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Growth of single salicylamide crystals has been investigated in a non-stirred growth cuvette and on a rotating disk. In the growth cuvette the crystal growth rates were measured for both primary nucleated crystals and seed crystals manually inserted into the cuvette. In the rotating disk experiments multiple seed crystals were attached to a disk that was rotated in a supersaturated solution. The crystal growth rates in the length and width direction were precisely measured *in-situ* for each individual crystal; and growth rates were also extracted for a specific crystal facet i.e. (200). In all cases, the growth rate was considerably faster in the rotating disk experiments, shown to be governed by surface integration. Solvent was found to impact the growth rates of the crystal facets in part by creating different surface features. The influence of the supersaturation on the crystal growth rate depended on the solvent, in general an increasing trend was observed. At relatively low supersaturations, it was discovered that the growth process will focus on repairing morphological defects. Within the range of experimental conditions, the growth kinetics were strongly affected by the temperature as was further indicated by the relatively high activation energy values obtained. The crystal seed quality was found to have a substantial impact on the growth rate, with rougher crystals leading to quicker growth. A wide growth rate dispersion was obtained for both crystal growth methods, found to be reduced by using seed crystals with high quality, lower supersaturations and also within certain solvents.

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Title Page

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Abstract

Growth of single salicylamide crystals has been investigated in a non-stirred growth cuvette and on a rotating disk. In the growth cuvette the crystal growth rates were measured for both primary nucleated crystals and seed crystals manually inserted into the cuvette. In the rotating disk experiments multiple seed crystals were attached to a disk that was rotated in a supersaturated solution. The crystal growth rates in the length

and width direction were precisely measured *in-situ* for each individual crystal; and growth rates were also extracted for a specific crystal facet i.e. (200). In all cases, the growth rate was considerably faster in the rotating disk experiments, shown to be governed by surface integration. Solvent was found to impact the growth rates of the crystal facets in part by creating different surface features. The influence of the supersaturation on the crystal growth rate depended on the solvent, in general an increasing trend was observed. At relatively low supersaturations, it was discovered that the growth process will focus on repairing morphological defects. Within the range of experimental conditions, the growth kinetics were strongly affected by the temperature as was further indicated by the relatively high activation energy values obtained. The crystal seed quality was found to have a substantial impact on the growth rate, with rougher crystals leading to quicker growth. A wide growth rate dispersion was obtained for both crystal growth methods, found to be reduced by using seed crystals with high quality, lower supersaturations and also within certain solvents.

Keywords: Crystal Growth Kinetics, Diffusion Control, Surface Integration Control, Rotating Disk Method, Solvent Effect, Morphology, Individual Facets, Growth Mechanism.

Introduction

Crystallisation is a very important technique, especially in the pharmaceutical industry, as it is used in the formation, purification and recovery of the majority of active pharmaceutical ingredients (API) [1-2]. Crystallisation is a two-step process: initial nucleation followed by subsequent crystal growth. Presently, crystallization fundamentals of both steps are still insufficiently understood, and the crystal growth kinetic data can differ by an order of magnitude for the same API depending on the laboratory generating the data. Literature depicts many ways in which the crystal growth process can be observed and associated growth rates measured dependent on the crystal growth method used [3-14]. These methods can be split into either single crystal growth or multiple crystal growth, the basic difference being that in the first type of method the actual growth rate of the individual crystal is recorded while in the second type the average growth rate of an ensemble of crystals is determined without distinguishing the growth of each individual crystal. An advantage of single crystal growth methods is that the detailed growth in different directions and of different faces can be measured [2, 15]. However, the hydrodynamic conditions that can be used are restricted and often far from those in a real crystallizer. Benefits of the multiple crystal growth methods is that a better statistical averaging can be obtained and the hydrodynamic conditions can resemble industrial conditions.

There have been surprisingly limited kinetic studies on the growth of the individual faces of spontaneously-nucleated crystals grown in stagnant solutions. Recent work by Nguyen studied the influence of solvent on the growth rate of ibuprofen crystal facets and overall crystal habit using a stagnant solution in a cuvette [14]. Such measurements are helpful in that they provide baseline crystal growth kinetic data from which the impact of e.g. seeds, agitation and mixing can be assessed subsequently. Since the 1970's researches have made attempts at introducing mixing of the solution into single crystal growth experiments in order to control the hydrodynamics. The most successful was a simple closed flow cell combined with an optical microscope to observe the growth of the (100) face of ammonium dihydrogen phosphate crystals [10]. Since then this single crystal growth method using liquid flow has been used by many to study the growth rates of other compounds such as glycine, α and β polymorphs of L-glutamic acid [3, 5, 11, 16-17]. The issue with this flow design results in growth being unidirectional, so growth of the crystal is not representative of a true crystal. In addition, it becomes very tedious to obtain statistically valid data over a number of crystals. Rotating disks have also been used a few times to study crystal growth in a mixed solution [18-19]. However, they only studied the growth of one compressed crystal plane. By using an agitated batch crystalliser combined with a high speed camera it has been shown to be possible to measure the growth rates of either the length and width or facet direction for a number of individual crystals grown at once [13, 20-21]. The disadvantage of this analysis is that the growth of a specific crystal can't be tracked, rather results are averages of the whole crystal population.

A similar approach to the work of Nguyen will be used in our study to determine the growth rates of single salicylamide crystals in a stagnant solution in a cuvette. Furthermore, an alternative multiple single crystal growth method has been developed where the hydrodynamic environment is controlled by attaching a number of seed crystals to a rotating disk, yet can also track multiple single crystals for their specific facet growth rates at once. Salicylamide's properties including its chemical, uses, classification, and solubility have already been described in detail [22-24]. The pharmaceutical industry is also interested in how the process conditions such as temperature, solvent, supersaturation, and seed quality effect the crystal growth kinetics and so these have been investigated in this study [2, 14, 25-27].

Experimental

Materials

The solute (salicylamide, SAM) and the solvents (acetone, AC, acetonitrile, MeCN, ethyl acetate, EA, and methanol, MeOH) all had purity ≥ 99.0%. All were purchased from Sigma Aldrich and used as received.

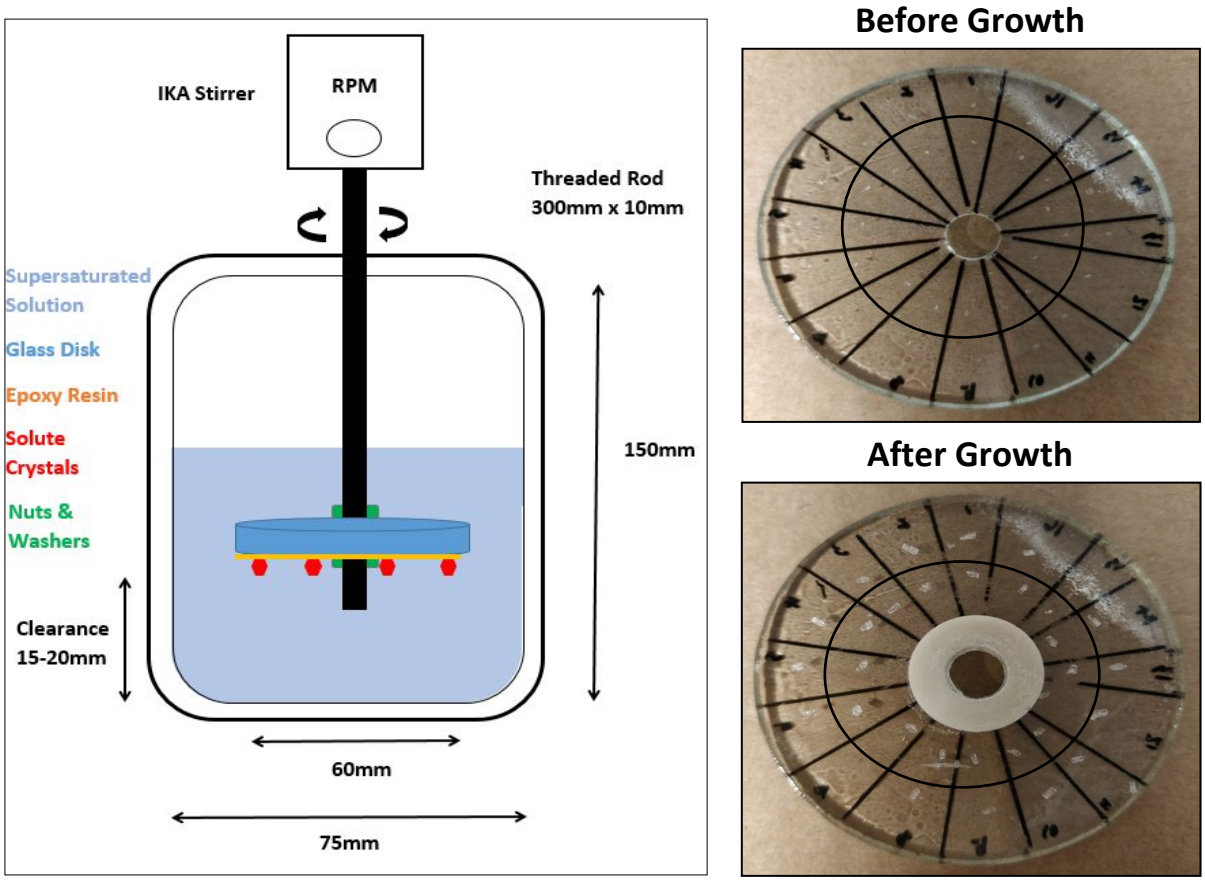
Seed Crystal Preparation

Salicylamide was supplied as crystalline material, the polymorphic form of which was confirmed by P-XRD (PANalytical Empyrean X-Ray diffractometer) and found to be the required stable form so was deemed suitable for use without the need for recrystallization. Crystals were sieved using fisherbrand stainless steel woven wire mesh test sieve with a 300-355 μm aperture; the resulting sieve fraction was used as the seed crystals in both crystal growth methods.

Cuvette growth experiments

A spectrophotometer cuvette 0.4 mL (55 x 10 x 1 mm, Starna Cells 21-SOG-1) was used as a growth vessel. Both the growth of seed crystals (sieve fraction 300-355 μm) and also spontaneous nucleated crystals were studied under stagnant growth. At the start, crystal seeds were either mechanically placed inside the cuvette before the start of the growth experiments or they were generated by primary nucleation *in-situ* in the cuvette. For both crystal types, the cuvette was filled with supersaturated solution; which was prepared by dissolving excess solute in solvent with sufficient mixing for minimum 1 hr and then let to settle and filtered with a 0.2 μm filter. This cuvette was placed into a shallow closed tank of water connected to a circulator (Lauda ECO Silver, RE415) to control the growth temperature at 15 °C and placed onto the microscope stage. Crystals were allowed to grow for 1 hr, with micrographs captured at either 1 or 10 min intervals

using the optical microscope. The spontaneously nucleated crystal growth experiments used a relatively higher supersaturation, S-1 in the range of 0.24 – 0.89, than compared with the seed crystal growth experiments, S-1 in the range of 0.02 – 0.12, to induce spontaneous nucleation. The growth of a minimum of 5 crystals was determined for each condition, so that an average of the growth rates could be calculated. Crystal growth of both single crystal types were studied in four solvents (AC, MeCN, EA or MeOH). Also, each crystal type was studied under two different supersaturations per each solvent. The crystal increased in size for the first 2 to 10 min for spontaneously nucleated crystals and 30 min to 60 min for seed crystals but then began to plateau as surrounding solution became saturated.



Rotating disk growth experiments

Figure 1. Schematic for the apparatus set-up for single crystal growth studies using a rotating disk. Glass disk has diameter 60 mm, and hole in center, for stirrer, is 10 mm.

A jacketed 500 mL glass reactor with inner diameter of 75 mm and a rotating 60 mm glass disk, as shown in Figure 1 was used as the growth vessel. Reactor was kept at a constant crystal growth temperature by using a circulator (Lauda, RE305 series). A total of 32 crystals of sieve fraction 300 - 355 μm were attached evenly onto the glass disk using a thin layer of epoxy resin, and allowed to set for a minimum of three hours at 40 °C. Crystals were orientated in such a way so that they were lying flat on the disk with their largest facet facing upwards, they were gently placed on top of the glue so they did not become embedded within the resin which allowed both the top and side facets of the crystals to grow. Slightly supersaturated solution was prepared in the reactor by adding a known amount of excess solute to 200 mL of solvent and let to mix at 250 rpm using a 60 mm 4-pitched-blade PTFE coated impeller with inclined blades at 6 °C above

crystal growth temperature for 20 min. Reactor temperature was then decreased to required growth temperature, and allowed to stabilise for a further 20 min. Impeller blade was removed and replaced with a 316 stainless steel rod which had the glass disk (with crystals) attached using steel nut and washers. Disk was left rotating at 200 rpm for a growth period of 1 hr. Micrographs of each crystal were captured before and after the growth period using an optical microscope. Crystal growth rate of single crystals were studied at 15 °C in four different solvents (AC, MeCN, EA or MeOH) and at different supersaturations (S-1 of 0.007 - 0.05). In acetonitrile also the influence of temperature was investigated by additional experiments at 10 and 20 °C. Growth rates for each of the 32 crystals were calculated and also the average growth rate of all the crystals grown in one system. To ensure that decay of supersaturation concentration was negligible throughout the growth period the concentration decay was measured experimentally and found to be <3 % i.e. maximum supersaturation decay would result in an initial supersaturation of 0.030 decreasing to 0.029 after the 1 hr growth time [refer to supplementary section for outline of these calculations].

Certain experimental variables were trialled to determine the optimum parameters for the rotating disk experiments which are defined above. The variables that were tested included the overall number of crystals attached on the disk (32 vs. 48) plus their respective position and also the growth time (10 min up to 2 hr). Also the method was repeated three times using the same conditions to determine reproducibility of experiments and proved successful (average growth rate of length was 0.28 ± 0.02 μm/s). Results of all of these trial studies can be found in the supplementary section.

Measuring crystal growth rate

For both of the single crystal growth experiments, micrographs of the crystals were captured using an inverted light optical microscope (Olympus IX53) integrated with Olympus SC100 camera. The size of the crystal in a certain dimension at each time point was measured directly from these micrographs using the image/ video capture and analysis software (Olympus Stream Essentials). Measurements were taken in both the length & width (maximum and minimum feret diameter respectively) direction and more precisely the miller indexed (200) face for SAM (as illustrated in Figure 3). Example of the micrographs and measurements taken at different stages during the growth period are shown in Figure 2. In this case, the (200) face was equivalent to the width measurements divided by two. It is worth noting from Figure 3 that

measuring the growth of SAM in the width direction is not always representative of the same crystal facet. For the SAM crystal shown on the left, the width represents the (200) face, whereas for the SAM crystal on the right hand side the length represents the (200) face. This causes issues when reporting growth rates in terms of length and width for SAM as it can lead to potentially larger GRD due to measuring growth of different faces. This highlights the importance of reporting growth rates for crystal facets rather than just directions.

The crystal growth rate of the crystal is determined by plotting the size of the crystal versus the time and obtaining the slope of the line i.e. the growth rate in specific direction, G (μms^{-1})

$$G = dL/dt \quad (1)$$

Where G is the rate of change of the crystal's characteristic dimension, L, has dimensions of velocity with respect to time, t.

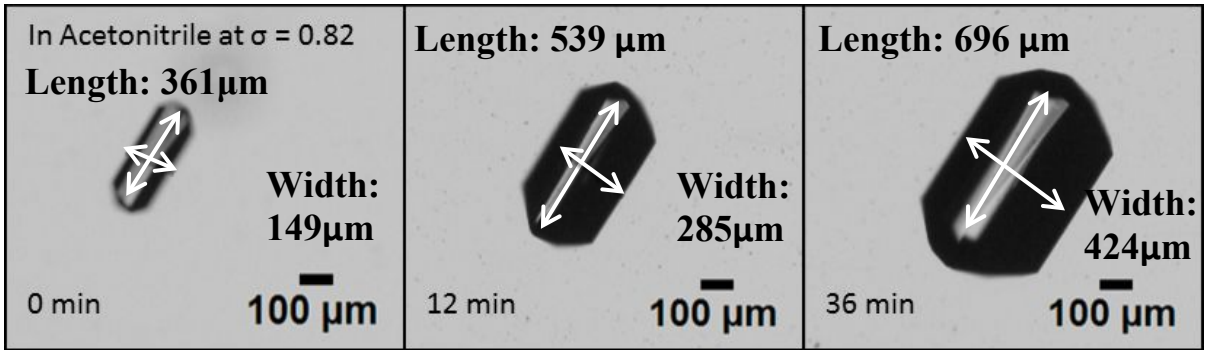


Figure 2. Series of micrographs of salicylamide crystals grown by the cuvette growth method using spontaneous nucleation in acetonitrile using S-1 of 0.82 at crystal growth temperature of 15 °C as a function of growth time.

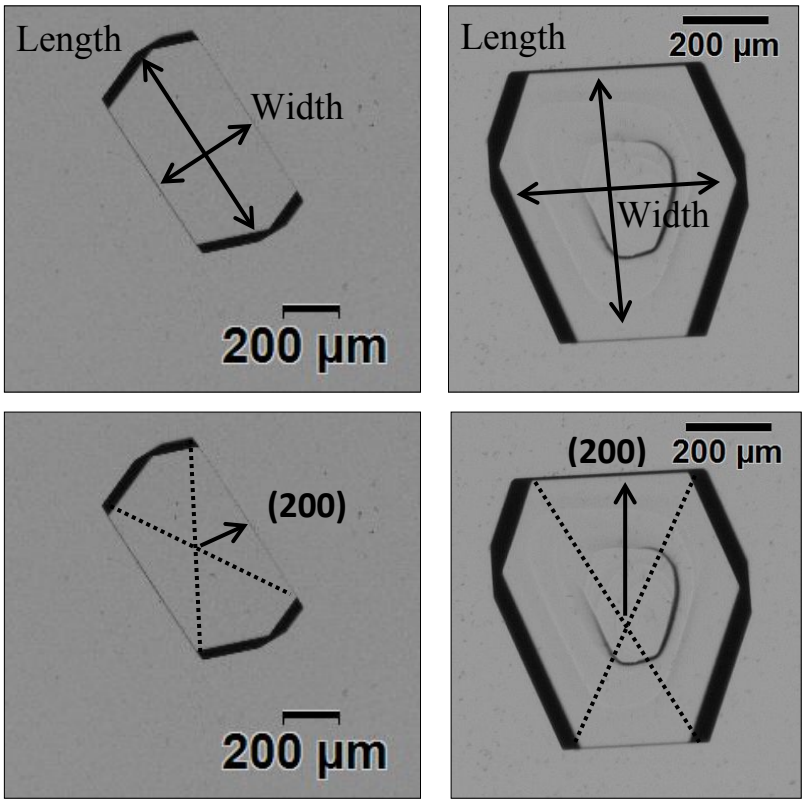


Figure 3. Micrographs taken during single crystal growth studies, with length and width and also (200) face identified of salicylamide crystals, for rectangle plate and block habit respectively.

Crystal surface analysis

The surface of the SAM crystals was analysed using a scanning electron microscopy (SEM), Carry Scope JEOL JCM-5700. Prior to visualisation with the SEM the crystal samples were gold coated with 20 mA for a maximum of one minute.

Results and Discussion

Cuvette growth experiments

Habit

Individual spontaneously nucleated crystals and seed crystals grown in a stagnant solution in each of the four solvents under different supersaturations are shown in Figure 4. Under certain conditions, spontaneously nucleated crystals and seed crystals can grow to a maximum width of 500 μm and 850 μm respectively. Seed crystals grew 2.5 times the size in width direction and 5 times the size in the length direction at certain conditions (850 x 1700 μm). For crystals that were spontaneously nucleated as shown in the top two rows, the crystal habit differed depending on the solvent and initial supersaturation. When crystals were formed and grown from acetone and methanol, the rectangle crystal habit of salicylamide depended on the level of initial supersaturation, while at the lower supersaturation less elongated particles were being observed. On the other hand, in acetonitrile, regardless of the initial supersaturation, elongated rectangle particles were formed. In ethyl acetate, the crystals formed irregular hexagonal plates regardless of the initial supersaturation. This habit change has been discussed in detail in our previous work were we also examined the underlying crystal structure of the main crystal facets of salicylamide at a molecular level in attempt to understand the growth process [30]. When performing similar single crystal growth studies but using seed crystals as shown in the bottom two rows, the influence of solvent on the crystal habit of salicylamide appears to be negligible. Instead, the initial rectangular plate habit of the seed crystal was maintained throughout the growth period in all four solvents.

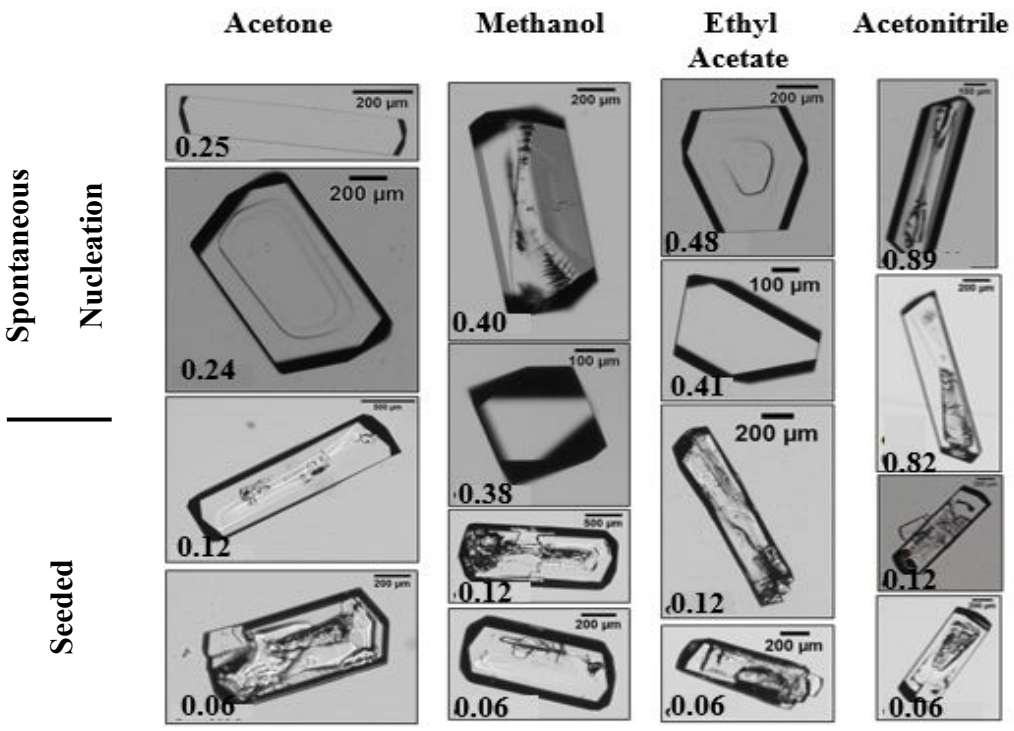


Figure 4. Micrographs of salicylamide crystals grown using the cuvette growth method at 15 °C. The top two rows refer to spontaneously nucleated crystals whereas the bottom two rows refer to the seed crystals. For both crystal types, micrographs are shown for each of the four solvents, under different supersaturations (the S-1 value is shown in the bottom left hand corner of each image, and ranges from 0.89 to 0.06). The crystals displayed here represent the dominant habit obtained in each condition, when each condition was repeated for a minimum of five crystals.

Kinetics – Effect of Solvent and Supersaturation

The average crystal growth rate of spontaneously nucleated and seed salicylamide crystals, as a function of solvent and supersaturation, is similar for length and width as shown in Figure 5. Growth rate of the length direction is faster than the growth rate of width direction of crystals at all conditions, by a minimum factor of 2. The average growth rate ratio of length to width increased with increasing supersaturation value for spontaneously nucleated crystals, whereas the ratio decreased with increasing supersaturation for seed crystals as shown in Figure 5 (e, f). In other words, spontaneously nucleated crystals grow at a similar rate in either dimension under the two supersaturations tested. Whereas seed crystals grow differently in the length and width dimensions depending on the supersaturation used; crystals grow proportionally faster in the width dimension than in the length at the higher driving force. The growth process of salicylamide was most strongly effected by change in driving force when EA was used as the solvent. The growth rate was found to vary not only from one condition to another, but also among the crystals grown in the same condition, this phenomenon being referred to as growth rate dispersion (GRD) [14]. GRD is observed at all conditions, the widest example is in EA at supersaturation 0.48 which used nucleation to form the crystal: from 0.1 µm/s up to 4.3 µm/s among the 5 crystals, see Figure 5 (a). The growth rate dispersion appears to increase with

increasing supersaturation in most of the solvents, and was higher for the spontaneously nucleated crystals. There was a significantly narrower growth rate dispersion among the seed crystals. In spite of the fairly strong GRD the influence of the supersaturation on the average growth rate in all cases meets the expectation, i.e. the growth rate increases with increasing supersaturation. However, the GRD is so significant that the evaluation of the influence of the solvent should only be taken as indicative.

The growth rates of salicylamide crystals growing in the cuvette are considerably influenced by the initial supersaturation as illustrated in Figure 5. In the experiments with spontaneously nucleated crystals, the driving forces are set to induce nucleation, and hence is different in the different solvents and an assessment of the actual influence of the solvent itself cannot be made. In the seeded experiments, the same initial supersaturation (S-1) of 0.12 and 0.06 was used in all solvents. The order of average crystal growth rate, with respect to solvent, changes somewhat with supersaturation. At high supersaturation (0.12) the average crystal growth rate of salicylamide is the highest in acetone and the lowest in acetonitrile, with methanol and ethyl acetate in between, for both the length and width direction. At the lower supersaturation (0.06) the growth rate of SAM is still the highest in acetone in both directions, but the order among the other three is less systematic as shown in Figure 5 (c) and (d). As the cuvette growth method uses a non-stirred solution the growth rate is likely to be governed by the rate of diffusion through the fluid surrounding each crystal, which in turn is inversely proportional to the viscosity of the solution. Methanol has the highest viscosity (0.54 mPa.s at 25 °C), compared to acetone which has the lowest viscosity of the four solvents (0.31 mPa.s at 25 °C) [28]. Using the Wilke and Chang method [29] for estimating the diffusivity, it ranks the solvents in the order AC> EA> MeCN> MeOH, which is quite similar to the order of decreasing solubility (mol/L) and in turn equalling the growth rate order of seed crystals AC>EA>MeOH>MeCN.

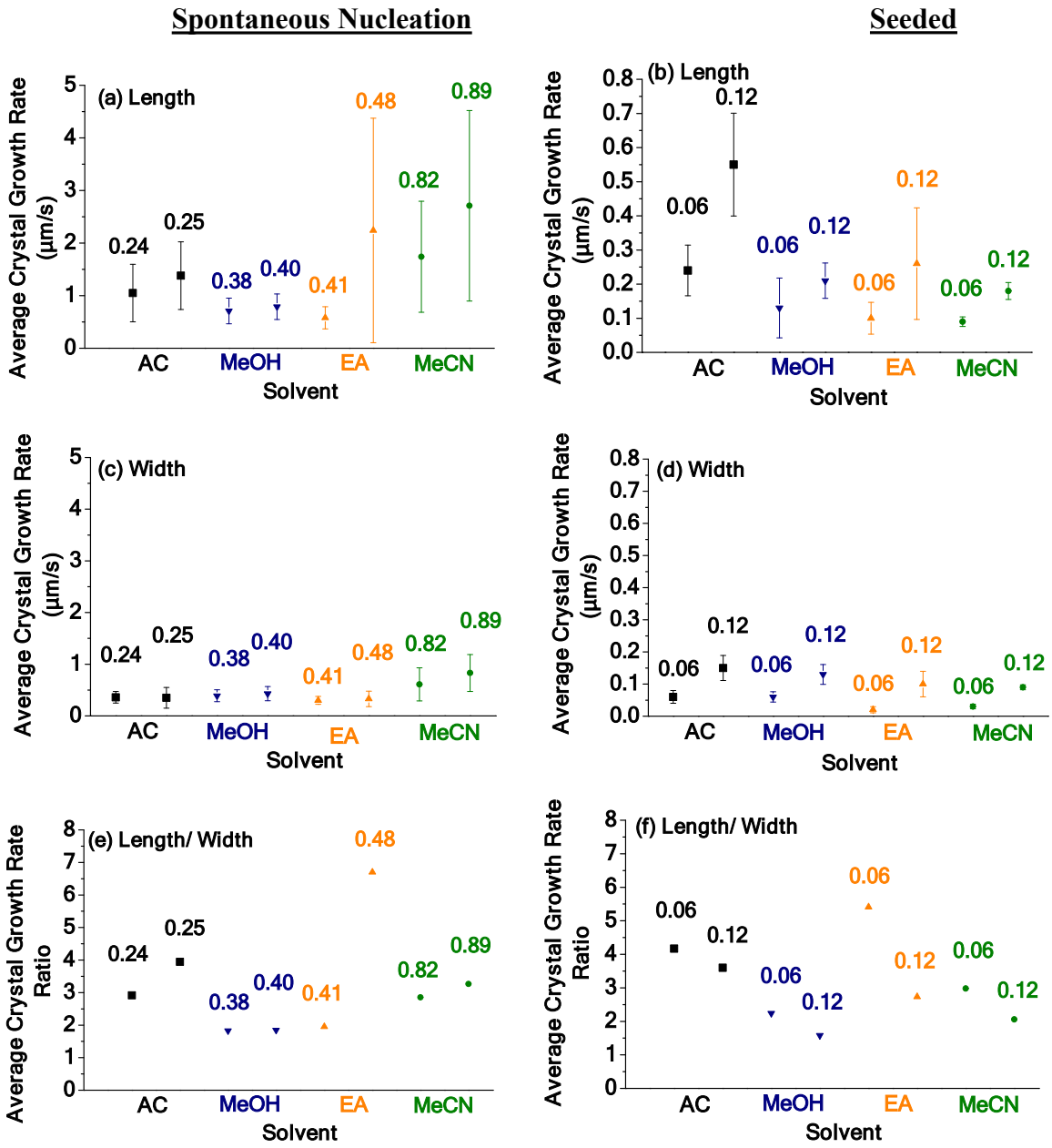


Figure 5. Average crystal growth rate (µm/s) of spontaneously nucleated (left) and seed (right) crystals in the length (a, b), width (c, d) direction and also average crystal growth rate ratio (e, f) as a function of solvent and supersaturation. Crystals are grown using the cuvette growth method at a growth temperature of 15 °C. Were AC is acetone, MeOH is methanol, EA is ethyl acetate and MeCN is acetonitrile; number above line is the supersaturation (S-1). The center point is the average crystal growth rate while the error bars on the graph illustrate the standard deviation of the data.

In our previous work we have face indexed experimentally grown salicylamide crystals using experimental and prediction techniques [30]. All salicylamide crystals grown in these studies were flat plate-like crystals, indicating growth is stunted in one facet direction, this is the (002) face. The growth rate of this face is not measured in this study, since it appears perpendicular to the direction of observation. A mix of three end faces (-112), (011), and (110) represent the length direction, however all three faces may not appear in each crystal and so are difficult to track between crystals. The width typically represents the growth of the (200) and (-200) faces; and as

the (200) face is consistent between crystals, Figure 6 shows the influence of the solvent on the growth rate of this specific face. Growth rate of the (200) face is found to follow the order of AC⩾MeOH>MeCN>EA at a supersaturation (S-1) of 0.06. Growth of the (200) face is slower in ethyl acetate than in the other 3 solvents. As previously stated, in the length direction the growth rate of SAM in ethyl acetate is faster than SAM in acetonitrile. These findings indicate that ethyl acetate provides the slowest growth of the (200) facet out of the four solvents tested yet only the second slowest growth rates of the faces in the length direction of the crystal. In other words not all faces of the salicylamide crystal habit grew at equivalent rates in the same solvent. This in agreement with findings in the literature that state solvents may accelerate, retard or even stop the further outgrowth of individual crystal faces, sometimes producing a habit change [31].

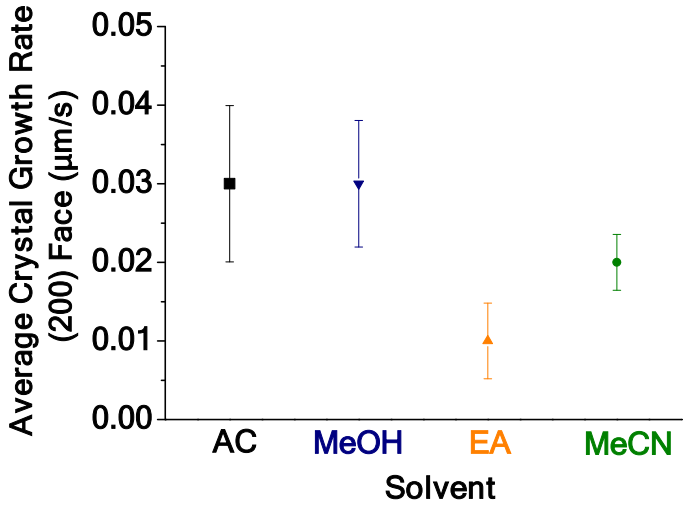


Figure 6. Average crystal growth rate of (200) face (µm/s) of seed crystals with respect to four different solvents. Crystals are grown using the cuvette growth method at a growth temperature of 15 °C and supersaturation (S-1) of 0.06. The center point is the average crystal growth rate while the error bars on the graph illustrate the standard deviation of the data.

Rotating disk crystal growth

Habit

Micrographs taken before and after the growth of salicylamide crystals in the rotating disk experiments are shown in Figure 7. The final habit appeared to be controlled by the shape of the seed as was also found for similar seed crystals grown via the cuvette crystal growth experiments. The outline of the seed is visible after growth in the final crystal only because the crystals are opaque and fixed to the glass disk which makes growth of that face rough.

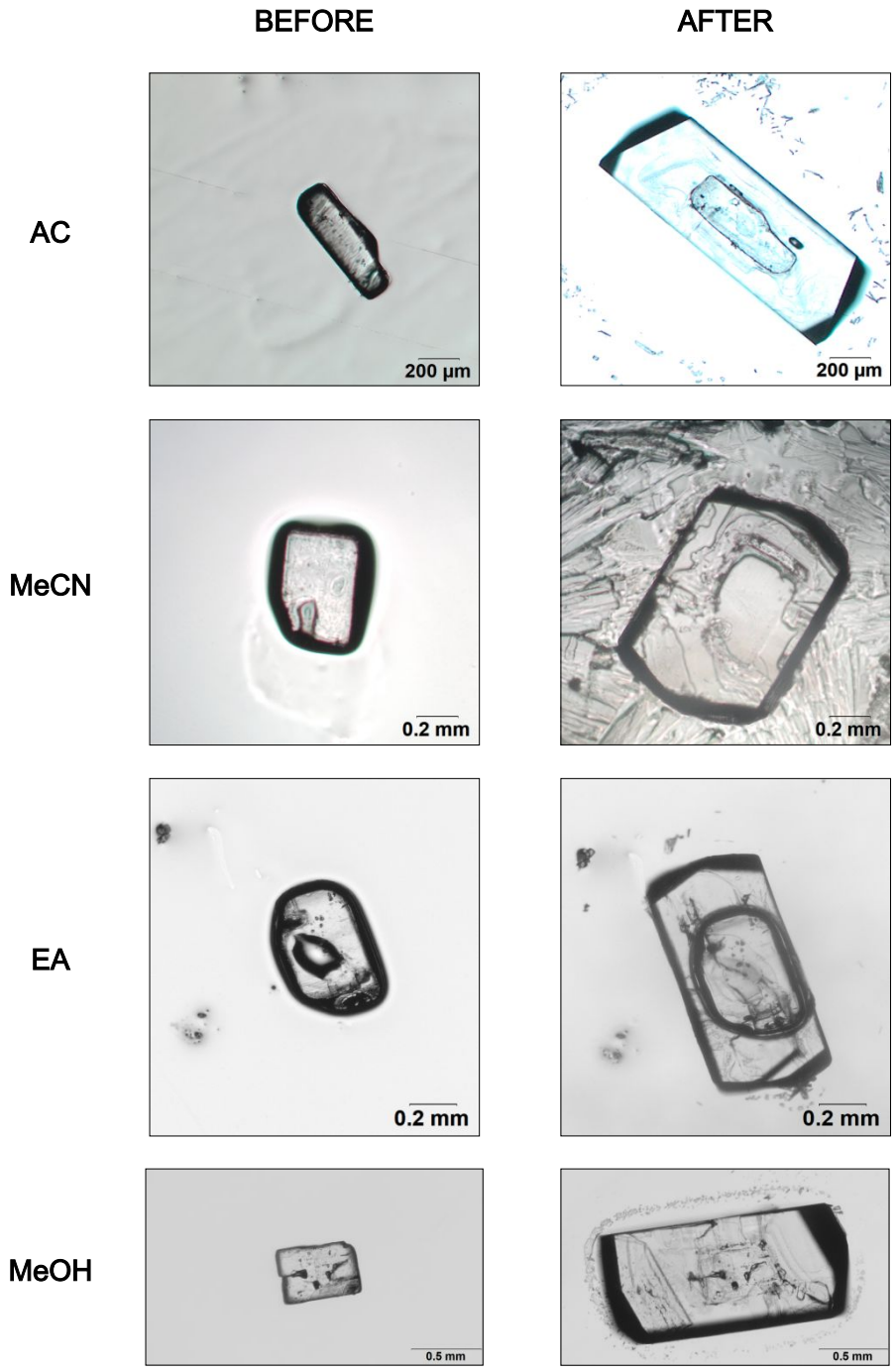


Figure 7. Micrographs of salicylamide crystals before and after crystal growth via the rotating disk method. Salicylamide seed crystals are grown in each of the 4 solvents at growth temperature of 15 °C under supersaturation (S-1) of 0.03 for 1 hr. Only one representative crystal out of the total 32 crystals for each condition are shown for each in this image.

Kinetics – Effect of Solvent

There is little difference between the average growth rates of the seed crystals in the different solvents except for in EA when using a crystal growth temperature of 15 °C and supersaturation (S-1) of 0.03 as illustrated in Figure 8. In both the length and width directions ethyl acetate provides the slowest growth rates of salicylamide compared to the other solvents.

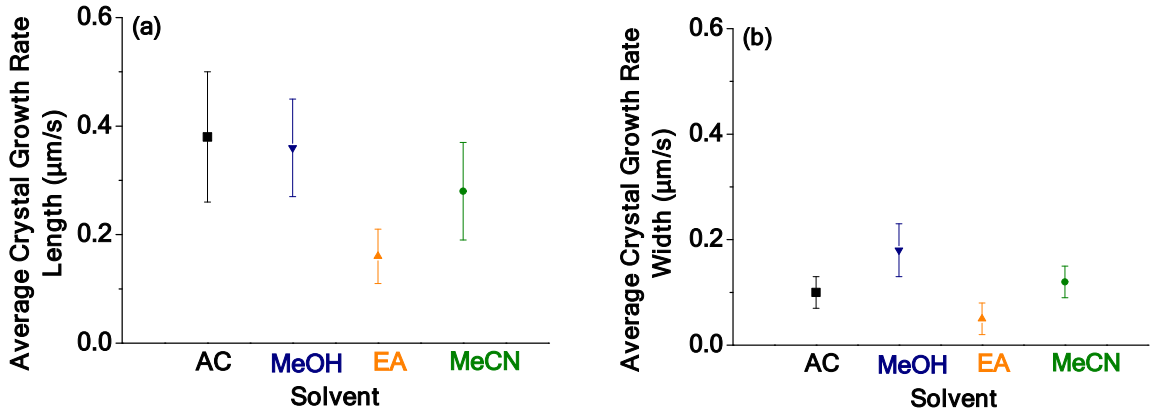


Figure 8. Average crystal growth rate of (a) length and (b) width (µm/s) of salicylamide seed crystals grown using the rotating disk method in four solvents (AC, MeCN, EA, MeOH) in temperature of 15 °C at supersaturation (S-1) of 0.03. Error bars are used to illustrate the standard deviation of the data.

The (200) facet of salicylamide seed crystal grows faster in methanol compared to the other solvents, with acetonitrile and acetone having similar growth rates and lastly ethyl acetate with the slowest growth rates as shown in Figure 9. As methanol provided the fastest growth rates and ethyl acetate the slowest growth rates of the (200) facet, crystals grown in these two solvents are examined and SEM images are shown in Figure 10. The (200) surface of salicylamide crystals is more regular and structured when grown in MeOH than in EA. When examined in more detail the topographical features of the surface are different in the two solvents; when grown in MeOH the surface appears to have rows of steps whereas when grown in EA the surface is slightly different with a corrugated step appearance. It is known that the solvent may change the growth mechanism by way of the surface roughness [33-34]. The rows of steps may allow for easy lattice integration in comparison with the corrugated step surface and thus explain the difference in growth rates in the two solvents. These findings are in agreement with our previous work that found

ethyl acetate to have a stronger adsorption energy with salicylamide crystal facet than methanol [30].

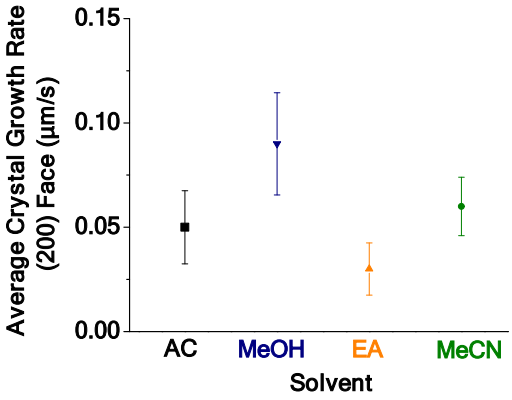


Figure 9. Average crystal growth rate of (200) face (µm/s) under rotating disk conditions with respect to four different solvents tested (200 rpm, 15 °C, 1 hr, S-1 of 0.03). Error bars are used to illustrate the standard deviation of the data.

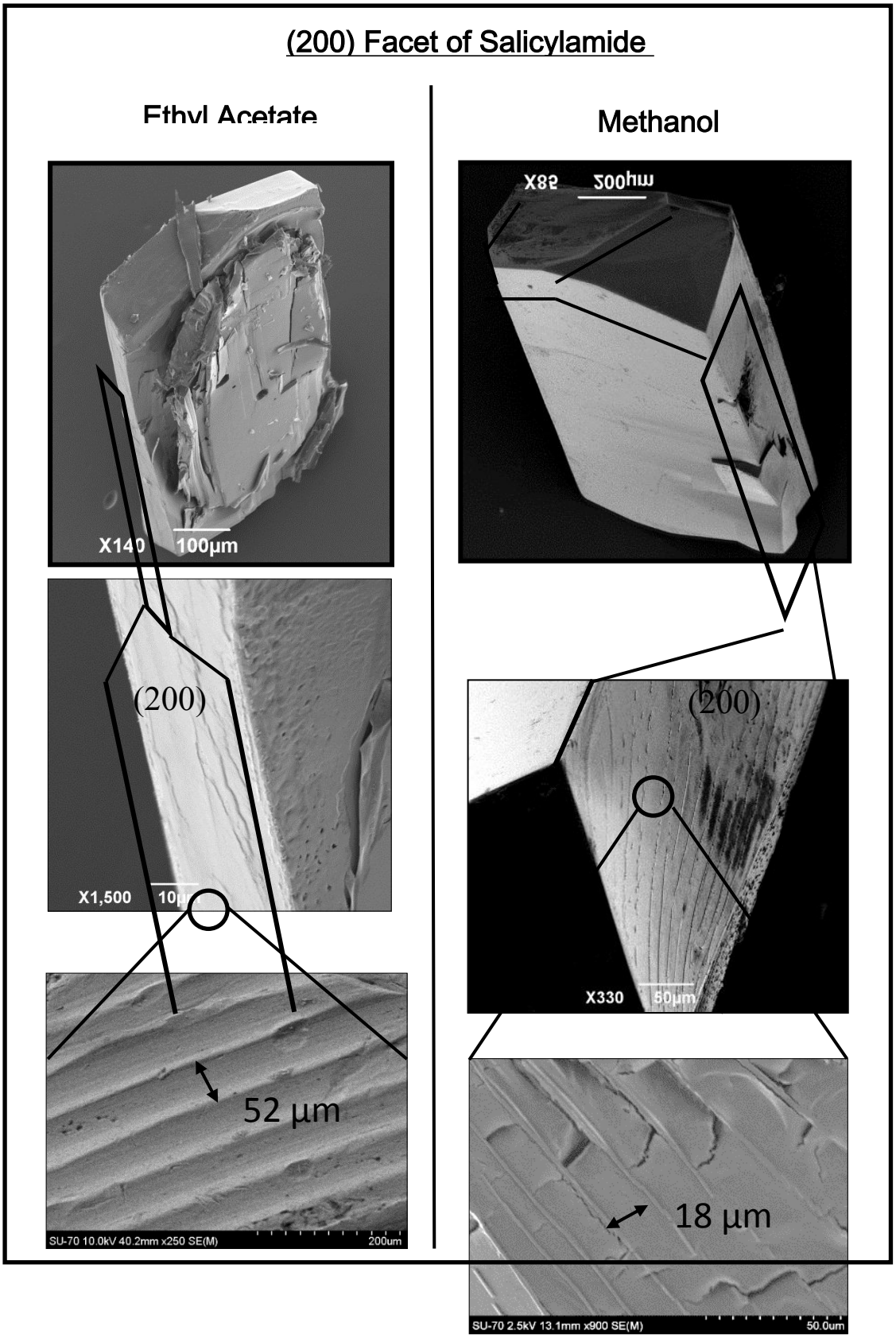

(200) Facet of Salicylamide
Ethyl Acetate
Methanol
X140 100µm
(200)
X1,500
52 µm
SU-70 10.0kV 40.2mm x250 SE(M)
200um
(200)
X330 50µm
18 µm
SU-70 2.5kV 13.1mm x900 SE(M)
50.0um

Figure 10. SEM images of salicylamide crystals after growth via the rotating disk method at 15 °C for 1 hr under S-1 of 0.03 in both EA and MeOH. The bottom two SEM images show the topographical features of the (200) facet after growth in both solvents.

Kinetics – Effect of Supersaturation

In general, increasing the driving force i.e. supersaturation leads to an increase in the average crystal growth rates in both the length and width dimensions as shown in Figure 11. The extent of the increase in growth rate is dependant on the solvent; increasing supersaturation (S-1) by 0.02 results in an increase in average growth of both length and width directions by a factor of 2.0, 1.6, 1.5, and 3.5 in AC, MeCN, EA, and MeOH, respectively. Methanol provides the largest increase in growth of salicylamide with respect to same increase in supersaturation in the other solvents. The average growth rate of the width direction in MeCN slightly decreases when increasing the supersaturation (S-1) from 0.025 to 0.037. Yet the maximum growth rate of SAM obtained in the lower and higher supersaturations were 0.19 μm/s and 0.24 μm/s respectively, proving that the higher driving force did in fact result in a higher growth rate for some seed crystals. Interestingly in the case of acetonitrile were a relatively low supersaturation of 0.012 was used, the average growth rate in both the length and width dimension was negligible. However, upon visual examination of the crystals before and after growth (Figure 12) under these conditions it is clear to see that a growth process has occurred, primarily repairing morphological defects.

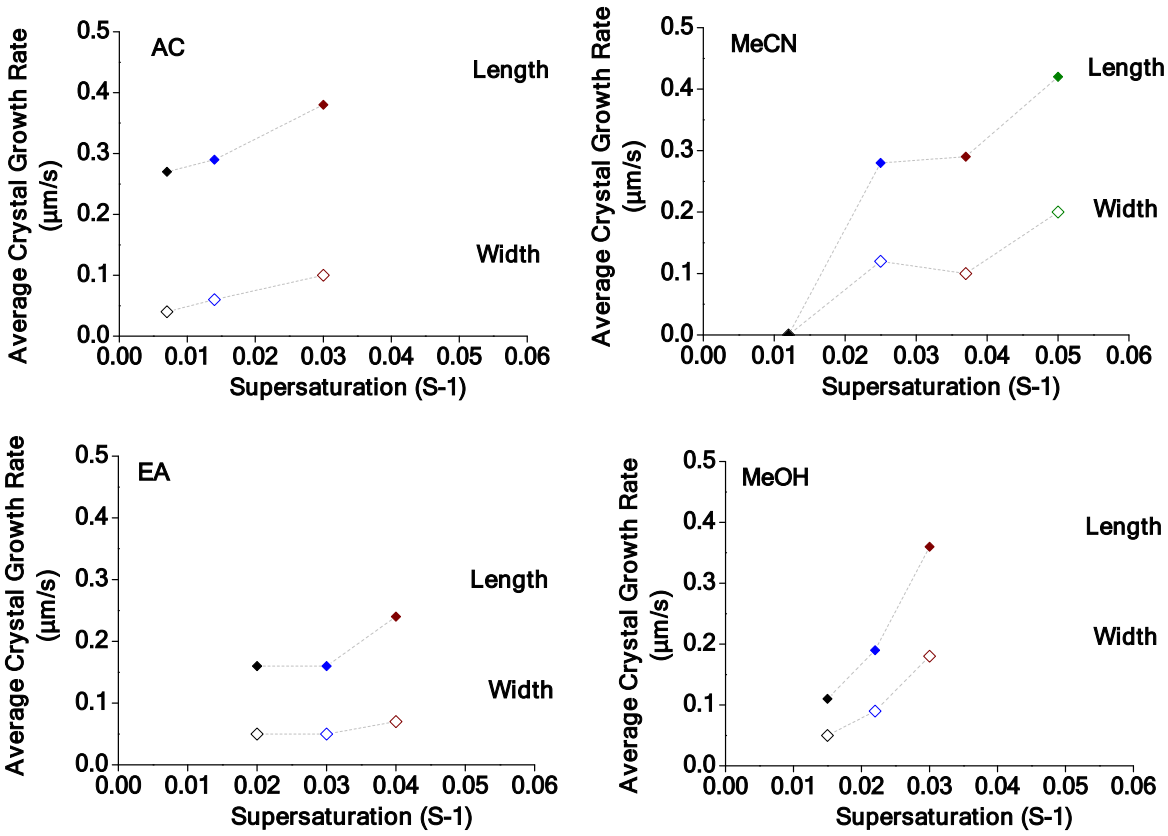


Figure 11. Average crystal growth rate (µm/s) of both length and width plotted against different supersaturations (S-1 of 0.007 to 0.05) for each of the four solvents.

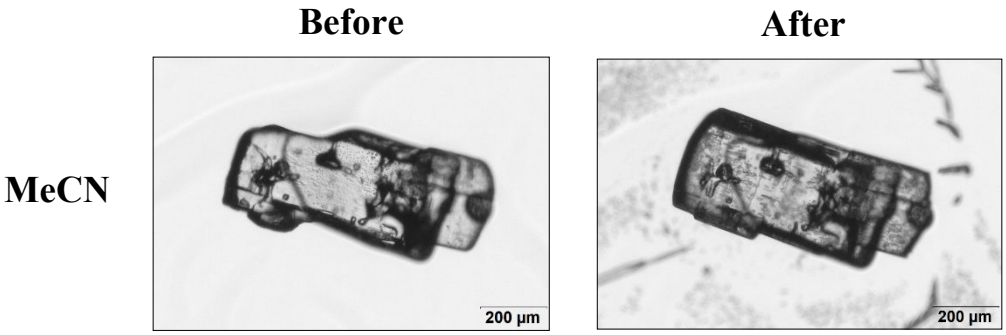


Figure 12. Micrographs show a salicylamide crystal before and after growth via the rotating disk method in acetonitrile at 15 °C for 1 hr at supersaturation (S-1) of 0.012.

Kinetics – Effect of Temperature

The influence of temperature on the average crystal growth of salicylamide in acetonitrile is shown in Figure 13. A 10 °C increase in the temperature results in a fourfold increase in the average growth rate of SAM in the fastest growth direction, length. This strong dependence is of course reflected in the activation energies, Ea, which can be obtained by fitting eq 3 to the average growth rates at the three temperatures, simultaneously. Ea values in the length and width directions are 93 kJ/mol and 96 kJ/mol, respectively.

$$G(s) = k_{gO}\exp\left(\frac{-E_a}{RT}\right)(S-1)^g \qquad (2)$$

$$ln\, G = \left(\frac{-E_a}{R}\right)\left(\frac{1}{T}\right) + ln\, C \qquad (3)$$

In our previous work [32], multiple salicylamide crystal seeds were grown in a batch reactor using an isothermal seeded desupersaturation crystal growth method. Increasing temperature within the same range from 10 °C to 20 °C in MeCN also led to a fourfold increase in the growth rate of salicylamide and the activation energy was found to be 96 kJ/mol. Despite significant differences between the two growth methods, it is of great reassurance that both methods estimate the same activation energy value. These activation energies are clearly higher than the values expected for simple molecular diffusion (5 – 20 kJmol^{-1}), and nearer those reported for surface integration (40 – 60 kJmol^{-1}) [2].

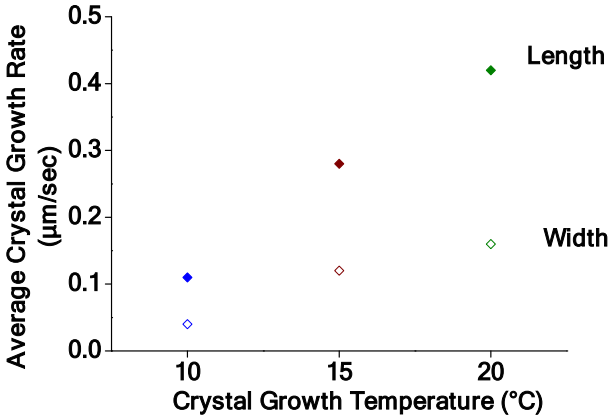


Figure 13. Average crystal growth rate (μm/s) of both length and width with respect to the crystal growth temperature (10, 15, and 25 °C) for acetonitrile at initial supersaturation (S-1) of 0.03 grown for 1 hr.

Kinetics - Effect of the Crystal Seed Properties (Quality)

As part of examining the influence of the properties of the seeds, the effect of the initial seed crystal quality was examined. For this purpose, the seed crystal quality is divided into three categories; “high” which refers to near perfect crystals in terms of symmetric shape and also surface, “medium” which refer to crystals that have an issue with shape or surface and lastly “low” which refer to crystals that have an issue with both the shape and crystal surface. An example of a seed crystal from each category is shown in Figure 14. Initial seed crystal quality is found to have an impact on the crystal growth rate, with the “low” seed crystal quality leading to the fastest growth rates whereas “high” seed crystal quality having slower growth rates. This can be rationalised due to the increased number of surface defects present on the “low” quality crystals which can act as attachment sites for crystal growth units and so result in faster growth. Initial seed crystal quality plays a large effect on the growth rate dispersion (GRD) observed, a lower quality inherently results in wider GRD. There is an increase in the GRD by a factor of 2 for the “low” quality seed crystals versus the “high” quality seed crystal; 0.2 μm/s range versus 0.1 μm/s range respectively. Industry require a narrow GRD and so using a high quality crystal seed would help in reducing it however at the pay-off of a reduced crystal growth rate.

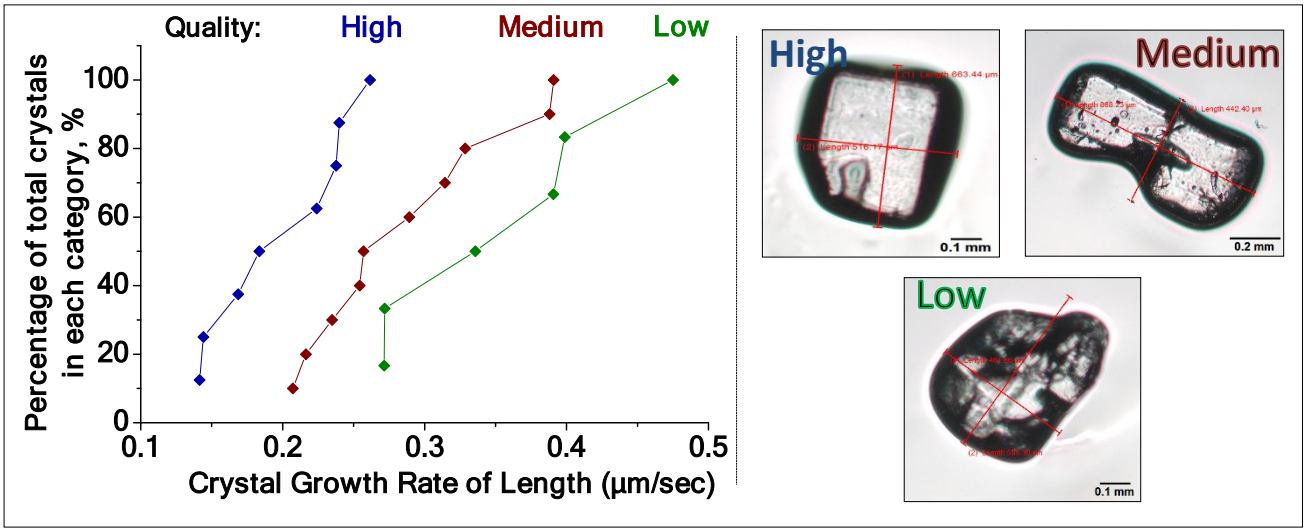


Figure 14. Comparing crystal growth rate of length (μm/s) of salicylamide in acetonitrile with respect to initial seed crystal quality (high, medium and low). On the right hand side of the figure are examples of a seed crystal from each of the crystal quality categories for clarity.

Comparison of growth rates obtained from the two crystal growth methods

Salicylamide seed crystal growth rates obtained from the cuvette and the rotating disk experiments at 15 °C are compared in Figure 15. The cuvette growth experiments are performed without forced convection whereas in the rotating disk experiments there is a fairly controlled hydrodynamic situation in the rotation of the disk at 200 rpm. Obviously the growth rate is much higher in the rotating disc experiments, e.g. at (S-1) of 0.03 the average growth increases by a factor of 20 (0.003 µm/s versus 0.060 µm/s) for cuvette growth method and the rotating disk method respectively.

Crystal growth is widely accepted to occur by two phenomena assumed to act in series; transport of solute through the liquid boundary layer to the crystal-liquid interface (volume diffusion) and integration of solute molecules into the crystal lattice (surface integration) [1-2, 35-37]. With increasing relative velocity between the crystals and the fluid the volume diffusion resistance decreases. The crystal growth rate increases and the crystal growth process becomes increasingly governed by the surface integration step. Accordingly, it is perfectly in accordance with expectation that the cuvette experiments would deliver a growth rate that is equal to or lower than the rotating disc growth rates [6]. The fact that there is a substantial difference reveals that at least the cuvette experiments are significantly influenced by the volume diffusion resistance.

The influence of the rotation rate from 50 rpm up to 350 rpm has been evaluated for crystal growth in acetonitrile and the result is illustrated in Figure 16. Above 150 rpm the growth rate no longer increases with increasing rotation rate. Accordingly, a stirring speed of 150 rpm is found to be sufficient to essentially eliminate the volume diffusion mass transfer resistance, and accordingly the growth experiments performed at 200 rpm can be assumed to be governed by surface integration.

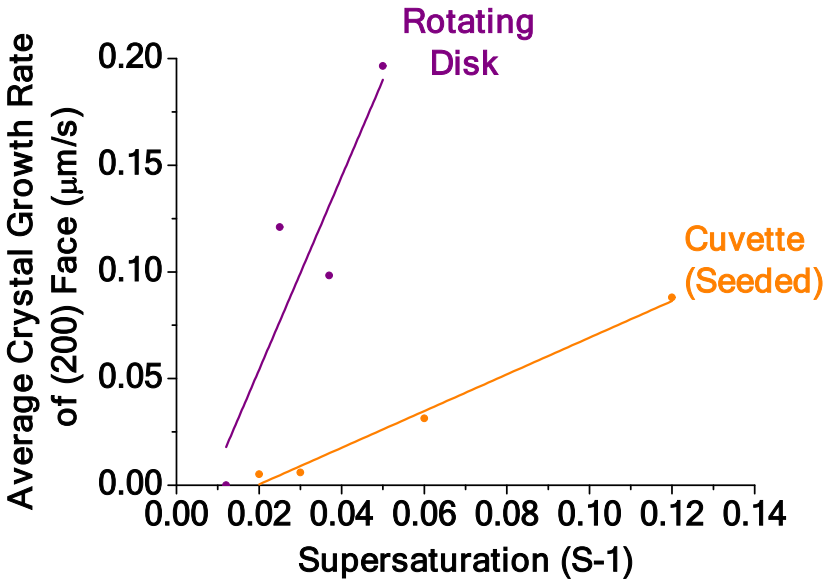


Figure 15. Average crystal growth rate (µm/s) of the (200) face of salicylamide seed crystals grown in acetonitrile in supersaturation (S-1) range of 0.01 – 0.12 at 15 °C by the two crystal

growth methods outlined in this paper. The cuvette growth method is shown as the orange triangles and the rotating disk growth method is shown as the purple circles.

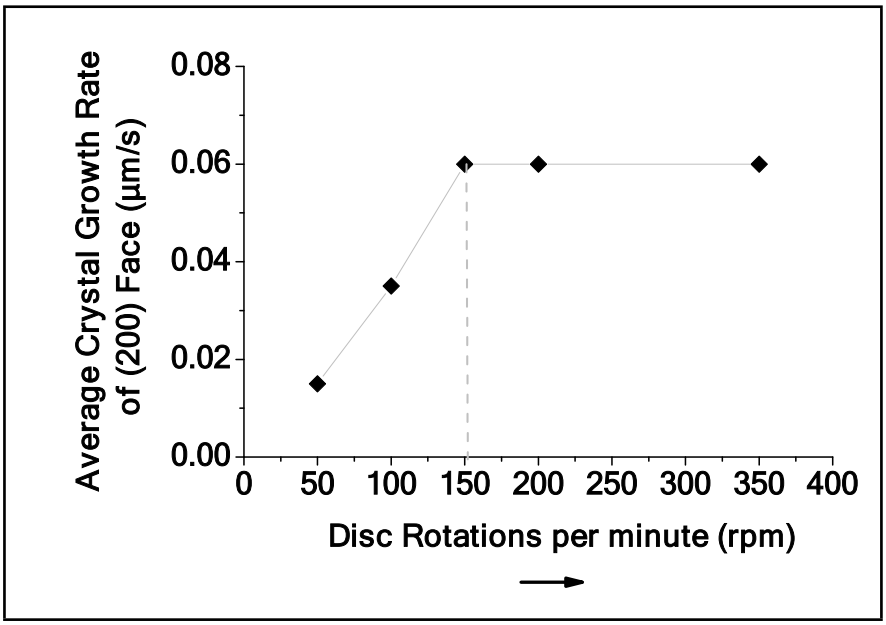


Figure 16. Average crystal growth rate (µm/s) of the (200) face of salicylamide seed crystals grown using the rotating disk growth method at different stirring rates (50 to 350 rpm) in acetonitrile with supersaturation (S-1) of 0.03 at 15 °C.

Comparison of rotating disk crystal growth with previously published crystal growth studies

In our previous work [32], a batch agitated reactor was used to grow multiple salicylamide seed crystals via a seeded isothermal desupersaturation crystal growth method. This study used the exact same sieve fraction 300 – 355 μm and solvents as were used in the rotating disk study, and the same crystal growth temperature and similar supersaturation range. The growth order parameter indicated that the growth process in the batch reactor was governed by surface integration. In Figure 18, these results are compared with the present rotating disk results. In all solvents, the magnitude of growth in the two methods is the same. In MeCN, EA and MeOH the growth rates are very similar, whereas in AC the growth is slightly faster in the rotating disk experiments. The slight variations in growth rates can be explained by the differences in the number of crystals involved; on average 12,000 crystals are grown simultaneously in the batch crystal growth study whereas the rotating disk studies only 32 crystals are grown at the same time. This paper has shown that the growth rate dispersion for salicylamide crystal growth data is relatively wide, hence the larger sample size in the agitated reactor experiments would lead to better estimation of the average crystal growth rate. In addition, it should be recognised that in the rotating disk method the growth in a specific direction for each crystal is directly measured as an increase in the linear dimension, whereas in the batch reactor method the overall average growth rate in terms of the linear dimension used to characterise the size over all crystals is determined indirectly by recording the decay in solution concentration and assuming a constant crystal shape. Accordingly, the two methods have different merits and drawbacks and complement one another, and the overall agreement is encouraging.

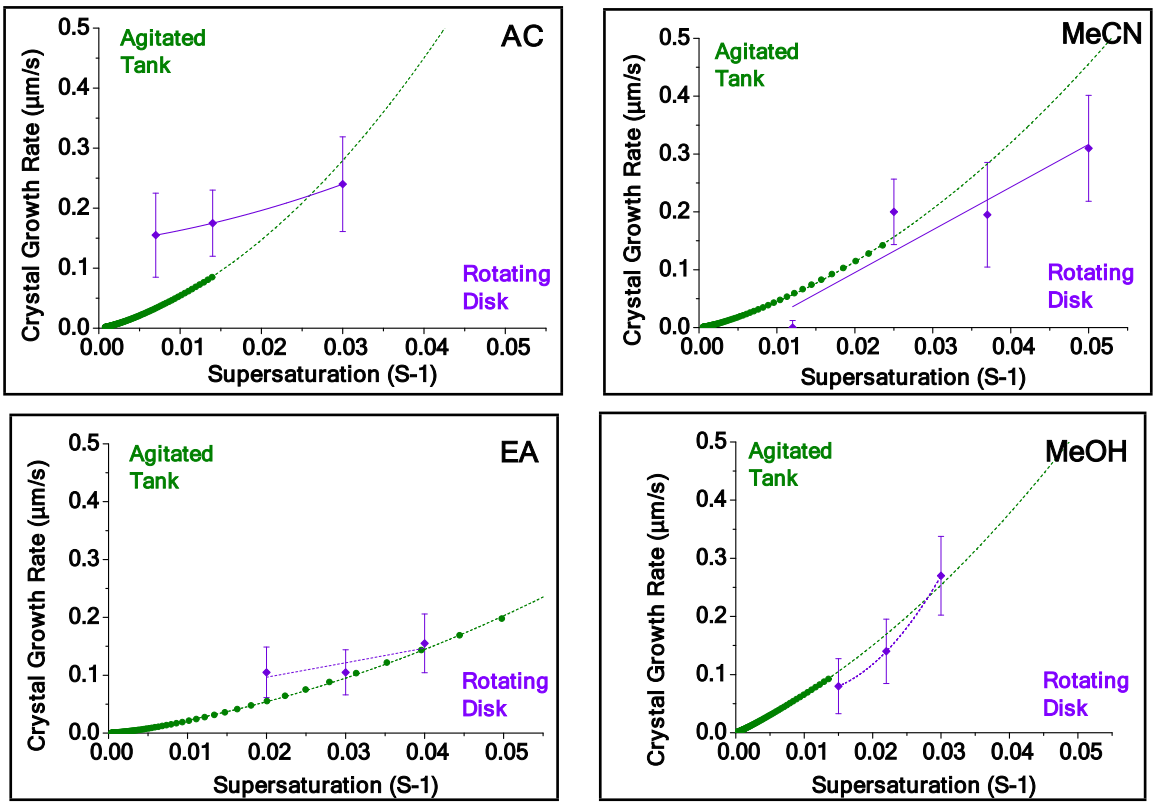


Figure 17. Crystal growth rate of salicylamide crystals grown by two methods in the four solvents at 15 °C with respect to supersaturation. The crystal growth rate (μm/s) for the rotating disk studies is equal to the average growth rate of length plus the average growth rate of width divided by two. The agitated tank crystal growth rates are obtained from our previous study [32].

Conclusion

Crystal growth of salicylamide was investigated under both diffusion and surface integration control, and the associated growth rates were measured. The crystal growth rates of the (200) facet obtained under surface integration controlled growth resulted in 20 times faster growth rates than when grown under diffusion controlled growth. Under surface integration controlled growth process, when salicylamide was grown in MeOH the surface appeared to have rows of steps whereas when it was grown in EA the surface was comprised of a corrugated step appearance. Within acetonitrile, increasing temperature by 10°C led to a fourfold increase in salicylamide's growth rates in the length direction. The rotating disk method delivered growth rates in good agreement with our previous data obtained by isothermal seeded desupersaturation experiments in an agitated tank. The rotating disk method allows for a more detailed examination of the growth in particular directions and of particular faces, while simultaneously allowing for data of a number of crystals to be collected simultaneously. By changing the rotation rate the relative influence of boundary layer diffusion can be changed, and in the presented work 200 rpm was sufficient to have full surface integration control.

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI: ####.

Supporting information for the rotating disk studies can be found including experimental supersaturation decay, testing reproducibility of the method, effect of crystal number/ position on disk and effect of growth time on the rotating disk method.

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Notes

The authors declare no competing financial interest.

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Crystal Growth of Single Salicylamide Crystals

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