribution of the seeds with two temperature cycles. Notable is that these seeds have the narrowest particle size distribution of all samples taken.

To see how cooling influences the seed samples without temperature cycles, next the seed samples without temperature cycles were compared. The results can be seen in Figure 43 and the process parameters are listed in Table 8.

Table 8:Seed generation parameters – seed comparison

Sample	Mass Ratio	$T_{dissolve}$	Cooling	Sampling
-	g_{ASA}:g_{EtOH}	°C	°C	°C
S1	0.6 : 2	40	13	13
S2	0.6 : 2	38	25	25
S3	0.6 : 2	38	25	25
S4	0.6 : 2	36	25	25

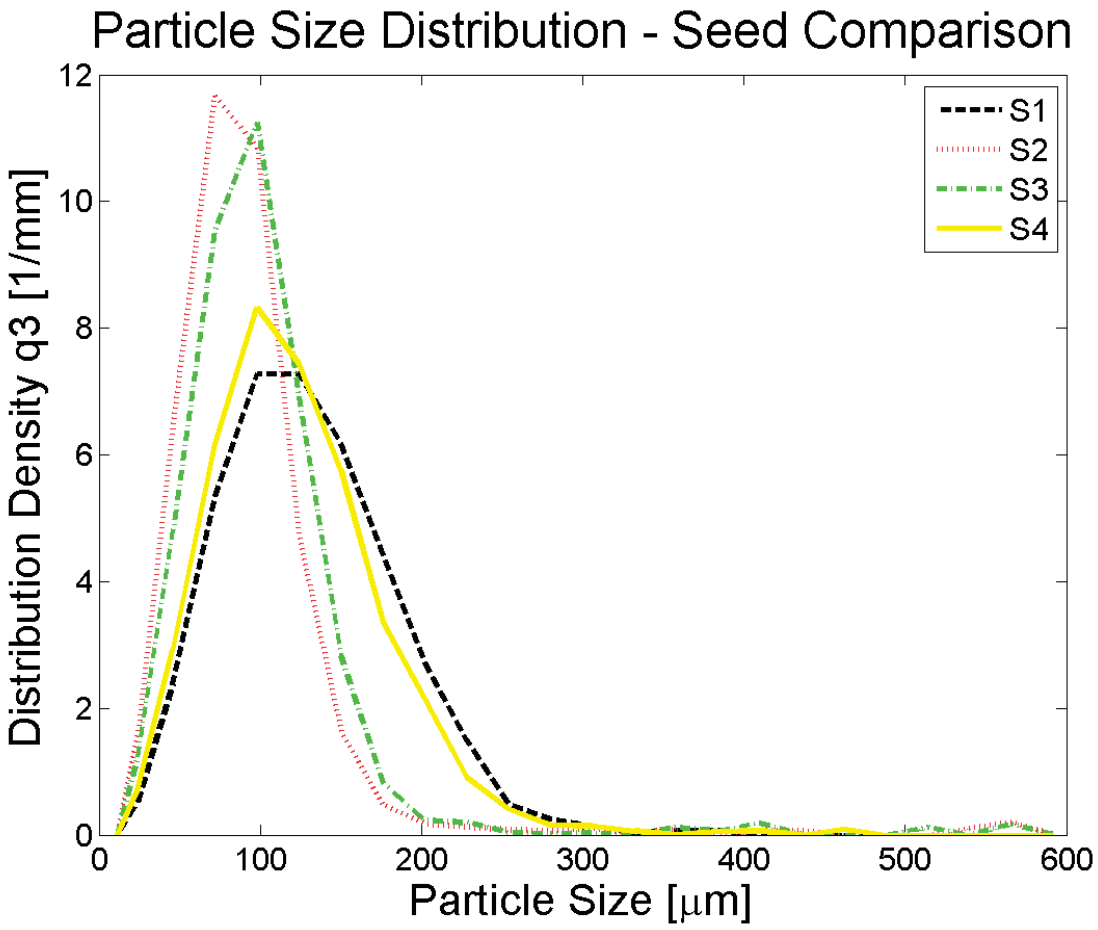

Figure 43: Particle size distribution – seed comparison

According to the graph in the diagram above, the seeds that were heated up to 38°C and then cooled, (S2 and S3) show the smallest size distribution and have the smallest particle size. The sample that was only heated up to 36°C and then cooled consists of the largest particles as shown in the yellow curve (S4). This may be possible because the solution can be cooled down faster if the initial temperature is not as high. This assumption correlates with the last

distribution shown in blue (S1). Even though sample S1 dissolved at higher temperatures, with 40°C water, as the other samples, it was then cooled with 13°C water instead of 25°C. However this sample cannot be effectively compared with the others because the sample was drawn at 13°C instead of the usual 25°C producing a further explanation for the larger particle sizes.

Previous experiments had shown that rapid cooling is better for producing smaller particles and therefore more **rapid cooling** experiments were performed including cooling with an ice/water mixture. Table 9 shows the seed generation parameters.

Table 9: Seed generation parameters – rapid cooling

Sample	Mass Ratio	Stir Speed	$T_{dissolving}$	Cooling		Sampling
-	g_{ASA}: g_{EtOH}	rpm	°C	°C	min	°C
Cooled with 13°C_1	0.6 : 2	300	33	13	09:20	24.2
Cooled with 13°C_2	0.6 : 2	200	33	13	06:45	24.3
Cooled with Ice/Water	0.6 : 2	300	33	Ice/water	05:10	24.3

The microscope pictures are shown in Figure 44, Figure 45, and Figure 46.

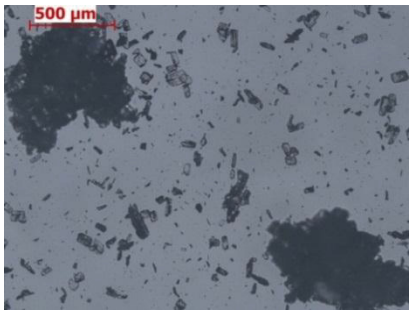

Figure 44: Cooled with 13°C water 1

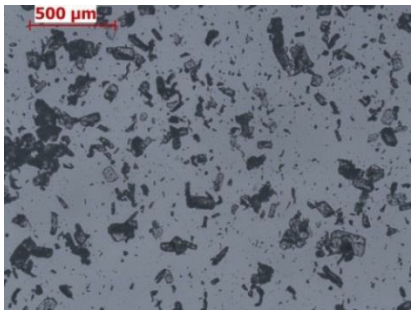

Figure 45: Cooled with 13°C water 2

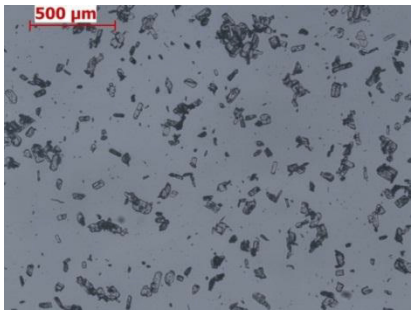

Figure 46: Cooled with ice/water mixture

According to these experiments the best results are realized through rapid cooling with an ice/water mixture. It is assumed that when the particles are cooled at lower temperatures less aggregation will occur.

Then **ice/water cooling** was carried out with **temperature cycles**. It does not seem as though the temperature cycles influence the crystals positively because samples with ice/water mixture cooling, combined with temperature cycles, have extreme aggregation. As a conclusion from these experiments no further temperature cycles were carried out.

Thereafter it was analyzed whether the **stir speed** influences the sample. For the first sample the stir speed was 200 rpm and for the other two samples 300 rpm. Table 10 shows the seed generation parameters.

Table 10: Seed generation parameters – stir speed

Sample	Mass Ratio	Stir Speed	$T_{dissolve}$	Cooling		Sampling
-	g_{ASA}:g_{EtOH}	rpm	°C	°C	min	°C
S_200	0.6 : 2	200	33	Ice/Water	06:10	24.2
S_300_a	0.6 : 2	300	33	Ice/Water	03:40	24.2
S_300_b	0.6 : 2	300	33	Ice/Water	04:15	24.6

Pictures are shown in Figure 47, Figure 48 and Figure 49. As visible the stir speed does not seem to have a great influence on the crystals.

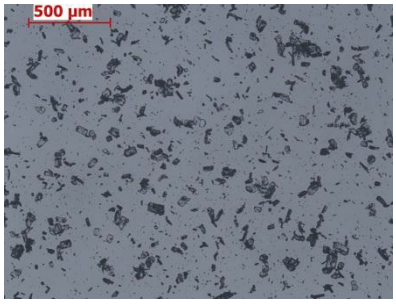

Figure 47: S_200

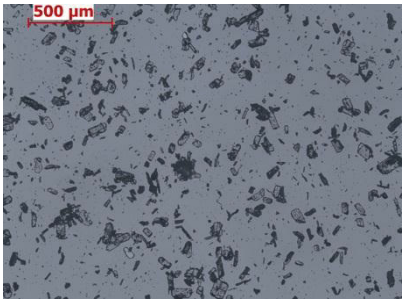

Figure 48: S_300_a

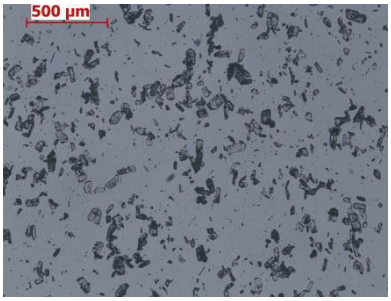

Figure 49: S_300_b

Next it was tested if the **speed of sampling** influences the sample (Figure 50, Figure 51, Figure 52). For this experiment a solution with high ASA concentration was used. The sample was taken at room temperature to exclude the possibility of a temperature change in the tube influencing the sample. The pump rotation speed was varied between slow, medium and fast. Table 11 shows the seed generation parameters.

Table 11: Seed generation parameters – sampling speed

Sample	Mass Ratio	Stir Speed	Pump	$T_{Dissolve}$	Cooling	Sampling
-	g_{ASA}:g_{EtOH}	rpm	-	°C	°C	°C
Slow	0.6 : 2	300	Slow	44	Ice/Water	RT
Medium	0.6 : 2	300	Medium	44	Ice/Water	RT
Fast	0.6 : 2	300	Fast	44	Ice/Water	RT

RT…Room temperature

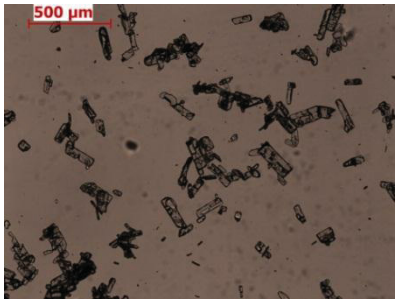

Figure 50: Slow pump speed

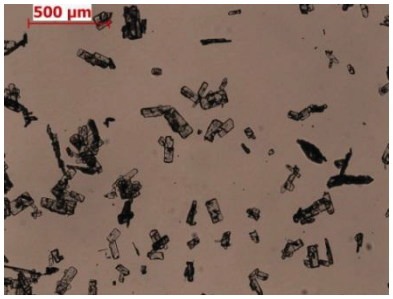

Figure 51: Medium pump speed

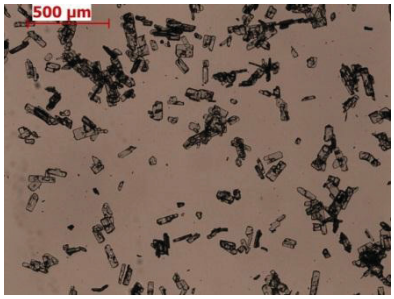

Figure 52: Fast pump speed

It does not seem as though the pump rotation speed has a great influence on the sample. Only minor differences were visible but could be variations in the sample itself as with microscopy only a small portion of the sample is analyzed. Even though the results shown above in Figure 50, Figure 51 and Figure 52 were satisfying it was problematic to reproduce these desired seeds because of varying influences like the room temperature.

Setup 2

It was tested to see if it is possible to create smaller crystals without fines by crystallizing the crystals at high concentrations and adding EtOH later on. Several experiments were carried out and all showed similar results. One of the microscope pictures is shown below in Figure 53. The sample was dissolved at 38°C and then cooled down to 22°C at which the particles had already nucleated. Then EtOH was added slowly over a period of 5 minutes.

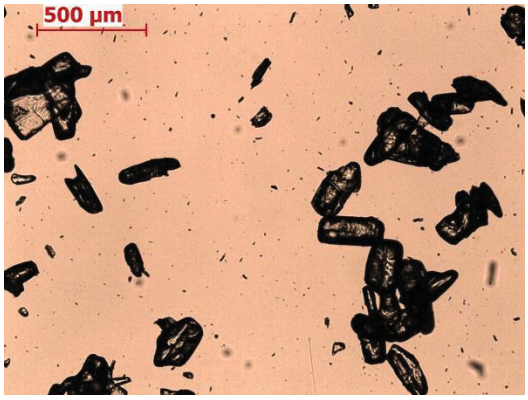

Figure 53: Dilution with EtOH

As visible above, many fines and also a lot of very large particles are created with this method. The sample also has a high number of aggregates. For these reasons the **dilution procedure** was not used for further experiments. A new method of creating seeds, the ultrasound was tested in pursuing experiments.

Setup 3

The **ultrasound** experiment showed following results. Following microscope pictures (Figure 54, Figure 55, Figure 56) display how ultrasound insonation on already formed crystals changes the crystals. Figure 54 are the crystals formed by cooling without ultrasound. The following pictures are first the formed crystals without insonation at 22°C, then the same sample with 30 seconds of ultrasound insonation after formation and the last one with another 120 seconds of ultrasound insonation after formation. Table 12 gives an overview of the settings for the seed generation.

Table 12: Seed generation parameters – ultrasound after nucleation

Sample	Mass Ratio	$T_{Dissolve}$	Stir Speed	Cooling	US 1		US 2		Sampling
-	g_{ASA}:g_{EtOH}	°C	rpm	°C	°C	min	°C	min	°C
Without	0.6 : 2	33	100	22					22
30 sec US	0.6 : 2	33	100	22	22	0:3			22
150 sec	0.6 : 2	33	100	22	22	0:3	22	2	22

US…Ultrasound

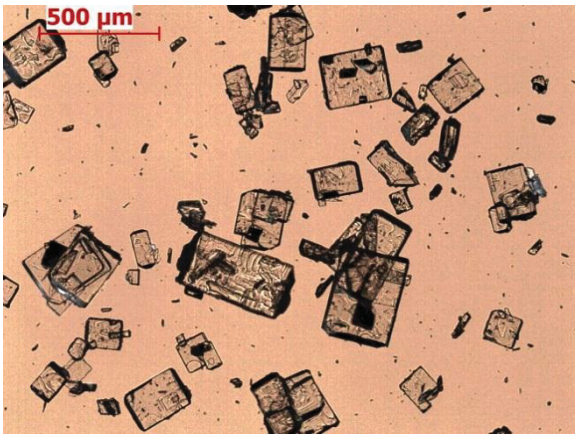

Figure 54: Seeds – without ultrasound

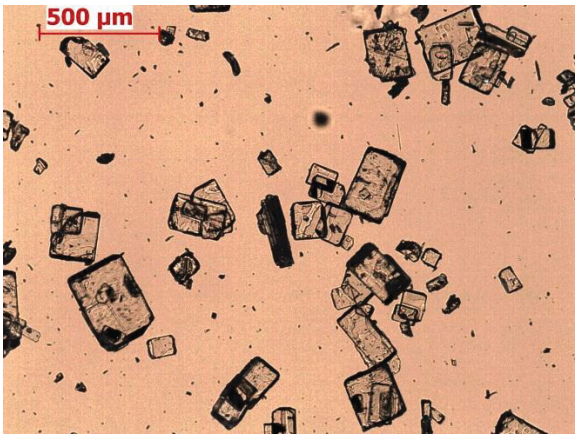

Figure 55: Seeds – 30 second ultrasound after formation

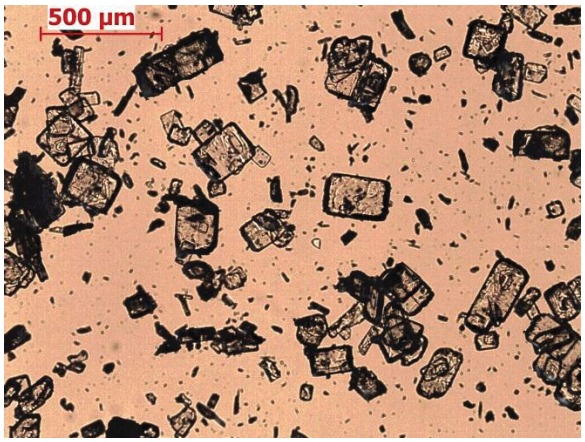

Figure 56: Seeds – 150 seconds ultrasound after formation

As visible in the microscope pictures, ultrasound insonation after formation of crystals does not seem to have a positive effect on the seeds. Clearly the seeds with more ultrasound insonation after formation have a larger amount of small crystals.

The next pictures show how the particles look like when ultrasound is used to create nucleation. Figure 57 displays the formed nuclei with 30 seconds and Figure 58 with 60 seconds of ultrasound sonication. The parameters for the seed generation are shown in Table 13.

Table 13: Seed generation parameters – ultrasound to enforce nucleation

Sample	Mass Ratio	T Dissolve	Stir Speed	Cooling	US 1		Sampling
-	g_{ASA}:g_{EtOH}	°C	rpm	°C	°C	min	°C
30 sec US	0.6 : 2	33	100	22	22	0:30	22
60 sec US	0.6 : 2	33	100	22	22	1:00	22

US…Ultrasound

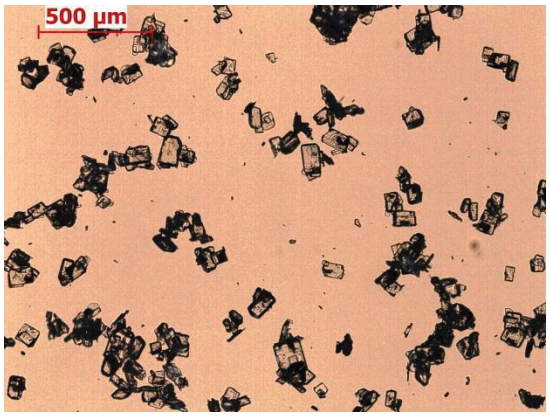

Figure 57: Ultrasound 30 seconds

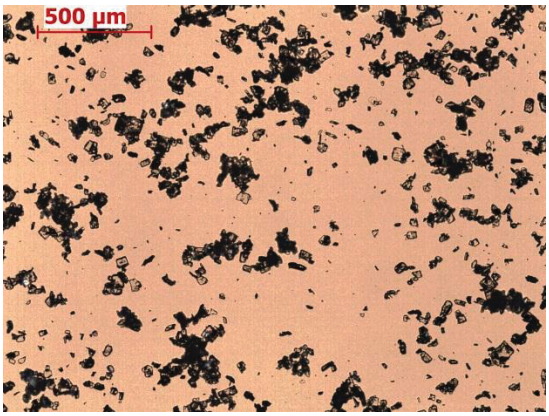

Figure 58: Ultrasound 60 seconds

The results show that the formed crystals are smaller if the duration of ultrasound insonation is longer. It is clearly visible that the sample with 60 seconds of ultrasound insonation has smaller crystals than the sample with only 30 seconds.

Further, test with different **stir speeds** were carried out. Tests with different stir speeds during nucleation showed that nuclei will develop at higher temperatures if the stir speed is increased.

To confirm all the results shown above for setup 3, the samples were additionally analyzed with the HELOS device as explained in chapter 2.3.1.

The first results in Figure 59 show that the particle size increases when ultrasound is applied and the solution is stirred for another ten minutes. The seed development parameters are shown in Table 14.

Table 14: Seed generation parameters – ageing

Sample	Ratio	$T_{Dissolve}$	Stir Speed	Cooling	Ultrasound		Stirring		Sampling
-	ASA:EtOH	°C	rpm	°C	°C	min	°C	min	°C
S1	0.6 : 2	33	100	22	22	0:30			22
S3	0.6 : 2	33	100	22	22	0:30	22	10	22

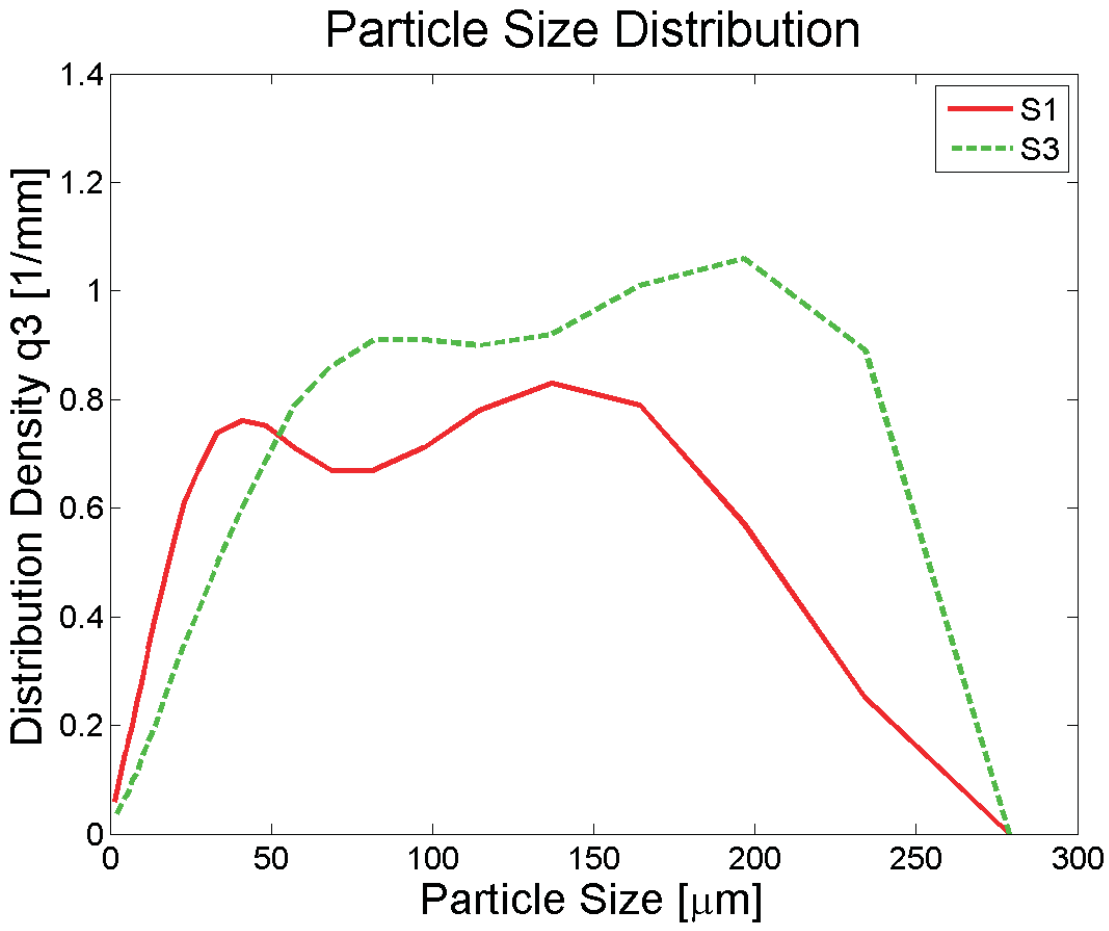

Figure 59: Particle size distribution directly after applying ultrasound and ten minutes later

Sample S1 was taken straight after ultrasound insonation and S3 was taken ten minutes later. Presumably the particles are larger in S3 because they keep on growing until equilibrium is reached. All the samples have a wide particle size distribution.

In the next diagram (Figure 60) samples that were treated with different ultrasound methods are visible.

Table 15: Seed generation parameters – pipetting sample

Sample	Ratio	T Dissolve	Stir Speed	Cooling	US 1		US 2		US 3		Sampling
-	g_A:g_E	°C	rpm	°C	°C	min	°C	min	°C	mi	°C
S1	0.6:2	33	180	22.5	22	2	22.	3	22.4	3	22
S2_p	0.6:2	33	180	22.5	22	2	22.	3	22.4	3	22
S3	0.6:2	33	180	22	22	2					22
S4_p	0.6:2	33	180	22	22	2					22

p…Sample taken with pipette
A…ASA
E…EtOH

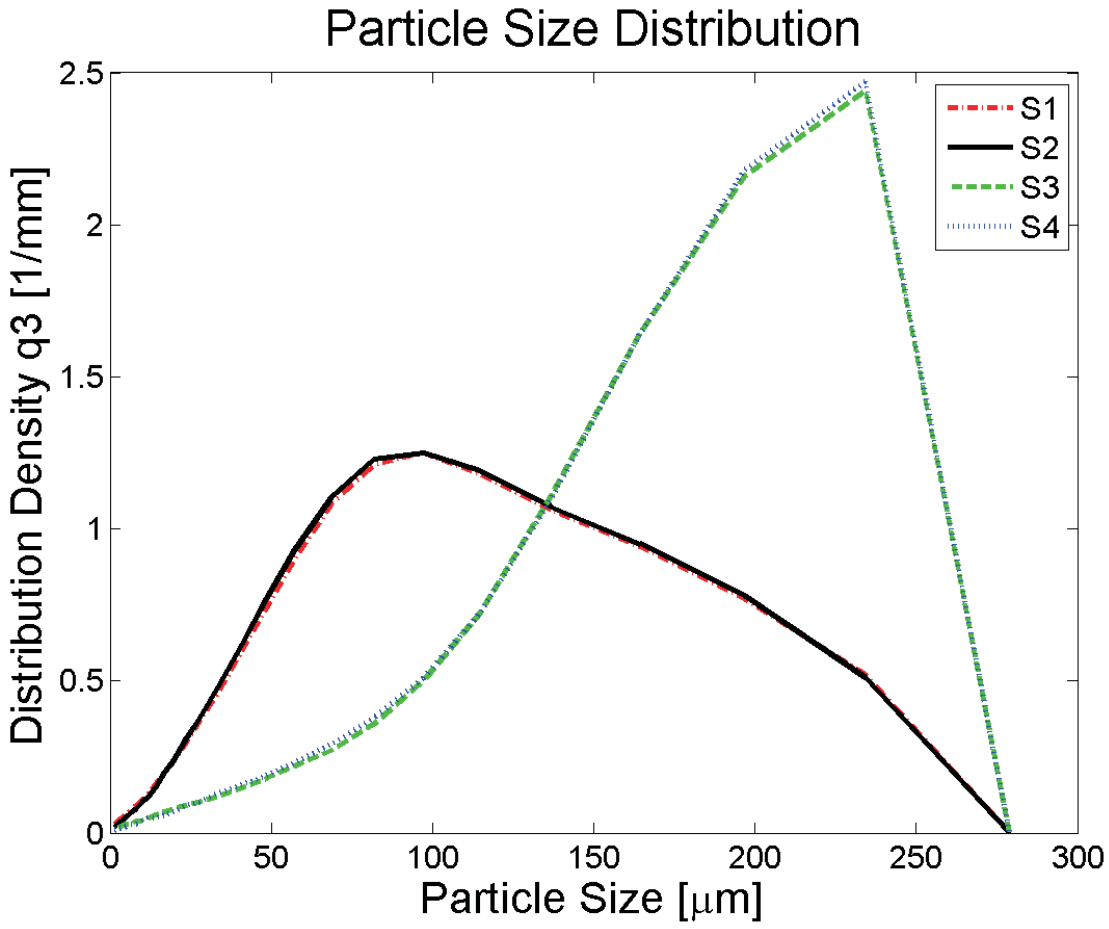

Figure 60: Comparison of the particle size distribution using different ultrasound methods.

S1 shows a sample that was taken after applying ultrasound in various stages during the cooling. Sample S2_p was taken straight afterwards to verify the results. Additionally the

sample S2_p was taken with pipette to eliminate possible errors due to the hose pump and to test the method of sampling. As visible both samples show nearly the sample particle size distribution whereas the next two samples are completely different. The next samples S3 and S4_p were taken after only one ultrasound application. Same as above, the second sample was taken with the pipette to test and verify the results. The results show that with HELOS it is possible to receive reproducible results. Another conclusion is that longer ultrasound insonate leads to smaller particles but a wider particle size distribution. A wider particle size distribution may result due to the fact that when ultrasound is applied on and off some particles are produced and able to grow and when ultrasound is turned on again smaller particles nucleate and some of the larger particles possible break apart, contrary to the solution where ultrasound is applied only once. If ultrasound is only applied once particles nucleate and keep on growing till equilibrium is reached, once the ultrasound is turned off. Hardly any new particles will develop and a narrow size distribution is reached.

These results confirm the information gathered by microscope analysis.

4.3.1 The Recommended Method of Creating Seeds

The recommended method of producing the seeds, according to the results, is using Setup 3 as described in chapter 3.2.3. These experiments were carried out with a concentration of 0.6 ASA : 2 EtOH and the 500 ml flask was filled with 105 g ASA and 350 g EtOH. Good results were created when cooling the solution down to 22°C and applying ultrasound for one minute before the particles were formed. The solution was cooled down to 22°C with water from basin B_{Feed}, with a temperature of 20,5°C. As soon as the 22°C were reached the water in the basin B_{Feed} was also heated up to 22°C to keep the temperature of the seed solution even. The water was circulated with pump P_{Air} at approximately 90 rpm. Ultrasound was applied as soon as the water had reached the temperature of 22°C. Most of the time at this temperature, no particles were visible before applying ultrasound and the nucleation was induced by turning on the ultrasound. Sometimes it was not possible to create nucleation with one minute of ultrasound insonation. This might be because the stirrer was placed slightly at a different height, creating a different flow pattern or that the solution had less heterogeneous particles. Heterogeneous particles can never be completely avoided and make nucleation possible at a lower supersaturation. If nucleation is not induced after one minute of ultrasound insonation, ultrasound insonation should be carried on until nucleation. Stir speeds should be kept at approximately 100 rpm.

4.4 Solubility Measurements – Solubility Curve

The solubility experiments were carried out as explained in chapter 3.3 and the analysis was performed with the density meter as described in chapter 2.3.2. For the calibration curve certain concentrations of ASA in the range of 0.17 – 0.34 (w/w)% were tested. Starting with low concentrations of 1:8 ASA:EtOH up until 3:8 ASA:EtOH.

The results were evaluated with Matlab® (Figure 61).

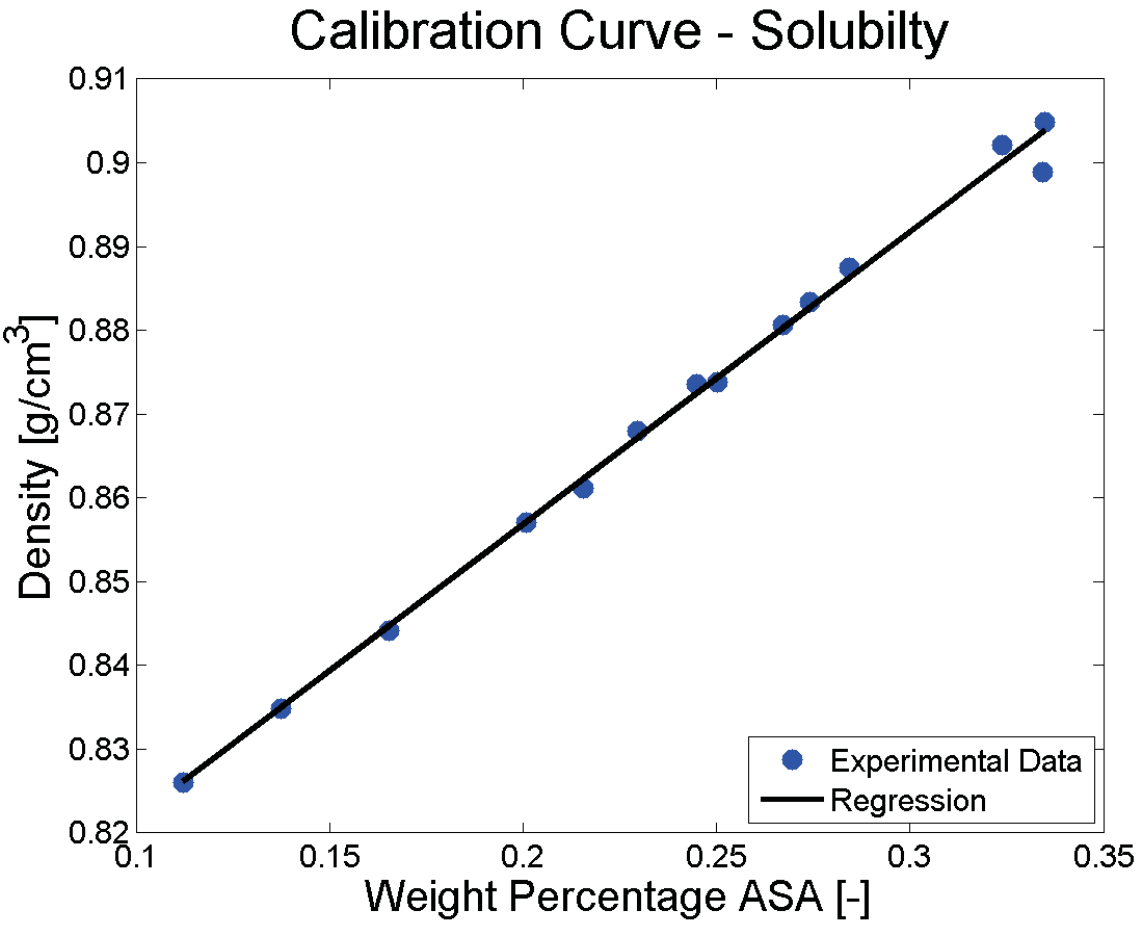

Figure 61: Calibration Curve - Solubility

The experiment was carried out for 47 samples. Each sample was tested 2 – 3 times and the mean density calculated.

In Matlab® the data was entered and a graph was calculated. With the data it was possible to draw a mean curve. The established curve is shown in Figure 62. Some of the analyzing results which may be afflicted with errors were not taken into account for the curve.

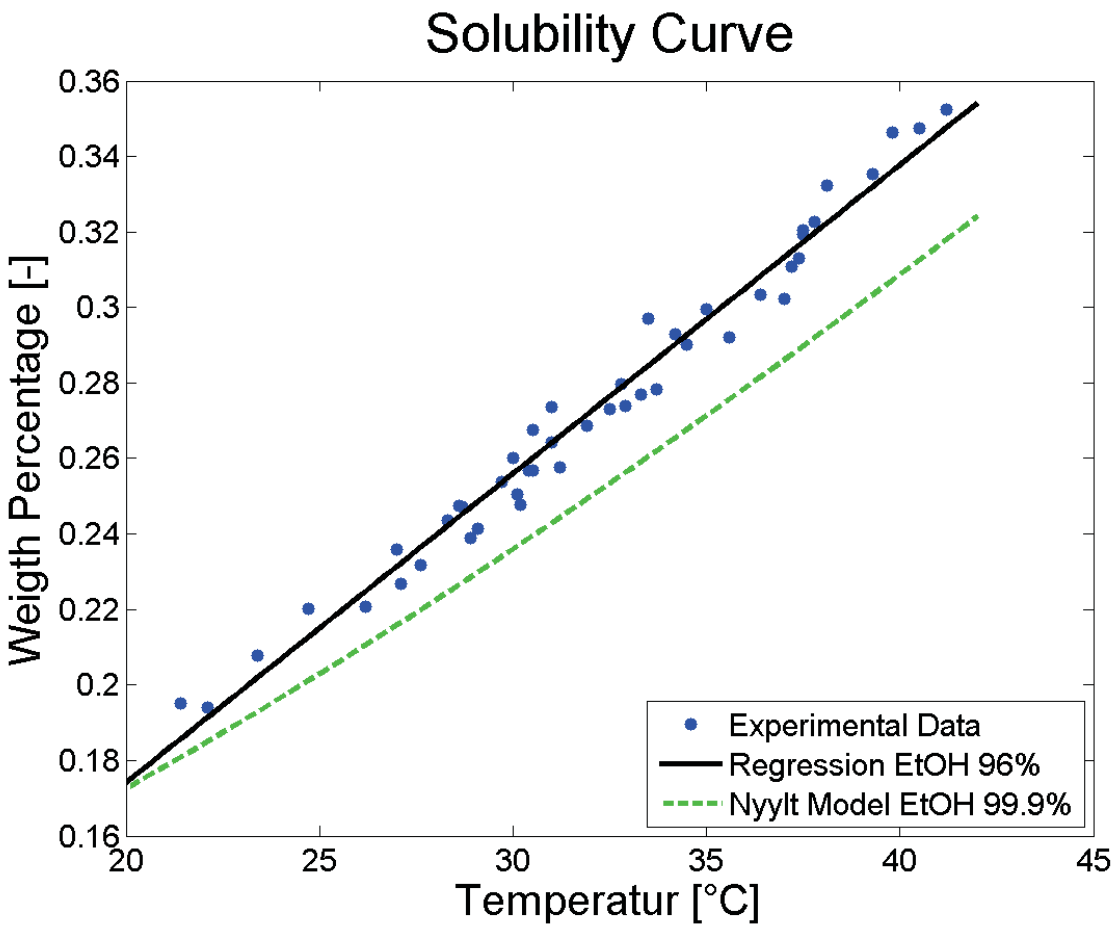

Figure 62: Solubility Curve

A regression curve was drawn through experimental data plots. A linear regression curve was drawn in order to compare the data with the ‘’Nývlt model’’. To compare the data, the plots of the ‘’Nývlt Model’’ [39] were taken and compared to the data. For the ‘’Nývlt model’’ 99,9% EtOH was taken and the plots experimentally taken have 96% EtOH. The solubility of EtOH should first rise with more water percentage and then sink again. As our EtOH only has a little bit more water than the 99,9% EtOH the solubility should rise. Clearly the experimental plots are located above the ‘’Nývlt model’’ curve and refer to this source, correctly.

4.5 Basin Temperature Experiments

Basin temperature experiments with sampling were carried out as described in chapter 3.3.2. They were either analyzed by measuring the weight difference or by analyzing the sample with the high speed camera according to chapter 3.3.1.

Mass Increase/Decrease Determination

For each temperature change, a sample was taken after basin B_1 and after the pump P_{Seed}. Both of the samples were weighed and the mass difference determined. Temperatures in the range of 34 and 37 °C were measured. Table 16 shows the results. The Samples named with S are the samples taken in front of the basin and the ones named with P after the basin.

Table 16: Mass difference (mass before and after basin B_1)

Sample	$T_{Solution}$	T_{Seed}	T_{Basin1}	m_{Seed}	m_{Basin1}	Δm	Mass Difference
-	°C	°C	°C	g	g	g	g
S1_37	37	25	34,7	2.5964	2.6647	0.0683	
P1_37	37	25	34,7	2.5383	2.6027	0.0644	**-0.0039**
S2_37	37	25	34,7	2.5656	2.6283	0.0627	
P2_37	37	25	34,7	2.6163	2.6678	0.0515	**-0.0112**
S1_35	35	25	33,1	2.618	2.6876	0.0696	
P1_35	35	25	33,1	2.5652	2.6661	0.1009	**0.0313**
S2_35	35	25	33,1	2.6266	2.691	0.0644	
P2_35	35	25	33,1	2.6055	2.7233	0.1178	**0.0534**
S1_33	33	25	31,5	2.5694	2.7063	0.1369	
P1_33	33	25	31,5	2.64	2.8404	0.2004	**0.0635**
S2_33	33	25	31,5	2.5966	2.7213	0.1247	
P2_33	33	25	31,5	2.629	2.8245	0.1955	**0.0708**
S1_31	31	25	29,8	2.6099	2.6903	0.0804	
P1_31	31	25	29,8	2.6224	2.7928	0.1704	**0.09**
S2_31	31	25	29,8	2.5406	2.6144	0.0738	
P2_31	31	25	29,8	2.6081	2.9054	0.2973	**0.2235**
S1_34	34	25	32,3	2.5817	2.6188	0.0371	
P1_34	34	25	32,3	2.5996	2.7118	0.1122	**0.0751**
S2_34	34	25	32,3	2.5825	2.6228	0.0403	
P2_34	34	25	32,3	2.647	2.738	0.091	**0.0507**

From the results in Table 16, following diagram (Figure 64) was established. According to the diagram the seed growth starts at temperatures below 37°C.

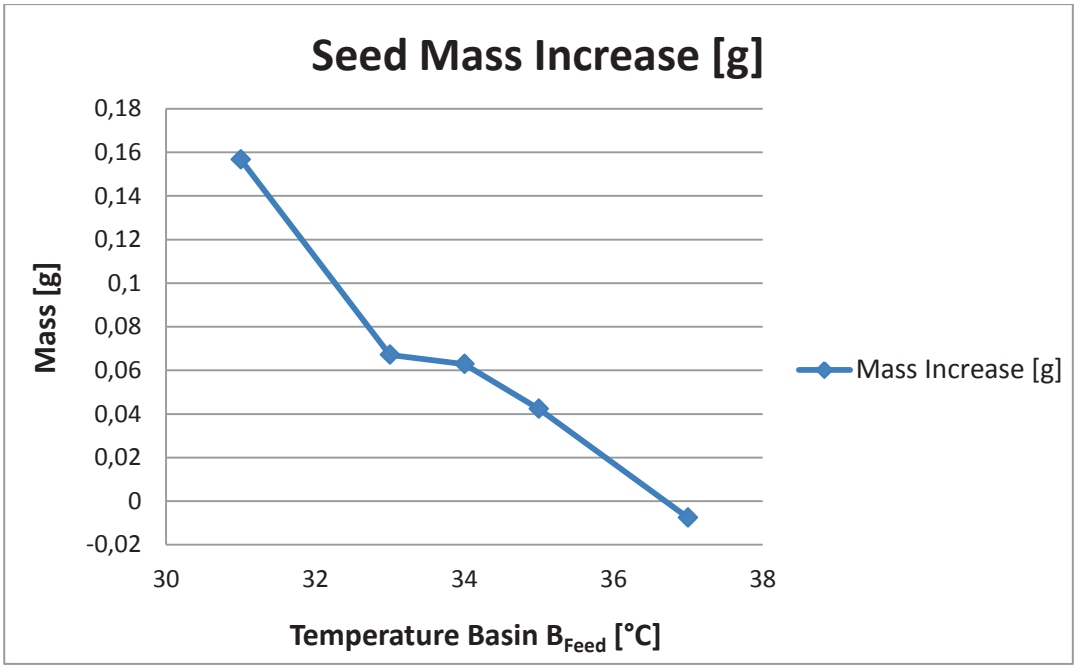

Figure 63: Mass increase measurements for basin temperature determination

Actually this trial should have been carried out together with the air bubbles but right after the trials, crystallization was performed with the determined temperatures and the particles did not dissolve. Even though it worked, the question if the particles dissolve in basin B_1 is not completely answered. It is possible that the particles partially dissolve in the basin. One of the problems when executing the experiment is that it is not easy to determine if the particles dissolve or not because it can only be estimated how many seeds are going in. A second camera is not installed in front of the basin to be able to observe what the solution looks like before it goes through basin B_1. So the results are estimated since they are taken from a perspective view.

Visual Mass Increase/Decrease Monitoring

The experiment was only done with a few conflicting temperatures. These were 35°C, 36°C and 37°C as listed in Table 17.

Table 17: Video analysis of particle visibility

Trial	Basin Feed	Basin 1	Basin Seed	Particles
-	°C	°C	°C	-
1	35	33.1	25	Particles visible
2	36	33.8	25	Not many particles visible
3	37	34.7	25	No particles visible

When the solution went through basin B_1 with its temperature at 34.7°C all particles dissolved and therefore no higher temperatures were tested. Best results were achieved at 35°C where the seeds are not dissolved. The temperatures used for further experiments are the ones listed as trial 1.

The basin temperature experiments should have been performed with the pump P_{Air}. Air bubbles can either slow down the process leaving the seeds more time to dissolve in basin B_1 or speed it up. Unfortunately at the time of the experiment this influence factor was not considered. Another possible error is in sampling as described in chapter 3.4. Furthermore the sample m_{Basin1} was taken at high temperatures and some seeds may have crystallized in the tube between the basin and sampling setup.

According to the mass experiments and video analysis the temperature of the basin B_{Feed} should be 35°C to have a visible seed growth. Higher temperatures cause seeds to dissolve.

4.6 Sampling Analysis

All the sampling analysis tests were performed according to chapter 3.4 and were either analysis with the microscope or as shown in chapter 2.3.4.

Analysis with Pipette

The following microscope pictures (Figure 64, Figure 65, Figure 66, Figure 67) show samples taken with the pump p_{seed} and with a pipette. These crystals were created using ultrasound.

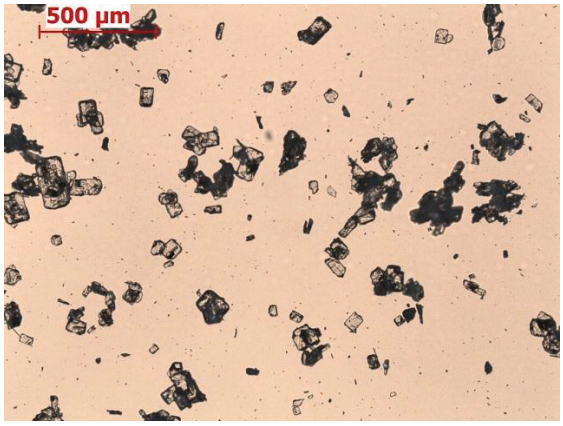

Figure 64: Sample with pump

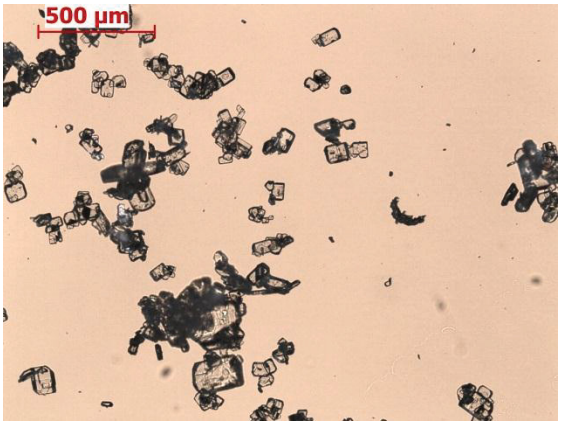

Figure 65: Sample with pipette

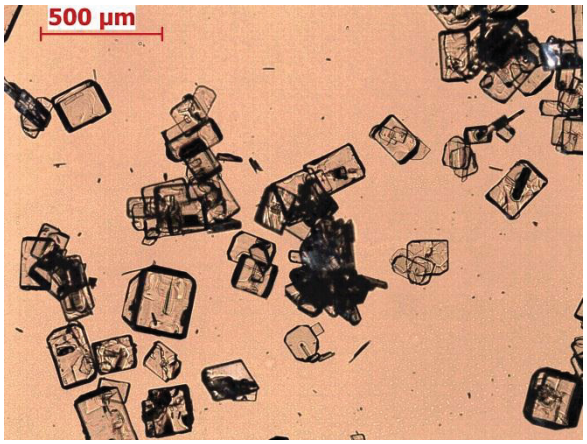

Figure 66: Sample with pump

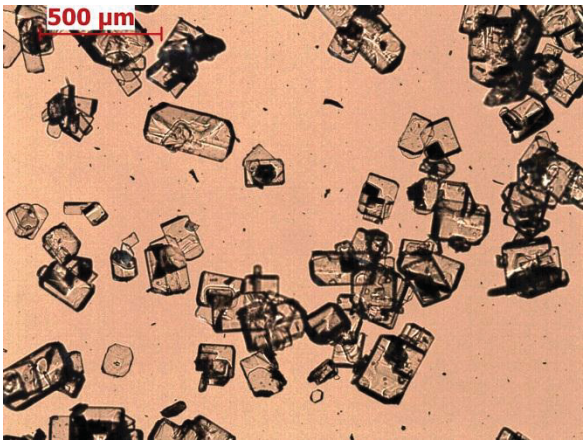

Figure 67: Sample with pipette

No major change in the sample can be detected with either method. The only possible difference is that the samples taken with pipette have a higher amount of aggregates. A reason for this could be that only a small portion of the sample can be analyzed with the microscope or that the aggregates are separated as they pass through the pump.

Analysis with Video

Pictures taken with the high speed camera before and after the pump P_{Seed} are displayed in Figure 68 and Figure 69.

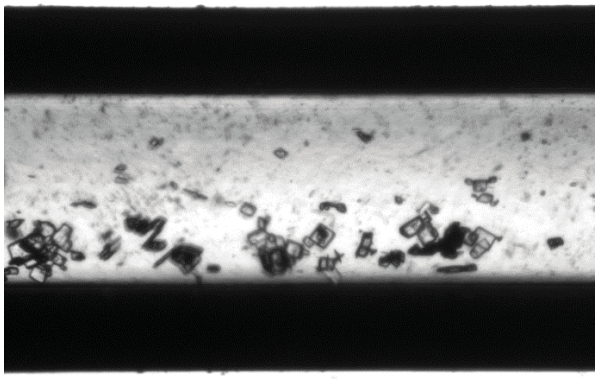

Figure 68: Seeds before pump

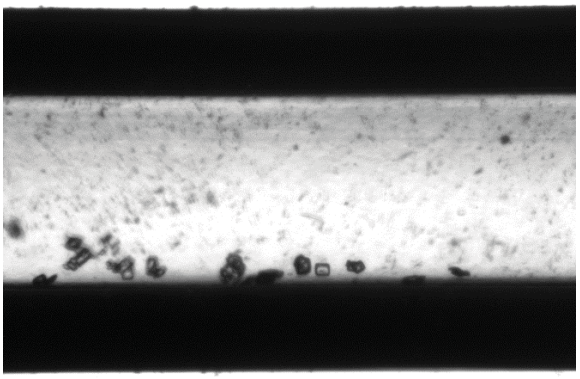

Figure 69: Seeds after pump

Concerning the method of taking a sample with the pipette instead of the pump, only errors due to the pumping and transportation can be ruled out. Other factors like the possible aggregation on the filter or the influence of the room temperature cannot be ruled out. Also with the high speed camera analysis only errors due to the pump are taken into account. Generally analyzing with the video camera was conflicted with errors because it is difficult to focus on the smaller part particles and therefore information on the development of fines could not be gathered. The same assumptions were made, as for the samples taken with the pipette. As a conclusion to the experiments with the pipette it was decided that the particles not passing the pump have less aggregates. The same assumption can be made in this case. This information confirms the belief that the aggregates are crushed in the pump.

As a conclusion it can be said that there are many other influence factors when taking a sample but since the test results are compared relatively to each other, the impact of these influencing factors is limited. Some of these are:

- Transportation
- Room temperature
- Possible aggregation on filter paper
- Scraping off filter paper

As the seeds are **transported** along the tube into the sampling device the surrounding temperature change possibly leads to a change in particle size or aggregation. Also the transport itself can influence the collision rate of the particles and the speed of transportation. The **room temperature** is different to the temperature in the bottle and this may lead to dissolution or growth of seeds during sampling. It is also possible that the particles **aggregate on the filter paper** during sampling. The suspension is dripped slowly onto the filter and the

solution sucked off the filter. It is possible that sometimes the solution is not removed fast enough and due to temperature changes new nuclei are created. The samples are **scraped off the filter paper** after drying. This is done as carefully as possible. Nevertheless it cannot be ruled out that some aggregates are broken up during this process.

4.7 Slug Flow

All the slug flow experiments were carried out according to 3.5. Altogether 40 different settings were tested and it was possible to take 38 results. 13 trials were carried out with tube 1, 13 with tube 2 and 14 with tube 3. As mentioned in the execution procedure in chapter 3.5, for each setting the liquid slug length was measured at the section over a distance of 20 cm. An example of this is shown in Table 18 which shows the results for tube 1.

Table 18: Slug flow results with tube 1 at section 1

Test	P_{Air} Display	P_{Seed} Flow Rate	Total Liquid Slug Length	Total Air Slug Length	Mean Distance Air Slugs	Number of Liquid Slugs	Standard Deviation
-	rpm	ml/min	mm	mm	mm	-	mm
1	6	20	0	-	-	-	-
2	6	20	133	67	10.23	13	5.90
3	10	20	120	80	10.91	11	5.26
4	18	20	101	99	11.22	9	9.39
5	25	20	90	110	9.00	10	5.68
6	6	30	108	92	13.50	8	8.86
7	10	30	132	68	13.20	10	5.59
8	10	30	110	90	13.75	8	6.47
9	18	30	134	66	12.18	11	3.25
10	25	30	112	88	7.47	15	5.42
11	10	40	158	42	15.80	10	11.34
12	18	40	137	63	11.42	12	11.40
13	25	40	53	147	5.89	9	3.95

Each liquid slug length as visible above was measured for pump P_{Air} settings between 6 and 25 rpm. For the tube 3 settings between 6 and 33 were tested. The slug lengths were added together to receive the total liquid slug length. Bearing in mind that the whole measured length was 20 cm, the total length of air slugs was calculated. With the results the mean distance of the liquid slugs and the standard deviation was calculated. Based on this table it can already be seen that the total liquid slug length decreases with increase of air flow. Nevertheless these

results cannot be solely taken into account because they only consider section 1 which is the section where the slugs are still in the process of formation. The results considering all sections and trials were evaluated by means of Matlab® due to the high number of variables.

The first diagram (Figure 70) shows the three tubes comparing the mean diameter of the slugs.

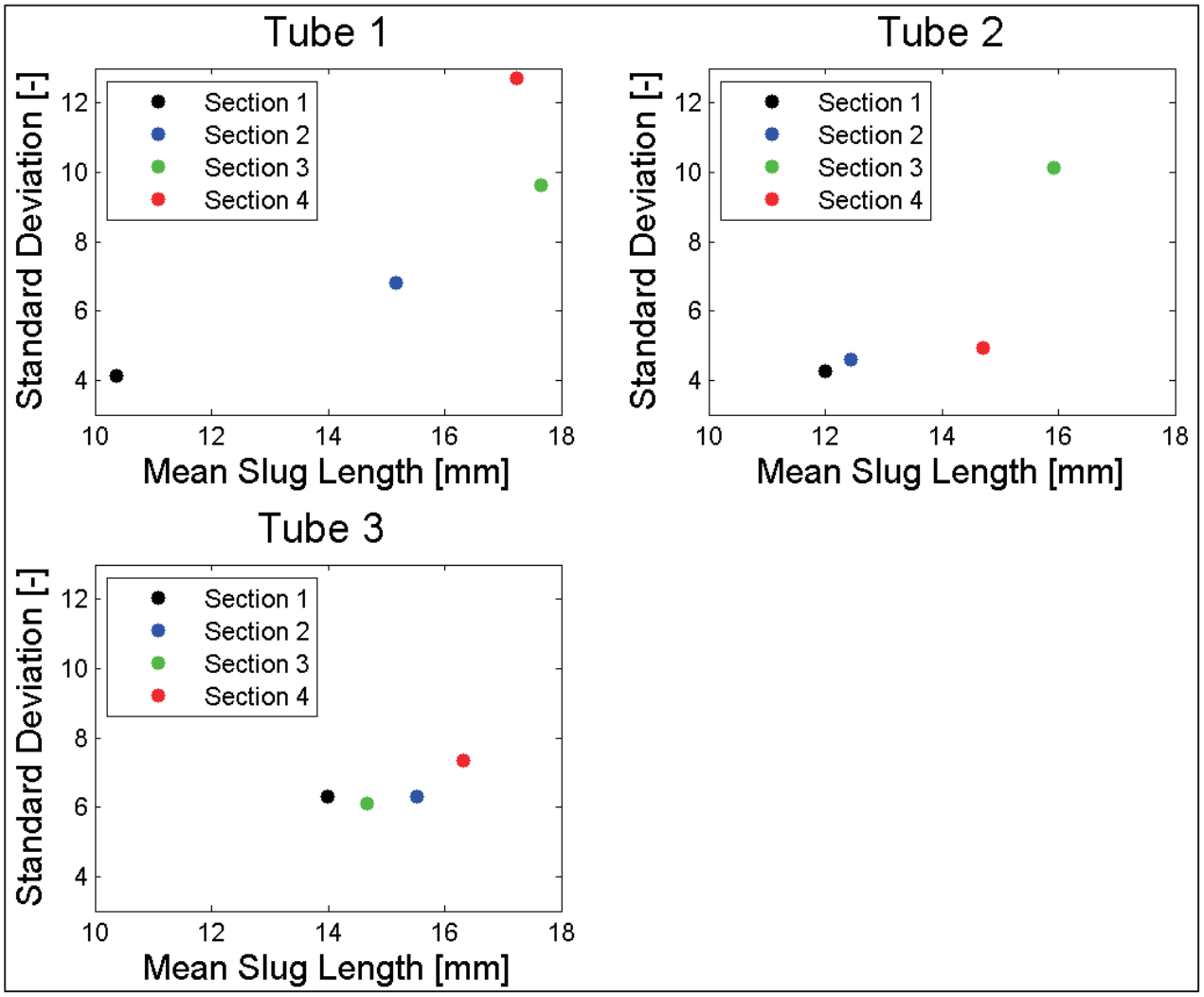

Figure 70: Slug Flow – tube Comparison

The diagrams above show the standard deviation of the mean liquid slug length of each section for all three tubes. The mean liquid slug length was taken of each section over all pump settings. In all diagrams the liquid slugs of the first section are the shortest and have a low deviation. The mean length and deviation increases along the other sections. It is assumed as mentioned in chapter 2.2 that the slugs grow with length of the tube due to the fact that the fronts of the bubbles travel faster than their tails, which would give a possible explanation for this behavior. The received results above hence support this assumption. It can also be seen in the diagrams that the standard deviation increases after section 1 and is the highest for section 3 and 4. The reason for the non-uniformity at the last sections is unknown. It can only be stated

that the deviation significantly increases. Only possible explanation is that some slugs are caught up and larger slugs are formed leading to different sizes. Another important association visible in the diagrams is that tube 1 has the widest mean slug length distribution and tube 3 the smallest. For tube 3 the mean slug length in all sections is similar and the deviation is in the middle field. Tube 1 not only has the highest mean slug length distribution but also the highest deviation. Therefore it can be presumed that tube 3 has the most constant slug flow and tube 1 the least. This would be an applicable assumption because tube 1 is the tube that has been used over the whole course of the thesis and may have signs of abrasion on the inner walls. Uneven surface can influence the flow of the slugs and their stability.

Figure 71 shows the mean liquid slug length during the whole experiment for each tube and the standard deviation.

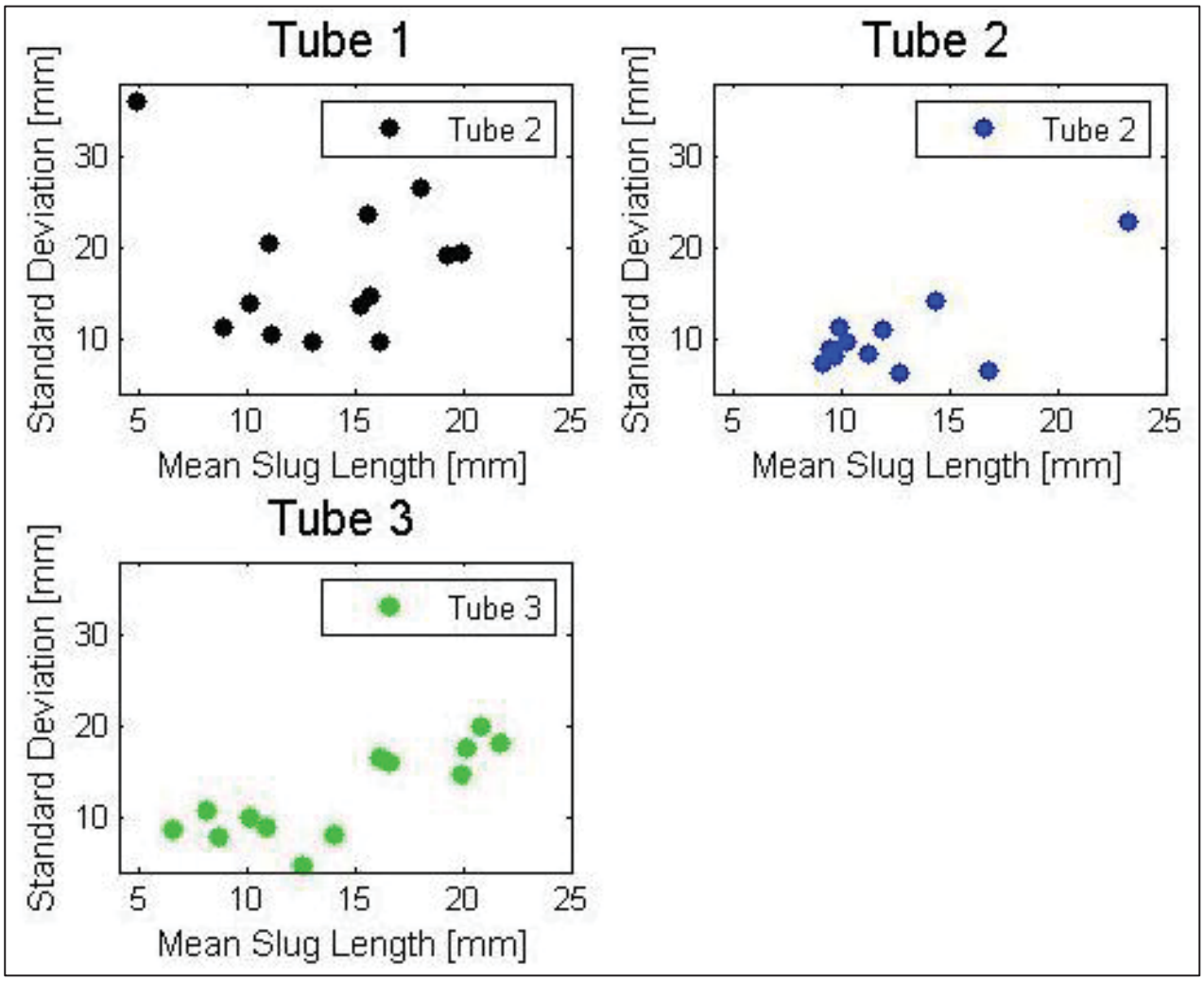

Figure 71: Slug Flow – mean slug length/standard deviation

For all diagrams above, the standard deviation increases with the mean slug length. Small slugs could therefore be more stable but another reason for this could be that the high mean slug

lengths occur at the last two sections which as has been shown, tend to be more unstable than the first two sections. As already concluded from Figure 61, the tube 1 here also has the highest standard deviation and the widest spread, contrary to the plots for tube 2, which are concentrated in one location. Tube 3 has the plots placed around two different spots. Further it is also visible that it was possible to achieve the smallest slugs with tube 3. This may be due to the fact that tube 3 has the smallest inner diameter.

The last significant diagrams that were established show the mean liquid slug length depending on the pump flow rates. The set of diagrams (Figure 72) shows the mean slug lengths at 20, 30 and 40 ml/min flow rate for the pump P_{Seed} and changing flow rates for P_{Air}. The mean liquid slug length is calculated over all sections of the tubes for the various pump settings.

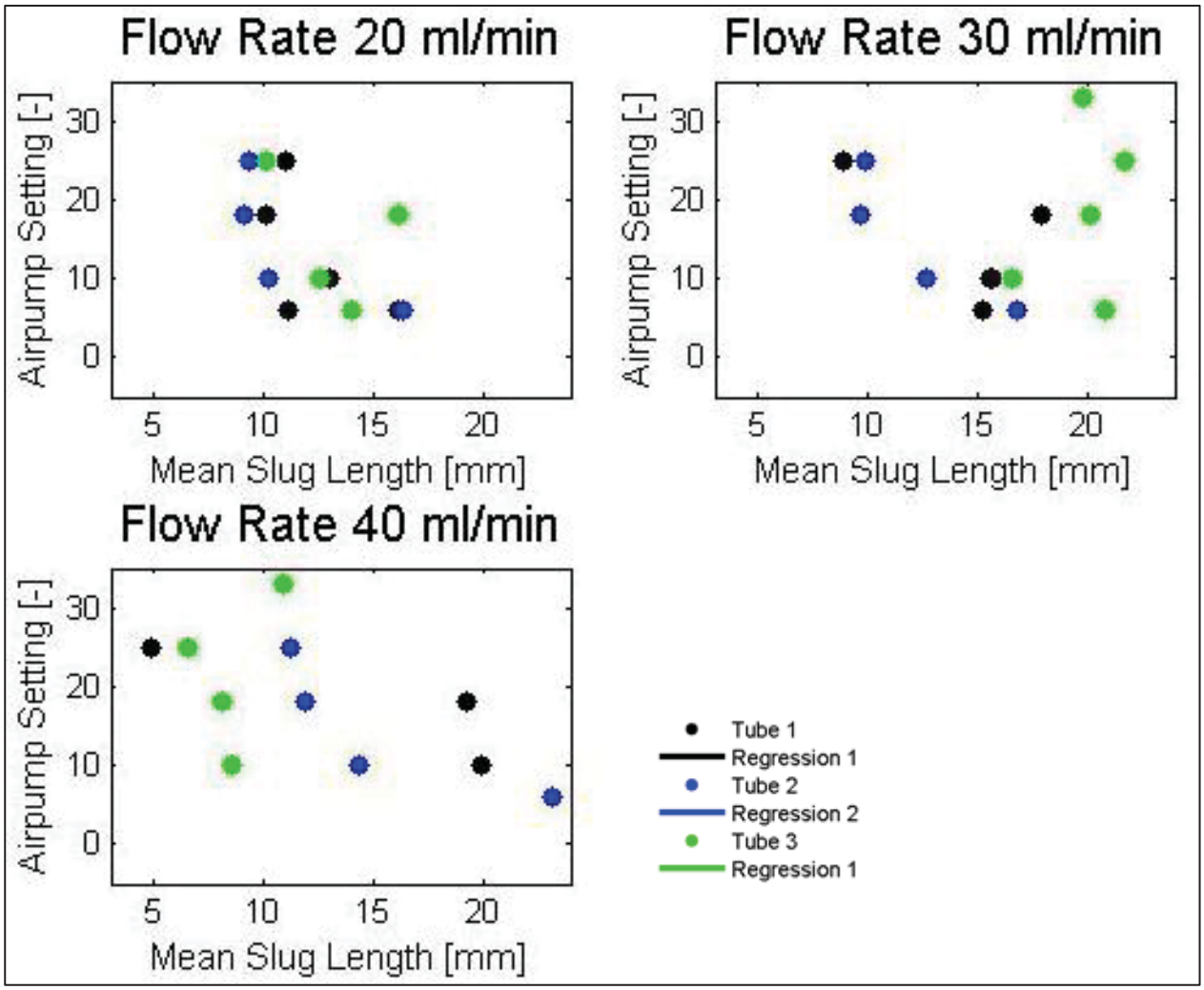

Figure 72: Slug Flow – various pump settings

From the diagrams above it is visible that at low P_{Air} settings, medium mean slug lengths are reached. In most of the diagrams the smallest slugs are reached at high P_{Air} settings. Throughout all the different P_{Air} settings the tube 2 always has a similar distribution with the longest slugs at lower pump settings and the smallest slugs at high pump settings. The pump P_{Air} settings do not seem to greatly impact its slug length.

It can also be seen in the diagrams that for tube 1 and 2 the mean slug length increases as the flow rate of pump P_{Seed} is turned higher. This seems applicable because more liquid is being pushed through the tube. Tube 3 reacts completely different. At first the mean slug length increases rapidly with the pump P_{Seed} and then drop drastically at flow rates of 40 ml/min. A reason for this could be the smaller diameter which may only be able to handle a certain amount of liquid flow.

5 Discussion and Conclusion

A series of small improvements were made to the crystallization process during the thesis. Knowledge of the seed preparation and sampling was gathered and theoretical assumptions could be confirmed through the experiments.

For the **seed experiments** it was first tested if temperature cycles can influence the crystal distribution by reducing the fines. Experiments showed that they do reduce the fines and that the other crystals increase in size but for the crystallization itself they were not suitable due to their size. The large crystals continued to grow in the tube during the crystallization and blocked the tubes. So starting from this point on, the temperature cycles were stopped. Experiments with temperature cycles also showed that they increase the probability of aggregation. At the beginning, the seed experiments were carried out with high mass fractions. With these high mass fractions, it was easier to create suitable seeds but the concentrations of seeds were too high for the actual crystallization process. Due to this the concentration was lowered and new seed experiments had to be conducted because the system reacts differently when they are cooled. Soon it was realized that the best seeds are created by cooling the solution very quickly at low temperatures. At low temperatures the least amount of aggregates and fines will occur. Even though this method worked most of the times, it was not possible to reproduce the results each time due to the changing room temperature. Therefore the setup was changed to setup 2 and the initial concentration increased and diluted after crystal development. These experiments did not have the wanted effect. It was hoped that with dilution, the seeds would all shrink in size but instead some seeds dissolved, some shrunk a bit and others did not change at all. Based on these observations it was decided to try crystallization with ultrasound as shown in setup 3. The results soon showed that ultrasound has a positive influence on nucleation. If it is applied after nucleation, it leads up to splitting of the particles and is not suitable. On the other hand if ultrasound is induced to create nucleation it results in less fines and aggregates. It was found this is a very effective method of producing suitable seeds. As conclusion the ultrasound method was the final and best method of producing the seeds. The longer ultrasound is induced during nucleation the smaller are the formed crystals. Seeing that small seeds are produced, medium sonation periods of one minute are considered as optimal. During these experiments it was realized that the temperature at which the ultrasound is applied is critical. If it is applied to early only a few nuclei will form and then grow if the solution is cooled further. On the other hand if it is applied too late, new nuclei will be formed and the already existing seeds will split up or grow even more, resulting in a large particle size distribution. The samples taken after application of ultrasound were analyzed with microscope and HELOS. Both independent examinations showed the same tendencies. The conclusions from the experiments are summarized below:

<u>Temperature Cycles:</u>

- More aggregates
- Larger particles

- Less fines

Low temperature cooling:

- Larger particles
- Less fines

Seeding:

- Further experiments need to be carried out to understand the process

Higher stir speeds:

- Faster nucleation

Ultrasound

- Smaller particles
- Less aggregates

Dilution with EtOH:

- Large particle size distribution
- Some very large particles
- High number of aggregates

Even though a lot of information was received on the behavior of crystal development, it was not possible to find a generally practicable way of producing them. In order to do so, it would be necessary to have a more complex process monitoring to receive additional information on the width of the metastable phase. It is no possible to define a certain temperature at which no nuclei exist and nuclei will develop as soon as ultrasound is turned on. This would be the wanted effect because small seeds would develop and a narrow size distribution would be achieved because no already existing seeds would have grown beforehand. It can only be assumed from the test, that with the final concentration this temperature is somewhere between 22 and 22.5°C. If ultrasound is applied in this gap during cooling, nucleation is very likely possible.

During the thesis the **procedure of sampling** was tested. Results showed that the pump does not have a great impact on the seeds. Minor changes can be found in the aggregates. It seems as though the pump decreases the amount of aggregates. This could be due to the fact that the seeds are crushed in the tube. The samples taken with the pipette and the analysis with the video camera both showed the change of aggregates. Therefore the existence of fines in the samples is not due to the pump. Other sampling problems with sampling could be the influencing factor. Consequently it can be assumed that the used sampling procedure does not have a major influence on the crystal parameters. Minor changes could only be found in the

number of aggregates which seemed to decrease due to pumping. Undesired results can therefore not be reduced to the method of sampling and it is suitable for further use.

The **determination of the solubility** of the crystals in the solvent, depending on the temperature was an important progress. Based on the solubility experiments it was possible to establish a solubility curve. Even if the factors causing possible errors are taken in account, the curve should still have a high accuracy because altogether 47 samples were tested. The established curve was also compared to the ''Nývlt model'' curve for 99,9% EtOH and showed the credible deviation. Also practical experiences showed that the curve can be put into practice. With the solubility curve it is easily possible to determine the solubility temperature of any concentration within the curve without having to proceed with extensive trials. The basin temperature experiments had to be carried out anyways because at that point the solubility curve had not been completed. For monitoring the process the solubility is of great importance and using the established solubility curve the necessary temperatures of the basins can easily be determined. Also the density of a sample can be checked while the process is running for the determination of the concentration.

Basin temperature experiments had to be carried out in order to determine the temperatures of the basins for the tubular crystallization due to the fact that seeds were dissolving in the basins instead of growing. The results that were determined with the mass difference and the visual experiment, both proved to be similar and when put into praxis enabled crystallization without dissolving the seeds.

Slug flow experiments were carried out to see if different types of tubes have a great influence on the development of the seeds. Results showed that the tubing has more influence than expected. The tube used up to the point of carrying out these experiments, the Versilic® silicone tube, is least suitable for creating a stable continuous slug flow. Even without considering the measured results, it was clearly visible when running the process that the Versilic® silicone tubing is not suitable for running the process. Findings concerning the slug flow were:

Settings pump P_{Air}

- For tube 1 and 2 the mean liquid slug length is reduced with higher air flow rates

Settings pump P_{Seed}

- For tube 1 and 2 the mean liquid slug length increases with flow rate

Standard deviation:

- Increases with the means liquid slug length for all tubes
- Increases with each section

Means liquid slug length:

- Increases along the sections
- Highest lengths at last two sections

Tubes:

- Tube 1 has the highest standard deviation and widest spread
- Tube 3 has the minimum mean slug length

Sections:

- High mean liquid slug lengths at last two sections
- Liquid slug lengths highest at first section
- Liquid mean slug length increases with the sections

Taking these results it can definitely be concluded that tube 1 is not suitable for the process and that both tube 2 and tube 3 are suitable for the process. It would be necessary to carry out further experiments to make a final and affirmed decision. If one would have to be picked at this point it would be tube 2 because not only did it achieve good results but also the formation of the slugs seemed best during the experiment. The pump p_{Seed} settings do not have a great influence and can be kept at 31 ml/min as usual for further experiments. The pump P_{Air} should then be adjusted depending on the desired mean liquid slug length which should be kept as low as possible because longer slugs have a higher standard deviation.

Conclusively many small changes were made to the process and it was possible to run it more smoothly due to the improvements. Many issues still need to be analyzed in order to obtain a continuous tubular crystallization. For example a major improvement was made to the seeds. A lot of experiments were done to find the right method of preparing the seeds. After many different experiments the method using ultrasound was used and implemented and a major step done towards running the process of crystallization in the tubular reactor. Yet a lot of issues still have to be resolved. For example determination of the exact pump speeds. Especially concerning the process monitoring there is still a lot of room for improvement. Other problems that have to be resolved to enable a better regulation would be an on-line measuring method for the seeds and products. Nevertheless if these issues are resolved there is a great change of being able to control the particle size distribution.

6 Summary

In this thesis crystallization in a tubular reactor was analyzed and various experiments were carried out to run and improve the running process. These experiments included the analyzing of the seeds that were fed into the reactor, determination of a solubility curve, the determination of the water basin temperature and the evaluation of the sampling and analyzing methods. These analyzing methods included the QICPIC, HELOS, high speed camera and microscope. Of all analyzing techniques the microscope seemed the most suitable for this process because the aggregation can only sufficiently be determined with this method. The QICPIC results concerning aggregates are not feasible because it only detects uneven particles as aggregates. QICPIC analysis was performed only to see how the particle sizes distribution varies because information solely on the seed size could already be gathered with the microscope. Seed experiments were done to feed seeds into the process without aggregation with less fines and small particles. Therefore about 100 experiments were carried out with the seeds using various methods including temperature cycles and shock cooling until a suitable method was discovered. This was the production of seeds by using ultrasound. According to various references listed in 2.1.4 the produced seeds should be smaller when ultrasound is applied and the amount of fines reduced. This was confirmed by the experiments that were carried out and consequently this method was settled on for the establishment of the SOP. During the thesis a solubility curve for the used solution of 96% EtOH and ASA was established. Means this curve it was then easier to define certain process parameters without having to establish them through trial and error. Other smaller experiments were carried out to test the method of sampling which turned out to be satisfying at this point of the project. For analyzing of the seeds it is primarily important to get information on the aggregation which can be sufficiently observed by microscope. At least it can be evaluated in relation to the other samples. The sampling procedure was tested with the high speed camera before and after the pump where no great differences were seen. Later the sampling was tested again by taking extra samples with the pipette instead of the pump. Likewise these samples showed little variation. Last experiments undertaken were the slug flow experiments. These were necessary to decide on an appropriate tube for the process and to determine differences in the slug flow by changing parameters like the air and solution flow speeds. Further different types of tubes were tested. Due to all the analyzing that was performed on the crystallization process it was possible to improve and develop a suitable method of running the process. Once all these mentioned issues are completely resolved, there is a great chance of being able to control the particle size distribution and eventually to introduce an innovative crystallization process at an industrial scale.

7 Directories

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7.2 Abbreviations

°C	Grad Celsius
etc.	et cetera
(w/w)%	Weight percentage

7.3 Tables

7.4 Figures