CRYSTAL GROWTH KINETICS
OF SALICYLAMIDE
AND TWO POLYMORPHS OF PIRACETAM

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This thesis is the original work of the author and due reference and acknowledgment has been made, when necessary, to the work of others. No part of this thesis has been accepted for any degree and is not being concurrently submitted for any other award.

Aisling Lynch

September 2019
The crystal growth process and associated kinetics of two active pharmaceutical ingredients (API) has been investigated using three crystal growth methods. The impact of organic solvent, supersaturation, temperature, polymorph form, and crystal seed quality on the crystal growth was studied. Isothermal seeded desuperaturation (ISD) growth method was used to investigate the growth rate of multiple salicylamide (SAM) crystals simultaneously. In-situ fourier transform infrared (FTIR) spectroscopy probe was employed for the determination of solution concentration and supersaturation decay data obtained was modelled using several growth rate equations and growth models, also tested different representations of the driving force. ISD provides kinetic data which was statistically representative of the crystal population due to the large number of crystals studied. Measuring the interfacial angle between faces combined with preferred orientation X-ray diffraction (XRD) was found to be the most accurate and reliable method leading to successful identification of each predicted SAM crystal face. Cuvette (CV) growth method was used to study the growth of single SAM crystals and the crystal growth rates were measured for both primary nucleated crystals and seed crystals manually inserted into the cuvette. As each facet had been face indexed it allowed for the growth of specific crystal facets, i.e. (200) of SAM, to be extracted directly from single crystals using a microscope. In an attempt to study multiple single crystals at once under controlled hydrodynamics, crystal seeds were grown using a new approach called the rotating disk (RD) growth method. Wherein seed crystals were attached to a disk that was rotated in a supersaturated solution by which the diffusion resistance was found to be eliminated. RD method was used to study the growth of two APIs including SAM and FII & FIII polymorphs of piracetam (PCM). It was deduced that ethyl acetate was adsorbed more strongly on the faces of SAM than the other solvents tested, the increased size of which, explained the irregular hexagonal plate habit obtained and relatively slow growth rates. Growth rate of the (011) facet of piracetam FII and FIII crystals was found to be reduced in isopropanol also due to its stronger interaction. Metastable PCM FII was found to have faster growth rates than the thermodynamically stable FIII. Within the range of experimental conditions, the growth rates of SAM and PCM were strongly affected by the temperature and also supersaturation. With a 10 °C increase resulting in a two to fourfold increase in the average growth rate depending on the solute – solvent system. Similarly, a two to fourfold increase in the average growth rate of both SAM and PCM was observed when the supersaturation was increased within the range of S-1 0.02 up to 0.10. Also SAM’s crystal seed quality was found to have a substantial impact on the growth rate, with rougher larger crystals leading to quicker growth due to the increased number of surface defects present which can act as attachment sites. Comparing the RD and CV growth rate data for SAM it indicated that the CV method led to growth rates which were controlled by the diffusion step. The growth order parameter determined in the ISD studies reveals a surface integration controlled growth process. Under similar conditions, both the RD and ISD methods produced comparable growth rates for SAM and also for PCM. Furthermore by examining the effect of the rotation speed on the crystal growth rates from RD method led to the finding that it was also surface integration controlled. The crystal growth rates of the (200) facet of SAM obtained via surface integration controlled growth resulted in 20 times faster growth rate than when grown under diffusion controlled growth.
This thesis is based on the following journal publications:


Publications related but not included in the thesis:


Conference contributions:

I. **Aisling Lynch** and Åke C. Rasmuson. “Crystal Growth Kinetics of Salicylamide Investigated Under Different Crystallisation Processes and Also Environmental Conditions”. Oral presentation at the 2018 American Institute of Chemical Engineers (AIChE) Annual Meeting, November 2018, Pittsburgh, USA.


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Last but far from the least, to my boyfriend, Steven. For all the big and small adventures we have had over the past number of years that were the best distraction from the PhD. We may not know where we will be this time next year but one things for certain, you will always be by my side. Can’t wait for our next adventure to begin!

“Research is formalized curiosity. It is poking and prying with a purpose”

Zora Neale Hurston
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<tr>
<td>a</td>
<td>Activity, dimensionless</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>BCF model parameter, K ms(^{-1})</td>
<td></td>
</tr>
<tr>
<td>A(_{BCF})</td>
<td>Pre-exponential factor, m(^3)L(^{-1})</td>
<td></td>
</tr>
<tr>
<td>A(_{surf})</td>
<td>Pre-exponential factor of surface diffusion equation, m(^3)s(^{-1})</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>BCF model parameter, K</td>
<td></td>
</tr>
<tr>
<td>B(_{\text{step}})</td>
<td>Two-dimensional nucleation rate</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>B&amp;S model parameter, ms(^{-1})</td>
<td></td>
</tr>
<tr>
<td>CV</td>
<td>Crystal volume, m(^3)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>B&amp;S model parameter, K</td>
<td></td>
</tr>
<tr>
<td>D(_{surf})</td>
<td>Surface diffusion coefficient, m(^3)s(^{-1})</td>
<td></td>
</tr>
<tr>
<td>dm/dt</td>
<td>Rate of increase of the linear dimension</td>
<td></td>
</tr>
<tr>
<td>E(_a)</td>
<td>Apparent activation energy, kJmol(^{-1})</td>
<td></td>
</tr>
<tr>
<td>E(_{asurf})</td>
<td>Activation energy of surface diffusion of adsorbed molecules, kJmol(^{-1})</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>Growth rate order, dimensionless</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>Growth rate of a characteristic dimension of crystal, ms(^{-1}) or (\mu ms(^{-1})</td>
<td></td>
</tr>
<tr>
<td>G(_n)</td>
<td>Estimated growth rate of nucleation, ms(^{-1})</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>Height of the growth step, nm</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>Rate of homogeneous nucleation, m(^{-3})</td>
<td></td>
</tr>
<tr>
<td>k</td>
<td>Boltzmann constant, JK(^{-1}) or m(^3)kgs(^{-2})k(^{-1})</td>
<td></td>
</tr>
<tr>
<td>k(_a)</td>
<td>Surface area shape factor, dimensionless</td>
<td></td>
</tr>
<tr>
<td>k(_g)</td>
<td>Parameter in modified growth rate equation (pre-exponential factor/frequency factor), unit depends on s term of the driving force</td>
<td></td>
</tr>
<tr>
<td>k(_v)</td>
<td>Volumetric shape factor, dimensionless</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>Characteristic dimension of crystal, m</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Molecular weight, gmol(^{-1})</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>Mass deposition rates per unit surface area, kgm(^{-2})s(^{-1})</td>
<td></td>
</tr>
<tr>
<td>N(_A)</td>
<td>Avogadro’s number</td>
<td></td>
</tr>
<tr>
<td>N(_i)</td>
<td>Total number of seed crystals, dimensionless</td>
<td></td>
</tr>
<tr>
<td>P(t)</td>
<td>Probability to detect crystals at time t, dimensionless</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>Gas constant, JK(^{-1})mol(^{-1})</td>
<td></td>
</tr>
<tr>
<td>s</td>
<td>Driving force, unit changes with representation</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>Supersaturation ratio, dimensionless</td>
<td></td>
</tr>
<tr>
<td>SA</td>
<td>Surface area, m(^2)</td>
<td></td>
</tr>
<tr>
<td>S-1</td>
<td>Relative supersaturation, dimensionless</td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>Time, s</td>
<td></td>
</tr>
<tr>
<td>t(_g)</td>
<td>Growth time, s</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>Temperature, K</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Volume of solution, m(^3)</td>
<td></td>
</tr>
<tr>
<td>V(_m)</td>
<td>Molecular volume, m(^3)</td>
<td></td>
</tr>
<tr>
<td>v(_{\text{step}})</td>
<td>Step advancement rate in the B+S model</td>
<td></td>
</tr>
<tr>
<td>x</td>
<td>Mole fraction concentration, dimensionless</td>
<td></td>
</tr>
<tr>
<td>x(_s)</td>
<td>Mean diffusion distance on the surface, m</td>
<td></td>
</tr>
</tbody>
</table>

**Greek Letters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>β’</td>
<td>Correction factor, dimensionless</td>
</tr>
<tr>
<td>ΔG</td>
<td>Gibbs free energy, kJmol(^{-1})</td>
</tr>
<tr>
<td>γ</td>
<td>Activity coefficient, dimensionless</td>
</tr>
<tr>
<td>γ(_{sl})</td>
<td>Interfacial energy between solid and liquid, Jm(^{-2})</td>
</tr>
<tr>
<td>Γ</td>
<td>Concentration of surface-adsorbed molecules, molm(^{-2})</td>
</tr>
<tr>
<td>Γ(*)</td>
<td>Equilibrium concentration of surface adsorbed molecules, molm(^{-2})</td>
</tr>
<tr>
<td>μ</td>
<td>Chemical potential, Jmol(^{-1})</td>
</tr>
<tr>
<td>Δμ</td>
<td>Chemical potential difference, Jmol(^{-1})</td>
</tr>
<tr>
<td>Δμ(_T)</td>
<td>Chemical potential difference, neglecting the temperature-dependence of the activity coefficient, Jmol(^{-1})</td>
</tr>
<tr>
<td>ρ</td>
<td>Density, kgm(^{-3})</td>
</tr>
</tbody>
</table>
### List of Abbreviations and Acronyms

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATR-FTIR</td>
<td>Attenuated total reflectance fourier transform infrared</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>AC</td>
<td>Acetone</td>
</tr>
<tr>
<td>BCF</td>
<td>Burton, Cabrera and Frank</td>
</tr>
<tr>
<td>B&amp;S</td>
<td>Birth and Spread</td>
</tr>
<tr>
<td>CCDC</td>
<td>Cambridge Crystallographic Data Centre</td>
</tr>
<tr>
<td>CG</td>
<td>Crystal Growth</td>
</tr>
<tr>
<td>CNT</td>
<td>Classical Nucleation Theory</td>
</tr>
<tr>
<td>CV</td>
<td>Cuvette growth method</td>
</tr>
<tr>
<td>DIOX</td>
<td>1,4-dioxane</td>
</tr>
<tr>
<td>EA</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>F#</td>
<td>Polymorph Form #</td>
</tr>
<tr>
<td>FBRM</td>
<td>Focused Beam Reflectance Measurement</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier Transform Infrared Spectroscopy</td>
</tr>
<tr>
<td>GRD</td>
<td>Growth rate dispersion</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>ISD</td>
<td>Isothermal seeded desupersaturation growth method</td>
</tr>
<tr>
<td>IPrOH</td>
<td>Isopropanol</td>
</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MSZW</td>
<td>Metastable Zone Width</td>
</tr>
<tr>
<td>PAT</td>
<td>Process analytical technology</td>
</tr>
<tr>
<td>PCM</td>
<td>Piracetam</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>P-XRD</td>
<td>Powder X-Ray Diffraction</td>
</tr>
<tr>
<td>RD</td>
<td>Rotating disk growth method</td>
</tr>
<tr>
<td>SA</td>
<td>Salicylic acid</td>
</tr>
<tr>
<td>SAM</td>
<td>Salicylamide</td>
</tr>
<tr>
<td>SC-XRD</td>
<td>Single Crystal X-Ray Diffraction</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning Electron Microscopy</td>
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</table>
CHAPTER 1

Introduction
1 Introduction

1.1 Context of Research

Crystallisation is one of the oldest separation and purification unit operations, and arguably the most important operation in the chemical industry [1-3]. Crystallisation is the process of formation of solid crystals from solution, melt or by deposition directly from a gas phase [3, 4]. Crystallisation from solution is a very important technique especially in the pharmaceutical sector, as it is used in the formation, purification and recovery of crystalline active pharmaceutical ingredients (API) [2, 4, 5]. It is a complicated processes unique for each substance and which can also vary with respect to the process conditions used e.g. concentration, temperature, solvent, and agitation etc. [3]. This process gives rise to the solid state properties of the crystal which play a part in both the downstream processing e.g. filtration, washing and drying and the end-use properties like tableting and dissolution rate [3, 6].

Over the past several decades there has been an increased demand to be able to control the crystallisation process as requested by both the pharmaceutical industry and also to satisfy the regulatory authorities [1, 2, 7]. With the goal of being able to consistently manufacture active pharmaceutical ingredients (APIs) of high and reproducible quality combined with the desired solid state properties [7]. In order to be able to control this process and isolate crystals with required purity, size, shape and polymorph, a better fundamental understanding of the mechanisms and phenomena involved in crystallisation is required [2, 6, 8, 9]. Presently, crystallisation fundamentals are still insufficiently understood which results in industrial crystallization processes mainly being developed by trial and error experiments. Computational and molecular dynamics simulations have started to be used to try predict the crystal habit grown in solvent and are beginning to show interesting findings which are matching to experimental work [10-15]. Unfortunately, these methods are only being used for rather simple compounds as we can't provide the models with adequate kinetics of nucleation and crystal growth. More research needs to be done in this area before it is possible to be able to fully predict the crystallisation of complex API, under a range of process conditions.

Crystallisation is a two-step process; initial nucleation followed by subsequent crystal growth. Efforts have previously been made to understand the process and kinetics of nucleation [16-30]. Presently, the crystal growth kinetics data can differ by an order of magnitude for the same API depending on the laboratory generating the data. As the pharmaceutical industry requires
reproducibility from batch to batch this variance in crystal growth is undesirable. Literature describes a number of methods which allow for the observation of the crystal growth process and associated growth rates to be measured [9, 31-41]. These methods can be largely split into single crystal growth and multiple crystal growth experiments. The single crystal growth experiments offer the advantage of observing the growth of specific crystals which allows for a fundamental examination of the growth process [31, 33, 38, 39, 42, 43]. On the other hand the multiple crystal growth method usually involves growing thousands of crystals at once in a batch reactor and uses process analytical technology (PAT) to detect growth within the system. Accordingly, the two methods have different merits and drawbacks and complement one another.

Furthermore, the effect of a number of process conditions such as mixing, temperature, solvent, and supersaturation on the crystal growth process has also been investigated previously [1, 2, 4, 5, 7, 9, 44-47]. Though there is still more research to be done in this section as it is still far from being predictable, in particular work needs to be focused on understanding the solvent effect on the growth step at a molecular level. Additionally, the API molecules are progressively becoming more complex due to different polymorph forms available which leads to increased difficulties to crystallize the material. So far research has been focused on understanding how polymorphism effects the nucleation stage [6–9], with little understanding of how different crystal polymorphs grow.

1.2 Aims of PhD

The initial objective of this work was to rationalise the crystal growth process, in particular the associated kinetics, of active pharmaceutical ingredients. The crystal growth of two organic compounds was investigated; including a complex organic compound with two polymorphs. Both single crystal growth and multiple crystal growth methods were used to investigate the growth process at a fundamental and also statistically relevant level. The single crystal growth methods initially used crystals which were formed by spontaneous nucleation in a stagnant solution from which the effect of seeds and agitation on the crystal growth process and kinetics could be investigated. Precise face indexing of experimentally grown crystals using a combination of experimental and prediction techniques was carried out in order to be able to measure the crystal growth of a specific crystal facet using an optical microscope. The multiple crystal growth method was used to give a good insight into the overall crystal growth kinetics and mechanism of a vast number of freely suspended API crystals. Process analytical
technology was utilised to record the growth within this batch reactor. Data was fitted to known empirical relationships and evaluated against current model theories. Additionally, an alternative crystal growth method has been developed which can combine the advantages of the single and multiple crystal growth methods into one experimental approach. An in-depth evaluation of the effect of several process conditions on the crystal growth was performed including solvent, supersaturation and temperature. Scanning electron microscopy was utilised to identify the growth features present on the crystal surface, in particular to distinguish any differences between surfaces when the crystal was grown in different solvents. Molecular modelling was used to support the experimental work. In particular, it was used to predict the crystal habit, examine the surface chemistry of different faces, and determine attachment energies of these faces. Also, it was used to quantify the adsorption energy of the various solvent molecules onto the crystal surface with an aim of providing insight into the solvent-solute interactions involved in the growth.

1.3 Thesis Chapter Outline

This thesis has been prepared in two sections. The first part of the thesis outlines the justification for the research, background on the research topic, the main experiments carried out, results obtained and conclusions drawn. The second part includes the journal publications associated with the work. These include additional results information, mainly molecular modelling which was utilised to compliment the experimental findings and was carried out by Vivek Verma and Jacek Zeglinski. Also includes SC-XRD data which was used to check unit cell data to ensure no new polymorphs and was carried out by Pauric Bannigan. Michael Svärd calculated the approximate representation of the activity coefficient ratios for a better estimation of the true driving force. Lijun Jia compiled the matlab script for fitting the growth rate equations to the multiple crystal growth data.
1.4 References for Chapter 1


CHAPTER 2

Literature Review
2 Literature Review

2.1 The Solid State

Molecular solids can exist in crystalline or noncrystalline (amorphous) phases depending on the three-dimensional order. Crystalline solids consist of regular repeating three-dimensional structures held together by uniform intermolecular forces to create a crystal lattice, whereas amorphous solids are not arranged in regular arrays. The smallest repeating unit within the crystalline solid is known as the unit cell and it is described using six lattice parameters; the three dimensions \((a, b, c)\) and the three angles \((\alpha, \beta, \gamma)\). Based on these lattice parameters there are 14 possible point lattices which can be constructed. These point lattices can be split into 7 crystal systems as shown in Figure 2.1. Within these systems, lattices can either be simple if they are primitive (one lattice point per unit cell) or body-centered / face-centered if they are non-primitive (more than one lattice point per unit cell). In order to define a plane within the crystal lattice a notation system known as miller indices is used. It is determined by three integers \(h, k,\) and \(l\) and are written in the form \((hkl)\). The external appearance of the crystal is referred to as its habit which is controlled by the relative areas of the faces. Habit describes the crystal shape without reference to the crystal structure whereas crystal morphology describes the shape of the crystal structure [1]. Crystals with the same crystal lattice can have different habits depending on the growth conditions used, which is of course controlled by the diverse growth rates of each facet. The crystal habit gives rise to the solid state properties which play a part in both the downstream processing (e.g. filtration, washing and drying) and the end-use properties (e.g. tableting and dissolution rate) so it is vital to be able to control the crystal habit [2, 3].

![Figure 2.1. Unit cell and the seven crystal systems and their permitted lattice parameters.](image-url)
2.1.1 Polymorphism

Polymorphism is the ability of a compound to crystallize into two or more crystalline forms or crystal structures [4, 5]. In some literature, it has been reported that between 32% and up to 51% of small organic molecules, which make up 90% of API used in pharmaceutical drugs, have polymorphs [5-7]. Different polymorphs can have different properties including solubility, dissolution rates (bioavailability), biological action, and stability [5, 8, 9]. Polymorphs are classified into one thermodynamically stable form with the rest being metastable. The stable polymorph has the lowest free energy, and so it will have the lowest solubility and therefore the lowest bioavailability [5, 8]. It is vital that the right polymorph with optimal properties is chosen during the design stage of the drug [5, 10-12]. There have been a number of well-known cases of pharmaceutical drugs which had to be withdrawn from the market due to new polymorph discovery; including Immunoprin (thalidomide), Norvir (ritonavir), and Neupro (rotigotine) [7, 9, 11, 13-15]. Due to these issues understanding the different polymorphs of each API, their properties and why they appear is of utmost importance to the pharmaceutical industry in order to be able to control the form.
2.2 Crystallisation

Crystallisation may be defined as the process of formation of solid crystals from solution via a two-step process of nucleation and subsequent crystal growth [3-5, 16]. A homogenous solution can be made by the addition of a solid solute to a liquid solvent. The solubility of this solution is equal to the maximum amount of solute that can dissolve in a given amount of solvent at a given temperature and pressure. When the solution contains the maximum amount dissolved it is said to be saturated, i.e. the system is at equilibrium. In other words, the chemical potential of the solute in the solution is the same as the chemical potential of the species in the solid phase. Solubility is known to vary widely for different materials, due in part to their different solute and solvent interactions. Also the solubility depends on the temperature, for most material solubility increases with temperature [17]. An example of a solubility curve for a solute in a solvent is shown in Figure 2.2. The solubility line defines the saturation level, with the region below the line describing an unsaturated solution and the region above referring to a supersaturated solution. A supersaturated solution is one that contains excess solute than can normally be dissolved at its equilibrium solubility. This metastable state can be created by cooling a saturated solution as illustrated in Figure 2.2 by the black circles labelled $x$ and $x^*$ respectively, or else by evaporation of the solvent or changing the solvent composition etc. [18]. In order for the supersaturated solution to move towards equilibrium, the excess solute crystallises. The supersaturation region can be split into two sections; the area closest to the saturation line is a region in which only crystal growth will typically occur and the area above this is the region where both nucleation and crystal growth can occur, see Figure 2.2. The crystal growth region is commonly referred to as the metastable zone width (MSZW). MSZW is a practical property, which is of significant industrial importance as it provides a working region for crystal growth to be performed without unwanted nucleation. The width of the metastable zone can be altered by a number of factors e.g. solution history, cooling rate, temperature, solution purity, and hydrodynamics etc. [3].
Figure 2.2. This graph shows the solubility curve of a solute in a solvent, below which the region is unsaturated. The metastable zone width limit is the region just above the solubility line which is slightly supersaturated and mostly only growth occurs here. The region above the MSZW is highly supersaturated and is where both nucleation and growth occurs. Points indicated using black circles on the graph refer to saturated, $x^*$, and supersaturated, $x$, states brought about through cooling.
2.2.1 Supersaturation

The true thermodynamic driving force for crystallization, $\Delta \mu$ (J mol$^{-1}$), is the difference in the chemical potential between the solute in the supersaturated solution and in the corresponding saturated solution (*): 

$$\Delta \mu = \mu - \mu^* = RT \ln \frac{a}{a^*} = RT \ln \frac{x \gamma}{x^* \gamma^*}$$  \hspace{1cm} (1)$$

This expression is commonly simplified by neglecting the activity coefficient ratio entirely, and is often represented simply by a concentration ratio, $S$, or by using eq 2 as being an approximate representation of the logarithmic function of eq 1.

$$\sigma = S - 1 = \frac{x}{x^*} - 1$$  \hspace{1cm} (2)$$

In a recently proposed method, an approximate representation of the activity coefficient ratio is obtained by neglecting only the temperature dependence, but not the concentration dependence, of the activity coefficient [19], resulting in the expression for the driving force given by eq. 3:

$$\Delta \mu_T = RT \ln \frac{x \gamma (T^*)}{x^* \gamma^*}$$  \hspace{1cm} (3)$$

where $\gamma$ for the supersaturated solution has been replaced by the corresponding value for the solution at its saturation temperature. For solutions that are not too dilute, i.e. in the Henry’s law region, this method is expected to be more accurate than neglecting the activity coefficient contribution to the driving force [19].
2.2.2 Nucleation

Nucleation is a phase separation and refers to the formation of a nuclei or critical cluster; small entities having crystalline structure [3-5, 20]. Nucleation can be classified into either primary or secondary nucleation. Primary nucleation is when no crystals are present in the starting solution whereas secondary nucleation is when solute crystals are present in the starting solution to induce nucleation. Primary nucleation is further divided into homogeneous nucleation, occurs spontaneously in bulk solutions, or heterogeneous nucleation, induced by foreign particles [3, 5, 21, 22].

Classical nucleation theory (CNT) is the most common theoretical model used worldwide to understand the kinetics of homogeneous nucleation [20]. CNT presumes that before nuclei are observed, initial clusters are formed in solution which have the same structure as the final crystalline material [23, 24]. Once the cluster reaches the critical size it becomes thermodynamically stable, and will form a nuclei provided the free energy gain of forming the crystalline material overcomes the free energy cost of creating the phase boundary. CNT uses an Arrhenius-type equation, eq. 4, to express the rate of nucleation i.e. the number of nuclei formed per unit time per unit volume [21, 25]:

\[ J = A \exp \left( \frac{-\Delta G'}{kT} \right) \]  

(4)

A is a pre-exponential factor that has a theoretical value of \(10^{30}\) nuclei per cm\(^3\) per s [26]. The thermodynamic considerations, \(\Delta G'\), take into account the free energy change for the formation of the nucleus surface and also the free energy change for the phase transformation and can be described by the following, eq.5, assuming a spherical nuclei:

\[ \Delta G' = \frac{16\pi\sigma^2v^2}{3(kT\ln S)^2} \]  

(5)

Fitting eq. 5 into eq. 4 it is clear to see that the nucleation rate would increase with increasing supersaturation and temperature, and decrease with an increase in surface energy. CNT is a rather analytically simplistic model which is based on a number of assumptions. It relies on the clusters being spherical droplets, also the growth of clusters is based on one unit at a time etc. In order to overcome these shortcomings, a two-step pathway known as ‘non-classical’ nucleation theory was proposed [26]. The first step of which involves a separation of a dense, disordered liquid phase which will then form a liquid like cluster and crystalline order will appear over time [20].

14
Nucleation is regarded as a stochastic phenomenon related to the random behaviour of the molecules in solution [23]. To account for this stochastic nature of nucleation, a number of probability distribution functions have been developed which can be fitted to experimental isothermal nucleation data. For example the Jiang and ter Horst probability distribution, eq. 6, which describes, under constant supersaturation, the probability of detecting crystals as a function of time, $P(t)$, within an agitated solution [27]:

$$
P(t) = 1 - \exp(-JV(t-t_g))
$$

(6)

Where $J$ is the stationary nucleation rate, $V$ is the volume of solution, and the term $(t-t_g)$ is used to account for the delay in time of detecting a nuclei due to the fact that it has to grow to an appreciable size before it can be detected.
2.2.3 Crystal Growth

2.2.3.1 Crystal Growth Process

The crystal growth process outlines the steps taken by a growth unit (atoms, molecules, ions, hydrated solute molecules, dimers, clusters, etc.) as it’s incorporated into the crystal surface as illustrated in Figure 2.3. Crystals are thought to grow in a layer-by-layer fashion and the process is understood to be made up of the following steps [4, 18, 21, 28, 29]:

1. Bulk Diffusion
   Transport of growth units through solution.

2. Surface Integration
   a) Attachment of growth units to the surface.
   b) Movement of growth units on the surface.
   c) Attachment of growth units into the crystal lattice.

These stages are essentially acting in series whereby the slowest one will be rate determining. Generally, diffusion governs the growth at high supersaturations and temperatures, whereas surface integration dominates at moderate supersaturations and temperatures. 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. The integration rate is low when there is a perfectly flat surface, whereas this rate can increase when there are steps and kinks on the surface that provide favourable sites for integration as shown in Figure 2.3 [30].

![Figure 2.3 Kossel’s model of a growing crystal surface showing flat surfaces (i), steps (ii), kinks (iii), edge vacancies (iv), surface-adsorbed growth units (v), and surface vacancies (vi) modified from [4].](image-url)
2.2.3.2 Crystal Growth Mechanisms

The growth rate of a crystal face is dependent on its underlying growth mechanism [4, 31]. Although these crystal faces appear flat to the naked eye, the crystalline surface is rarely so at the molecular level. The surfaces of crystal facets have been examined with scanning electron microscopy and atomic force microscopy which have shed light onto the possible growth structures and mechanisms, such as spiral, kinks, steps, layers, 2D nucleating islands etc. [32, 33]. Crystal growth mechanisms have been discussed extensively throughout the literature, from initial concept stage [34] to implementation into current crystal growth studies [35]. Different mechanisms may be in operation depending on the conditions used such as supersaturation, temperature etc. Specifically for the surface integration step, two face growth rate models are commonly used.

Burton, Cabrera and Frank (BCF) described the screw dislocation mechanism, eq. 7 [34, 36]. The BCF model involves a dislocation center which acts as a continuous source for generating spiral shaped surface steps [31, 32]. As there is a permanent supply, growth can continue at relatively low supersaturation. The rate of growth is determined by the propagation of these steps which in turn depends on the crystal surface and also the physical properties of the crystal growth system, elements of which are taken into account within parameter A (eq. 8) and parameter B (eq. 9) respectively. Parameter A is here treated as temperature-dependent, Λ* is the solute molecular adsorption coverage, D_{surf} is the surface diffusion coefficient, V_{m} is the molecular volume of the solute, x_{s} is the diffusion mean free path over the surface. Parameter B is considered independent of temperature in this work and it too includes the terms V_{m} and x_{s}, it also incorporates γ_{sl} the solid-liquid interfacial energy and k the Boltzmann constant. The interfacial energy occurs in the equation as a transformation of the edge energy of the growth step. The edge energy determines the radius of the critical two-dimensional nucleus that determines the radius of the Archimedes spiral describing the screw dislocation. The higher the edge energy the greater the distance between two nearby steps, and the longer the average distance of surface diffusion becomes [35]. BCF model calculates crystal growth rates to vary from a parabolic dependence on supersaturation to a linear dependence as the supersaturation increases. The model predicts growth to depend on the step height, surface diffusion and surface defects [37, 38].
The Spiral Growth model (BCF):

\[
G_{BCF} = \frac{AT}{B} (S - 1)(\ln S) \tanh\left( \frac{B}{T \ln S} \right) 
\]  

(7)

\[
A = \frac{\Gamma^* D_{surf} V_m}{x_s^2} \quad B = \frac{19V_m \gamma_{sl}}{2kx_y} 
\]  

(8, 9)

The birth and spread (B&S) growth mechanism, eq. 10, relies on crystal surface nucleation (birth), followed by the growth (spread) of the monolayers. B&S is likely to occur at higher supersaturations than the BCF mechanism as it requires a higher driving force to generate the two dimensional (2-D) surface nucleation. This surface nucleation can develop at any location on a crystal surface, e.g. edges, corners and on the faces. Further surface nuclei can absorb and integrate into the monolayer allowing it to spread across the crystal face [4]. Where \( h \) is the height of the growth step, \( B_{step} \) denotes the rate of two-dimensional nucleation, and \( v_{step} \) is the rate of step advancement. The B&S model contains two parameters, \( C \) (eq. 11) and \( D \) (eq. 12), which describe very similar properties of the crystal growth system as their respective counterparts (\( A \) and \( B \)) in the BCF model. Also, analogous to the BCF model, \( C \) and \( D \) are considered to be temperature dependent and independent, respectively. The solid-liquid interfacial energy in the B&S model within parameter \( D \) (eq. 12) describes the radius of the 2D critical nuclei that form on the surface and are the source of new growth steps. B&S predicts that the growth rate of the crystal increases with increasing supersaturation and increasing temperature [17].

The Birth and Spread model (B&S):

\[
G_{B+S} = h v_{step}^{2/3} B_{step}^{1/3} = C(S - 1)^{2/3} (\ln S)^{1/6} \exp\left( \frac{-D}{T^2 \ln S} \right) 
\]  

(10)

\[
C = \left( \frac{16}{\pi} \right)^{1/3} h^{1/6} D_{surf} \left( \frac{\Gamma^*}{x_s} \right)^{2/3} (V_m \Gamma N_A)^{5/6} \quad D = \frac{\pi}{3} V_m h (\frac{\gamma_{sl}}{k})^2 
\]  

(11, 12)
The two facet growth models contain parameters A and C, respectively, which both rely heavily on a $D_{\text{surf}}$ term, eq. 13. This is simply an Arrhenius equation with emphasis on the activation energy of the surface diffusion of adsorbed molecules, $E_{a,\text{surf}}$.

\[
D_{\text{surf}} = A_{\text{surf}} \exp\left(-\frac{E_{a,\text{surf}}}{RT}\right)
\]  

(13)
2.2.3.3 Crystal Growth Methods

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 [31, 32, 39-49]. These methods can primarily be split into two categories; single crystal growth or multiple crystal growth methods. The basic difference being that in the former method the direct growth rate of the individual crystal is recorded while in the latter the average growth rate of an ensemble of crystals is determined without distinguishing the growth of each individual crystal.

The simplest version of the single crystal growth method involves observing the growth of one crystal in a stagnant solution. This approach was used in 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 [31]. 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 [46]. 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 [40, 42, 47, 50, 51]. 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 due to the phenomenon of growth rate dispersion (GRD) whereby growth rates have been found to vary from crystal to crystal when grown within an identical system [31, 52]. Rotating disks have also been used a few times to study crystal growth in a mixed solution [53, 54]. However, they only studied the growth of one compressed crystal plane rather than a single crystal. In most cases, crystal growth rates of single crystals can be measured directly from microscopic images of the growing crystals taken at different time points. The growth rate in a specific direction, $G$ (ms$^{-1}$ or μms$^{-1}$), can be represented by eq 14 [31].

$$G = \frac{dL}{dt}$$  (14)

Where $G$ is the rate of change of the crystal’s characteristic dimension, $L$, has dimensions of velocity with respect to time, $t$. Measurements can be taken in a number of characteristic
dimensions including the length & width (maximum and minimum feret diameter respectively) or else the specific crystal faces which make up these dimensions [52].

Multiple crystal growth studies have been performed over the years both in academia and industry using a simple batch reactor design [55-61]. The supersaturation often has to be low to avoid nucleation, breakage or agglomeration, and the concentration decay has to be recorded with high accuracy. One of the most widely accepted approaches involving the batch reactor has been the isothermal seeded desupersaturation crystal growth method. It has been used to successfully determine the crystal growth rates for multiple crystals of a number of organic compounds including salicylic acid, paracetamol, ibuprofen etc. [29, 30, 35, 62-72]. Significant advances in the process analytical technology (PAT) available in recent years has allowed for more accurate estimations and control of the crystal growth rates obtained from these batch reactors. Crystal growth rates have successfully been determined by recording the solution concentration using *in situ* ATR-FTIR and Raman spectroscopy without calibration [73]. Often a simple empirical power law equation, eq 15, can be fitted to the desupersaturation data that is obtained in these growth experiments to relate the overall linear growth rate of the crystals to the supersaturation. It is known to correlate experimental data well over narrow supersaturation ranges. This equation can be modified to also include explicit temperature dependence on the rate constant in accordance with an Arrhenius-type equation as in eq 16.

Simple Overall Growth Rate Equation:

\[
G(s) = k_g s^g, \text{ where } s = S - 1 \text{ or } \Delta \mu_r
\]  

(15)

Modified Overall Growth Rate Equation:

\[
G(s) = k_{g0} \exp \left( \frac{-E_a}{RT} \right) s^g, \text{ where } s = S - 1 \text{ or } \Delta \mu_r
\]  

(16)

Where \( k_g \) is an overall crystal growth rate constant, \( s \) is the measure of supersaturation and \( g \) is the growth rate order.

An advantage of the single crystal growth methods is that the detailed growth in different directions and of different faces can be measured which is of fundamental interest as different facets of a crystal have been found to grow at different rates under identical environmental conditions [4, 74]. 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. Previous efforts have tried to combine the advantages of both the single and multiple crystal growth methods into one experimental approach by using an agitated batch crystalliser combined with a high speed camera. Using this methodology, 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 [49, 75, 76]. 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.
2.4 Factors Affecting Crystallisation

Significant research has gone into discovering the process conditions which can affect the crystallisation process, and in particular trying to understand each of their effects on a molecular level [22, 77]. The key factors can be divided into three main sub-groups:

1. Molecular recognition (Chemical)
   - Seed
   - Solute-Solute Interactions
   - Solvent-Solute Interactions

2. Thermodynamics (and or Physical)
   - Solvent
   - Solubility
   - Temperature
   - Hydrodynamics

3. Kinetics
   - Supersaturation
   - Growth Rate
   - Metastable Zone Width

From a molecular point of view, the crystal seed properties including its size and quality will ultimately have a large effect on the crystallisation process as they will dictate the roughness of the surface i.e. the number of attachment sites present to begin with. The solvent-solute interaction can cause different polymorphs to form [4, 15, 78-84]. A number of studies have focused on the nucleation step and the kinetics of the different polymorphs [6–9]. The effect of solvent on the formation of four polymorphic forms of sulfathiazole was examined with respect to the crystal facets of each. The results stated that there was “no obvious relationship between the appearance of a particular polymorph from solution and the growth of its fastest growing surface”, instead claiming the polymorph which formed was as a result of the nucleation stage [85]. However work with L-histidine polymorphs suggests that the crystal growth rate of form A controls the solution-mediated transformation of the polymorphs [86]. Additionally, the morphology and growth rates of two polymorphs of L-glutamic acid in a batch crystalliser was detected using an on-line imaging system, which showed the metastable $\alpha$
polymorph had faster growth rates than the stable β form [87]. Illustrating the importance of studying both the nucleation and crystal growth processes of different polymorphs in detail.

Furthermore, solvent plays a key role in influencing both the nucleation and crystal growth processes [25, 29, 35, 60, 69, 72, 88-97]. Solvents may accelerate, impede or even inhibit the growth of specific crystal faces, which can lead to a change in the resulting habit [98, 99]. It is hypothesised that the solvent can increase the growth rate when it has favourable interaction with the solute and so reduces the interfacial tension which causes the crystal surface to alter from smooth to a rough interface. In an alternative theory, solvent is thought to preferential adsorb to specific faces and so will inhibit their growth as removal of the bound solvent poses an additional energy barrier for continued growth [100]. In keeping with the latter theory, polar solvents which had stronger interaction with phenacetin crystals have been found to create smaller crystals than when same solute was grown in aprotic solvents [101]. Solvent was also found to reduce the growth rate of the polar faces of α-resorcinol [92], succinic acids (001) face containing carboxylic acid groups [102], and also a number of polar crystals which had a high binding compatibility with a solvent and thus strong interaction [103]. To support these experimental approaches, computational and molecular dynamics simulations have been used to examine and try to understand the effect of solvent on the crystal growth process at a molecular level [104-107]. Similarly, the effect of additives on the crystal growth process of urea and ibuprofen has also been investigated [108, 109]. Despite these efforts, the effect of solvent is only recently beginning to be predicted for small simple organic molecules [110]. In order to be able to predict the crystal growth for large complex molecules in a range of solvents there is still a great amount of detail that needs to be understood about these interactions.

As a simple rule-of-thumb the Arrhenius equation can be used to assess the effect of temperature on a reaction rate. It estimates that a 10 K increase in the temperature will result in the reaction rate doubling on the basis that the fraction of molecules with energies equal or in excess of the activation energy will double and the frequency factor will remain approximately constant for such a small temperature change. Crystal growth surfaces tend to be rougher at higher temperatures which also results in faster growth rates [48]. It has been found that at higher temperatures, thermal-induced grown-in-defects form [16]. Crystal growth of salicylic acid was investigated under a range of temperatures using a multiple crystal growth method and found that increasing the temperature led to an overall increase in crystal growth rates by a factor of 4 and 2 with a 15 K increase within ethyl acetate and acetonitrile,
respectively [35]. For this reason temperature effect on growth still needs to be examined. Growth rates have also been found to increase with increasing supersaturation to different extents, again depending on the solvent type [31, 35]. Similar to the temperature effect, the overall effect of increasing solubility is a roughening of the surface and so results in a faster growth of the crystal facets [102], as also shown by [29, 54]. However, this has been proven to be overruled when the solvent-solute interaction are stronger [102]. The effect of surface roughness on the crystal growth rates has been investigated and found the rate to be partly controlled by the level of defects within the crystal [111]. Thus crystal seed quality will be play a large effect on the growth rates.
2.5 References for Chapter 2


79. Little, L.J., et al., Controlling the crystal polymorph by exploiting the time dependence of nucleation rates. Journal of Chemical Physics, 2017. 147.


CHAPTER 3

Materials & Experimental Methodology
3 Materials & Experimental Methodology

3.1 Materials

3.1.1 Solvents

Acetone (AC), acetonitrile (MeCN), 1,4-dioxane (DIOX), ethanol (EtOH), ethyl acetate (EA), isopropanol (IPrOH), and methanol (MeOH) were purchased from either Sigma Aldrich or Fisher Scientific. All solvents had a purity $\geq 99.7\%$ and used without further purification. These organic solvents were selected as they are commonly used in the pharmaceutical industry [1]. A list of their key physical and chemical properties are outlined in Table 3.1.
Table 3.1. Physical and chemical properties of solvents used in this work, data obtained from PubChem [2].

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Structure</th>
<th>Molecular Formula</th>
<th>Molecular Weight (g/mol)</th>
<th>Density at 20 °C (g/cm³)</th>
<th>Viscosity at 20 or 25°C (cP)</th>
<th>Hydrogen Bond Donor</th>
<th>Hydrogen Bond Acceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isopropanol</td>
<td><img src="image" alt="Isopropanol Structure" /></td>
<td>C₃H₈O</td>
<td>60.10</td>
<td>0.790</td>
<td>2.04</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Methanol</td>
<td><img src="image" alt="Methanol Structure" /></td>
<td>CH₄O</td>
<td>32.04</td>
<td>0.798</td>
<td>0.54</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td><img src="image" alt="Ethyl Acetate Structure" /></td>
<td>C₄H₈O₂</td>
<td>88.11</td>
<td>0.900</td>
<td>0.42</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ethanol</td>
<td><img src="image" alt="Ethanol Structure" /></td>
<td>C₂H₆O</td>
<td>46.07</td>
<td>0.789</td>
<td>1.07</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1,4 Dioxane</td>
<td><img src="image" alt="1,4 Dioxane Structure" /></td>
<td>C₄H₈O₂</td>
<td>88.11</td>
<td>1.034</td>
<td>0.01</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td><img src="image" alt="Acetonitrile Structure" /></td>
<td>C₂H₃N</td>
<td>41.05</td>
<td>0.787</td>
<td>0.35</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Acetone</td>
<td><img src="image" alt="Acetone Structure" /></td>
<td>C₃H₆O</td>
<td>58.08</td>
<td>0.785</td>
<td>0.32</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
3.1.2 Solutes (API)

Salicylamide (SAM), C$_7$H$_7$NO$_2$, is classified as a non-prescription drug with analgesic and antipyretic properties, and used as an over-the-counter pain remedy. SAM was purchased from Sigma Aldrich with $\geq$ 99.0 % purity and used without further purification. SAM is supplied as white, mainly blocky or plate-like crystals, with molecular weight 137.14 g mol$^{-1}$, and melting point of 138.7 °C [3-5]. SAM has two polymorphs reported in the literature; FI and FII. FI, monoclinic, is the stable polymorph at ambient conditions whereas FII, orthorhombic, is only obtained under high pressure (>0.5 GPa) [4]. The single crystal structures for both of the polymorphs have already been determined, CIF files available [4, 6, 7]. The solubility of SAM FI in acetone, acetonitrile, ethyl acetate and methanol has been determined between 10 °C and 50 °C [3].

Piracetam (PCM), C$_6$H$_{10}$N$_2$O$_2$, is classified as a nootropic drug and is used to treat cognitive impairment. Piracetam was purchased from Baoji Guokang Bio-Technology with $\geq$ 99.0 % purity and used without further purification. PCM is supplied as white crystalline powder, with molecular weight 142.16 g mol$^{-1}$, and melting point of 152.0 °C. PCM has five polymorphs reported in the literature; FI (6.747), FII (6.403), FIII (6.525), FIV (8.954) and FV (6.390) [8-10]. For clarity of the nomenclature of the polymorphs, the $\alpha$-lattice parameter of the crystal structure is included within the brackets. FI is only formed when either FII or FIII is heated above 130 °C and quickly transforms back, FII is the metastable form, FIII is the stable form at ambient conditions, and FIV and FV are only obtained at high pressure (>0.5 GPa). The solubility and stability of PCM FII and FIII in ethanol and isopropanol has already been determined between 10 °C and 50 °C [11, 12].

![Molecular structure of the active pharmaceutical ingredients of a) salicylamide and b) piracetam](image)

**Figure 3.1.** Molecular structure of the active pharmaceutical ingredients of a) salicylamide and b) piracetam [2].
3.2 Experimental Methodologies

3.2.1 Preparation & Characterisation of Crystal Seeds

Crystal seeds were prepared using standard methodology as described in the literature [13, 14]. Both SAM and PCM were supplied in the form of crystalline powder and so were characterized by optical microscopy (Olympus IX53) and P-XRD (PAnalytical-Empyean X-ray Diffractometer) to check their polymorphic form. P-XRD data was collected in reflectance mode with an Empyrean diffractometer (PAnalytical, Phillips) equipped with CuKα1,2 radiation (γ = 1.5406 Å) operating at 40 kV and 40 mA at room temperature. Samples were scanned between 20 values of 5 and 50° at a step size of 0.079° 2θ/s, 90.27s per step. The experimental P-XRD patterns were compared with reference P-XRD diffractograms for SAM and PCM polymorphs which were obtained from the Cambridge Crystallographic Data Centre (CCDC) using the software Mercury 3.9 and compared with Highscore Plus. SAM was comprised of the required pure FI (matched with SALMID01) whereas PCM was comprised of impure FIII (matched with BISMEV01). In order to obtain pure PCM crystals with the required polymorphic forms the material supplied was recrystallized. PCM FII and FIII polymorphs were formed in DIOX and MeOH respectively using a cooling crystallisation method [10, 11]. Once more, P-XRD was used to confirm the polymorphic identity. SAM FI, PCM FII, and PCM FIII crystals were then sieved using fisherbrand stainless steel woven wire mesh test sieve with square apertures of nominal sizes 100-180 µm, 180-250 µm and 250-400 µm or 250-300 µm and 300-355 µm. These sieve fractions were used as the seed crystals in the subsequent growth experiments.

SAM crystals were also grown via a slow solvent evaporation crystallisation method under controlled room temperature from initially saturated solutions. Saturated solutions were prepared by dissolving sufficient amount of SAM in four solvents (AC, MeCN, EA and MeOH), and left mixing at 19 °C (room temperature) for 1 hour. 10 mL of solution was filtered and poured into new vial of width 27.5 mm and covered with parafilm with 3 pin holes with diameter 1.2 mm to control evaporation. Vials were left for 1 week to allow crystals to form, in the fastest system crystals appeared in two days. Crystals which formed in each of the solvents were used in the subsequent face indexing study.

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 20mA for a maximum of one minute.
3.2.2 Metastable Zone Width Determination

Metastable Zone Widths (MSZW) were determined in order to establish suitable levels of initial supersaturation to be used in the subsequent crystal growth experiments. The MSZW studies involve cooling a saturated solution in an agitated jacketed 500 mL glass reactor with an inner diameter of 75 mm, using a 60 mm 4-pitched-blade PTFE coated impeller with inclined blades rotating at 400 rpm, under a specific decreasing temperature rate, controlled by a circulator (Lauda, RE305 series). A Focused Beam Reflectance (FBRM) probe (Mettler-Toledo) was used for in situ detection of nucleation. The MSZW is quantified by taking note of the time when the experiment started, the time at which nucleation occurred and the temperature in vessel at this time. MSZW determination experiments were performed for SAM at four saturation temperatures (15 °C, 20 °C, 25 °C, and 30 °C) using two or three cooling rates (0.5 °C min⁻¹, 1°C min⁻¹, and 1.5°C min⁻¹) for each of the four solvents (AC, MeCN, EA and MeOH). MSZW for PCM have already been determined using similar equipment so was not repeated in this work, it was advised to limit the initial supersaturation ratio to S < 1.20 [15].
3.2.3 Multiple Crystal Growth Method

3.2.3.1 Isothermal Seeded Desupersaturation Growth

An isothermal seeded desupersaturation (ISD) approach was used to grow multiple crystals of SAM at once. Experiments were performed at four crystal growth temperatures (10 °C, 15 °C, 20 °C, and 25 °C) for each of the four solvents (AC, MeCN, EA and MeOH). A known amount of 300-355 μm sieve fraction seeds (< 1 g) were suspended in a slightly supersaturated solution (200 mL) in the same reactor as was used for the MSZW studies with inclined blades rotating at 500 rpm. The initial supersaturation was low to avoid nucleation so worked in the MSZW close to solubility line ($S < 1.06$), solution was heated to 6 °C above the growth temperature. The reactor was kept at a constant crystal growth temperature by using a circulator (Lauda, RE305 series), and the decay in supersaturation was recorded over time. An attenuated total reflectance Fourier transform infrared probe, ATR-FTIR (Mettler-Toledo ReactIR™ iC 10), was utilized to measure the solution concentration in-situ. The system operates in the mid-IR region, from 1900 cm$^{-1}$ to 650 cm$^{-2}$, with 152 scans every minute. This concentration decay undergoes first principles data treatment using the built-in feature within the IR software to smoothen the data from the IR spectra. IR data was converted to concentration by assuming that the relation between the measured IR responses and the concentration of involved component in the solution was linear. A FBRM probe was used to detect the total counts of crystals in situ i.e. this ensured that no unwanted nucleation was observed. Examples of both IR and FBRM signals obtained during the growth experiments are shown in Figure 3.2. In order to avoid a significant change in crystal shape the extent of growth was less than a 30 % linear dimension increase, by adjusting the mass of seeds added to the mass being deposited during crystal growth. Assuming nucleation, growth rate dispersion, agglomeration and breakage all to be negligible and that the crystal shape was constant, the solution concentration decay over time can be related to the size change of the seed crystals through a mass balance, eq. 17:

$$\Delta c(t) = \Delta c_0 - \left[ \left( \frac{L}{L_0} \right)^3 - 1 \right] \frac{W_0}{M}$$

where $W_0$ is the weight of seed crystals and $M$ is the weight of solvent when the unit of concentration is g solute / g solvent. $L_0$ is the original crystal size, which is determined by sieving. The crystal length $L$ at time $t$ can be obtained by integration of the growth rate, eq. 18:

$$L = L_0 + \int_0^t G(\Delta c(t))dt$$
for $G(\Delta c(t), T) = f(\alpha, \beta, \chi, \ldots)$, where $\alpha, \beta, \chi, \ldots$ are parameters of the growth rate equations (eqn’s 7, 10, 15 or 16) to be determined by optimization. For the optimization, the *lsqcurvefit* function in MATLAB was used and confidence intervals were calculated using the *nlparci* function. Certain complexities were not taken into account, for example the size and shape distribution in the real population of seeds, as this will lead to a much more complex analysis.

![Figure 3.2](image-url)

**Figure 3.2.** Example of IR and FBRM signals obtained during the growth of salicylamide in ethyl acetate at 15 °C. (a) IR spectra of the solute-solvent solution (SAM – EA) and pure solvent (EA), and (b) IR absorbance at 1630 cm$^{-1}$ and FBRM signal (number of counts) vs time.


3.2.4 Face Indexing of Crystals

Preferred orientation P-XRD was employed to identifying the crystal faces which were present on each of the crystals grown in the different solvents. Same P-XRD settings were used as previously described in this chapter. Whole individual SAM crystals grown in each of the four solvents were orientated on separate disks with their largest face facing upwards. Furthermore, to make identification of the smaller end faces of the crystal possible the long rectangle crystals were also cut in half with a blade and positioned on the disk with their end faces facing upwards and re-ran. Also, to check if a different polymorph formed during growth in EA, a powder sample was made by grinding SAM after growth in EA with a pestle and mortar and again analysed by P-XRD.

BIOVIA Materials Studio Morphology Prediction was used to predict the vacuum growth morphology of SAM and PCM FII/ FIII using the attachment energy method, in which the growth rate of each crystal face is assumed to be proportional to the attachment energy, viz. the energy released upon attachment of a growth slice to a given crystal face. All modelling was ran using previously published salicylamide or piracetam crystallographic data (Ref: SALMID01 for SAM FI, BISMEV for PCM FII, and BISMEV01 for PCM FIII) [6, 7]. The COMPASS II force-field was used for both the morphology prediction and the attachment energy calculations. Force-fields are a mathematical description of classical forces or potential energies between both covalent bonded atoms (bonds, angles, torsions) and also non-bonded atoms (van der Waals and electrostatics). Additionally, this software was used to model the surface chemistry of the dominating crystal faces. Within the Morphology Prediction, interfacial angles can also be calculated. Experimental interfacial angles were measured directly from micrographs using built in measurement tools on Olympus Stream Essentials software.
3.2.5 Single Crystal Growth

3.2.5.1 Cuvette Growth Experiments

![Figure 3.3](image)

*Figure 3.3. Apparatus set-up for crystal growth studies using a cuvette placed in a closed tank and positioned onto an optical microscope stage.*

A spectrophotometer cuvette 0.4 mL (55 x 10 x 1 mm, Starna Cells 21-SOG-1) was used as a growth vessel to study the growth of single salicylamide crystals. Both the growth of seed crystals (sieve fraction 300 - 355 μm) and also spontaneous nucleated crystals was 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 a supersaturated solution; which was prepared by dissolving excess solute in a solvent with sufficient mixing for a minimum of 1 hour 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 as shown in Figure 3.3. Crystals were allowed to grow for 1 hour, with micrographs captured at either 1 or 10 minute intervals using the optical microscope. The spontaneously nucleated crystal growth experiments use 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 were 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 within each solvent. The crystal increased in size for the first 2 to 10 minutes for spontaneously nucleated crystals and 30 minutes to 60 minutes for seed crystals but then began to plateau as surrounding solution became saturated.
3.2.5.2 Rotating Disk Growth Experiments

![Diagram of rotating disk growth experiment]

**Figure 3.4.** Apparatus set-up for single crystal growth studies using a rotating disk. The schematic on the left is not to scale: glass disk has diameter 60cm, and hole in center, for stirrer, is 10cm.

A jacketed 500 ml glass reactor with inner diameter of 75 mm and a rotating 60 mm glass disk, as shown in Figure 3.4, was used as the growth vessel to study the growth of multiple single crystals of salicylamide and also two polymorphs of piracetam. The 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 and 250-400 μm for SAM and PCM respectively, 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 crystal to grow. A slightly supersaturated solution was prepared in the reactor by adding a known amount of excess solute to 200 mls 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 minutes. Reactor temperature was then decreased to the required growth temperature, and allowed to stabilise for a further 20 minutes. The impeller blade was removed and replaced with
a 316 stainless steel rod which had the glass disk (with crystals) attached using steel nuts and washers. The disk was left rotating at 200 rpm for a growth period of 1 hour, and removed from solution after and dried for 10 minutes at room temperature. Micrographs of each crystal were captured before and after the growth period using an optical light microscope. Growth rates for each of the 32 crystals and also the average growth rate of all the crystals grown in one system were calculated. The crystal growth of single SAM 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. The crystal growth of single PCM FII and FIII crystals were studied at 20 °C in two solvents (ETOH and IPrOH). In ethanol the influence of supersaturation (S-1 of 0.05 - 0.30) and temperature (25 and 30 °C) on the crystal growth of the two polymorphs was also investigated.

Certain experimental variables were tested to determine the optimum working parameters for the rotating disk experiments which are defined above. To ensure that the 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 one hour of growth. The rotating disk method was repeated three times for salicylamide using the same conditions and proved reproducible results (0.29 ± 0.02 µm/s). Different growth times were trialled and found that a minimum of 20 minutes was required but 2 hours led to a decrease in the growth rate (Growth rate of width was 0.09 µm/s, 0.28 µm/s, 0.28 µm/s and 0.25 µm/s for 10, 20, 60 and 120 mins respectively). The use of a higher number of crystals (48) also resulted in a reduced growth rate and so was not deemed feasible. The position of the crystal on the disk was found to have no impact on the growth rate obtained.

3.2.5.3 Measuring Single Crystal Growth Rate

For both of the single crystal growth experiments, micrographs of the crystals were captured using an inverted optical light 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 3.6) and the (011) facet for PCM FII and FIII polymorphs. Example of the
micrographs and measurements taken at different stages during the growth period are shown in Figure 3.5. In this case, the (200) face was equivalent to the width measurements divided by two. It is worth noting from Figure 3.6 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. Highlighting the importance of reporting growth rates for crystal facets rather than just directions.

**Figure 3.5.** 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 3.6** 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.
3.3 References for Chapter 3

CHAPTER 4
Multiple Crystal Growth of Salicylamide
4 Multiple Crystal Growth of Salicylamide

This chapter attempts to rationalise the crystal growth process of multiple crystals of salicylamide, in particular the kinetics and mechanism by using an isothermal seeded desupersaturation growth method [1-5]. These multi-particle crystal growth experiments provided overall growth kinetics for the entire crystal population in the crystallisation reactor with mixing, which represented industrial process conditions with a controlled hydrodynamic environment [6, 7]. The growth kinetics obtained were modelled using several growth rate equations, using different representations of the driving force. Furthermore, the crystal growth process was examined under a variety of conditions including different solvents, supersaturations and temperatures [8-11]. Within the range of experimental conditions, the growth kinetics were found to be strongly affected by the temperature and to a lesser degree by the solvent choice. Comparison of the growth order parameter revealed a surface integration controlled growth. Higher than expected activation energies indicated desolvation as a governing process. A comparison of the influence of the solvent on the crystal growth of salicylamide against previously published nucleation data at much higher supersaturation showed good agreement, but the influence on the interfacial energy was opposite to that observed for crystal nucleation. In a detailed comparison with crystal growth data of salicylic acid, there was a consistency in the influence of the solvent on the crystal growth of the two compounds. Salicylamide growth kinetics was more strongly affected by increasing temperature than salicylic acid.
4.1 Results

4.1.1 Kinetics

4.1.1.1 Effect of Solvent, Supersaturation and Temperature

Figure 4.1 shows the recorded supersaturation decay data as a function of time and the corresponding curve obtained in the fitting of the simple overall growth rate equation, eq 15, to the data. The corresponding crystal growth rate as a function of supersaturation in the four solvents at four different temperatures are given in the diagrams to the right. The growth rates increases with increasing temperature in all four solvents as expected, but the increase is not entirely even. The growth rates increase with supersaturation, and range up to 0.4 μm·s⁻¹ which is in agreement with growth rates previously reported in the literature [5]. The maximum growth rate depends on the solvent and the temperature, but this is mostly governed by experimental conditions and limitations (e.g. assuming that nucleation does not occur). Parameters of eq 15 are given in the Table 4.1. The growth order parameter $g$ is in all cases above unity, indicating that crystal growth is at least partly controlled by the surface integration as was also found for salicylic acid [5]. No clear trend can be found in how the parameters, $g$ and $k_g$, change with temperature or with solvent, since a significant parameter correlation is likely to exist between the $g$ and the $k_g$ values for each case [13].

The modified overall growth rate equation, eq 16, has also been fitted to the experimental desupersaturation data using the two driving force representations given by eq. 2 and eq 3, $S-1$ and $\Delta\mu_T$. A similar good fit of the data was obtained for eq 16 as was obtained for eq 15 which was shown in Figure 4.1. As shown in Figure 4.2 ($S-1$) and ($\Delta\mu_T$) regardless of the driving force approximation used, the temperature dependence becomes more even compared to using eq 15. This is expected since the temperature dependence is built into the growth rate equation and is determined by fitting to all data at all temperatures for each solvent. As is shown in Figure 4.4, with respect to the influence of the solvent there is a difference between the two driving force representations, originating from the fact that the correction for the activity coefficient ratio is solvent and temperature dependent. Notably, using $\Delta\mu_T$ leads to a less temperature dependent influence of the solvent, i.e. at both temperatures shown in Figure 4.4, the order of growth rates at equal driving force essentially is: MeCN > MeOH > AC > EA. When representing the driving force in terms of relative supersaturation ($S-1$), the order between the solvents changes with temperature: at 25 °C, the order is the same as when using $\Delta\mu_T$, whereas at 10 °C the order is MeOH > AC > MeCN > EA. The growth model, eq 16, takes temperature effects on kinetics into
account. $\Delta_{HT}$ also takes temperature effects on the driving force into account, which is not the case using $S\cdot1$ as a driving force representation. The results stress the importance of the choice of representation of the driving force when growth rates in different solvents and at different temperatures are compared, as previously found for salicylic acid [5].

Figure 4.5 shows the saturated solution properties of salicylamide in acetone, acetonitrile, ethyl acetate and methanol. The mass ratio solubility shown in Figure 4.5a were calculated from the mole fraction solubility. In mass ratio terms, the solubility of salicylamide is relatively high in acetone and lower in methanol, ethyl acetate and acetonitrile. Solubility regression curves are also plotted in the figures over a temperature range from 10 °C to 25 °C, which is used in this study. Activity coefficients of salicylamide at saturation in these four solvents were measured experimentally from solid-liquid equilibrium data and are plotted in Figure 4.5b. The activity coefficient of salicylamide at saturation in acetonitrile (2.13 – 1.95) is greater than in methanol (1.62 – 1.61), ethyl acetone (0.87 – 0.79) and acetone (0.51 – 0.44). A value of the activity coefficient higher than unity implies that solute-solute interactions are more favourable than interactions between solute-solvent (acetonitrile or methanol); in contrast, relatively strong interactions between solute-solvent result in values of the activity coefficient below 1 (ethyl acetate and acetone). The comparatively strong solute-solute interactions predicted in acetonitrile and methanol are substantiated by experimental findings showing these solvents do in fact lead to faster growth rates compared with the other systems. With increasing temperature, the solution behaviour approaches ideality, and values of the activity coefficient in all solvents tend towards unity. The molar ratio of solvent to solute in saturated solution and mole fraction solubility are compared at different temperatures in Figure 4.5c,d. Unsurprisingly, the molar ratio of acetonitrile to salicylamide is much higher compared with the values in other solvents due to the lower solubility of salicylamide in acetonitrile.

In Table 4.2 the parameters obtained by fitting eq 16 to the experimental data are given. Regardless of solvent and driving force representation used, the $g$ value is above unity as was also found using eq 15, indicating again that the crystal growth is at least partly controlled by the surface integration. The $g$ value changes with the solvent, overall corresponding to the influence on the growth rate. The lowest $g$ value is found in methanol where the growth rate is the highest, and the highest $g$ value is found in ethyl acetate where the growth rate is the lowest. This relation is logical since a lower growth rate can be due to a slower surface integration for which we would expect a higher $g$ value, and vice versa. The order between the solvents with respect to the value of $g$ does not depend on the driving force representation, and in fact the numerical value is only
moderately influenced by the driving force choice, with a tendency of being lower when using $S$-1. The rate constant value $k_{g0}$ when using $S$-1 has the units of m/s and in all cases receives a numerical value of the expected order of magnitude. The corresponding rate constant when using $\Delta \mu_T$ has units of J/mol and the variation depending on the solvent is several orders of magnitude. Again, it can be suspected that much of the variation stems from numerical correlation between parameters.

As shown in Figure 4.3, the growth rate is strongly dependent on the temperature. In methanol, at a driving force of $\Delta \mu_T = 20$ J mol$^{-1}$, the growth rate increases by a factor 7 when the temperature is increased from 10 °C to 25 °C. The corresponding factor in acetone is 4. This strong dependence is of course reflected in the activation energies, $E_a$, with values given in Table 4.2. The activation energy order with respect to the solvent when using $\Delta \mu_T$ is: MeCN > MeOH > EA ≥ AC. When using $S$-1 the activation energy obtained in EA is lower than in AC. It is worth noting that while $g$ does not depend strongly on the driving force representation, the activation energy, $E_a$, does, and the higher value obtained in methanol when using $\Delta \mu_T$, is more in line with expectations. These activation energies are clearly higher than the values expected for simple molecular diffusion (5 – 20 kJ mol$^{-1}$), and nearer those reported for surface integration (40 – 60 kJ mol$^{-1}$) [14]. The surface integration step contains different physicochemical processes like desolvation, surface diffusion and lattice integration. All data together suggest that the crystal growth depending on the solvent and temperature is at least partly governed by the surface integration, and since there is a clear dependence of the solvent perhaps desolvation plays an important role.
Figure 4.1. Graphs to the left show supersaturation decay curves (dots are experimental values and lines are fits of eq 15), and graphs to the right show the corresponding growth rate curves for salicylamide at four temperatures in four solvents.
Table 4.1. Parameters of eq 15 given with 95% confidence limit for desupersaturation experiments in 4 solvents.

\[ G = k_x (S - 1)^g \]

<table>
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<tr>
<th>Solvent</th>
<th>Temperature, °C</th>
<th>( k_x \times 10^5 ), m/s</th>
<th>( g )</th>
</tr>
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<tr>
<td>MeOH</td>
<td>25</td>
<td>2.00 ± 0.65</td>
<td>1.05 ± 0.06</td>
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<td></td>
<td>20</td>
<td>2.11 ± 0.69</td>
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<td></td>
<td>15</td>
<td>3.94 ± 1.39</td>
<td>1.34 ± 0.07</td>
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<td></td>
<td>10</td>
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<td>1.30 ± 0.07</td>
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<tr>
<td>AC</td>
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<td>1.26 ± 0.10</td>
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<td>15</td>
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<td></td>
<td>10</td>
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Figure 4.2. Growth rate curves of salicylamide at four temperatures in four solvents obtained by fitting experimental results to the modified rate eq 16 using driving force representations of S-1.

Figure 4.3. Growth rate curves of salicylamide at four temperatures in four solvents obtained by fitting experimental results to the modified rate eq 16 using driving force representations of $\Delta \mu T$. 
**Figure 4.4.** Effect of temperature and driving force representation on growth rate of salicylamide in four solvents, at two temperatures, obtained by fitting experimental results to the modified growth rate eq 16 with the driving force $s$ represented by $S-1$ and $\Delta \mu_T$, respectively.

**Figure 4.5.** Solubility of salicylamide: scatter plot obtained from experimental data and solid line obtained from regression curves (a); activity coefficients in saturated solution (b); molar ratio of solvent to solute (c) and mole fraction of solute (d).
**Table 4.2.** Parameters of eq 16, given with 95 % confidence limit for desupersaturation experiments in four solvents.

\[ G = k_{g0} \exp \left( \frac{-E_a}{RT} \right) (S - 1)^g \]

\[ G = k_{g0} \exp \left( \frac{-E_a}{RT} \right) (\Delta \mu_r)^g \]

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<th>Solvents</th>
<th>( k_{g0} \times 10^5, \text{m/s} )</th>
<th>( g )</th>
<th>( E_a, \text{kJ/mol} )</th>
<th>( k_{g0}, \text{m/s/(J/mol)} )</th>
<th>( g )</th>
<th>( E_a, \text{kJ/mol} )</th>
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<td>55.90 ± 3.3</td>
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</tbody>
</table>
It should be stressed that the difference between the different driving force representations can be significant, and moreover, the difference is highly solvent-dependent. The largest difference observed between $\Delta \mu$ calculated by including and neglecting the activity coefficient contribution, respectively, is 37% in acetone, while in methanol the difference is close to zero. This is due to the fact that activity coefficients, and their influence on $\Delta \mu$, depend on the solvent. The difference between the two representations not only depends on solvent, however, but also on temperature; increasing temperature results in a decrease in the difference between the representations in MeOH (from 5% to -3%) and EA (from 28% to 24%), while it remains virtually constant at all temperatures in AC (37%) and MeCN (22%). $\Delta \mu_T$ accounts for the concentration dependence of the activity coefficient, which in many cases is expected to dominate the total influence of non-ideality on the driving force. [15] However, it should be noted that some solutions evaluated in this work are fairly dilute, and thus that the temperature dependence of the activity coefficient is expected to be more important than assumed in the derivation of eq 3. For these cases, we cannot state with certainty that $\Delta \mu_T$ is a better approximation than S-1.
4.1.1.2 Facet Growth Rate Models: Effect of Solvent and Temperature

In applying the BCF and the B&S equations 7 and 10 respectively, it should be noted that the crystal growth rate data obtained from the isothermal seeded desupersaturation experiments represents an average over a number of crystals growing simultaneously, as well as an average over the growth of different faces. Accordingly, in the application of face growth models to such data the physical parameters determined have to be understood as averages over the different faces [5]. Both growth models provide a good fit to the experimental data as shown in Figure 4.6. The BCF model gives a slightly better fit at 10 °C and 25 °C according to the residual curves.

Table 4.3 and Table 4.4 list the fitted parameters of the BCF and B&S models, and the surface diffusion dependent parameters A and C for each solvent are plotted versus the inverse temperature in Figure 4.7. In all cases the graphs show a reasonably linear increase in the parameter value with decrease in inverse temperature from which the surface diffusion activation energy, $E_{a,surf}$, is determined according to eq 13. The surface diffusion activation energies are given in Table 4.3 and Table 4.4 and for both models follow the same order with respect to the solvent as obtained for the activation energy above for eq 16 using $\Delta\mu_T$: MeCN > MeOH > EA $\geq$ AC.
**BCF & B&S Growth Mechanisms Fitted to Kinetics**

**Figure 4.6.** Desupersaturation curves in acetonitrile at two different temperatures (a) showing experimental data (scatter) and fits of two layer growth models (solid lines), and corresponding residuals (b).

**Figure 4.7.** Influence of temperature on BCF and B&S parameters in different solvents.
The following table provides the fitted kinetic parameters of the BCF crystal growth model with 95% confidence limits for desupersaturation experiments.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( A \times 10^6 ), K m/s</th>
<th>( B ), K</th>
<th>( E_{a,\text{surf}}, \text{kJ/mol} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH</td>
<td>15.5 ± 0.1</td>
<td>4.04 ± 0.01</td>
<td>0.49 ± 0.10</td>
</tr>
<tr>
<td>AC</td>
<td>12.2 ± 1.30</td>
<td>4.28 ± 0.13</td>
<td>0.77 ± 0.20</td>
</tr>
<tr>
<td>MeCN</td>
<td>16.8 ± 1.90</td>
<td>2.57 ± 0.01</td>
<td>0.79 ± 0.13</td>
</tr>
<tr>
<td>EA</td>
<td>7.74 ± 0.84</td>
<td>2.53 ± 0.01</td>
<td>3.15 ± 0.47</td>
</tr>
</tbody>
</table>

The following table provides the fitted kinetic parameters of the B&S crystal growth model with 95% confidence limits for desupersaturation experiments.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>( C \times 10^6, \text{m/s} )</th>
<th>( D, \text{K}^2 )</th>
<th>( E_{a,\text{surf}}, \text{kJ/mol} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH</td>
<td>8.15 ± 0.57</td>
<td>87 ± 14</td>
<td>61.39</td>
</tr>
<tr>
<td>AC</td>
<td>6.59 ± 0.80</td>
<td>151 ± 30</td>
<td>46.53</td>
</tr>
<tr>
<td>MeCN</td>
<td>8.41 ± 1.11</td>
<td>125 ± 17</td>
<td>79.88</td>
</tr>
<tr>
<td>EA</td>
<td>3.93 ± 0.43</td>
<td>344 ± 52</td>
<td>46.97</td>
</tr>
</tbody>
</table>
CHAPTER 4

4.2 Discussion

4.2.1 Comparison of Crystal Growth with Nucleation

According to the results, the crystal growth rate of salicylamide in the four different solvents at equal driving force ($\Delta \mu_T$) decreases in the order: MeCN > MeOH > AC > EA. Regardless of temperature, the growth rate in EA is clearly lower than in the other solvents and the growth rate in MeCN and MeOH is quite similar. When the driving force is described by $S-1$ the order is more dependent on temperature, but at 15 °C the order is MeOH > AC > MeCN > EA. In Figure 4.8 the latter data are compared with data from a study over primary nucleation of salicylamide in the same solvents [16], from which also approximate crystal growth rates are estimated by calculating growth rates to be the inverse of growth time parameter ($t_g$) which is taken from eq 6. These estimates assume that the crystals become visible when they reach a size of 1 μm, which of course is only an arbitrary value based on the findings of R. Devi, M. Svard et al [17]. However, within this assumption, the crystal growth rates from the nucleation experiments are in the order of 20 times higher, as would be expected from the much higher supersaturation under which the crystals are grown in the nucleation experiments. However, the order of growth rates with respect to the solvent exactly matches the order found in the present study. Methanol provides the fastest growth for salicylamide crystals, both at the nucleus stage at high supersaturation and for the much larger seed crystals at lower supersaturation, whereas ethyl acetate leads to the slowest growth rates. This shows that the growth of salicylamide crystals of varying size (< 1 μm and 355 μm up to 1000 μm) and under different driving forces were influenced in the same way by the different solvents even though the growth mechanism may actually be different.

![Figure 4.8. Growth rates of salicylamide obtained from multi-particle crystal growth studies at 15 °C with S-1 of 0.01 (this work), compared with the growth rates obtained from nucleation studies at 15 °C with S-1 of 1 [16].](image)
The $B$ parameter in the spiral growth model is directly proportional to the interfacial energy (eq 9), and the $D$ parameter in the birth and spread model is proportional to the interfacial energy raised to the power 2 (eq 12). Accordingly, based on the parameter values given in Table 4.4 and that the molecular volume, $V_m$, of salicylamide is equal to 0.171 nm$^3$ as obtained from the crystal density, and assuming the height of the growth step, $h$, is equal to the cubic root of $V_m$ i.e. 0.56 nm., the interfacial energy was determined using the B&S model and found to follow the order of EA > AC > MeCN > MeOH. According to eqs 9 and 12, a low interfacial energy leads to a high crystal growth rate, which is in agreement with the results from the growth rate experiments reported in this work. It is widely accepted that the solid-liquid interfacial energy appears as a governing parameter also in crystal nucleation. For this reason, values previously reported from nucleation experiments are compared with interfacial energies obtained from crystal growth data using the B&S model in Figure 4.9. The interfacial energies obtained from nucleation experiments follow an order exactly opposite to that of the B&S growth data: MeOH > MeCN > AC > EA. In the BCF theory the interfacial energy determines the radius of the growth spiral, while in the B&S theory the interfacial energy is based on the "birth" term of the B&S equation which can be considered as a 2D nucleation on a substrate surface, which explains why the interfacial energy obtained from crystal growth data is expected to be significantly smaller than that obtained from nucleation data (3D nucleation). However, at present we have no clear explanation why the influence of the solvent on the interfacial energy as determined from crystal growth and nucleation experiments, respectively, show completely opposite trends, and this disagrees with our previous findings for salicylic acid [16]. One possibility would be that the faces governing the crystal growth process do not have the same importance for the formation of nuclei. It is well understood that the supersaturation dependence of the growth rate of different faces can be different leading to that faces governing the growth at low supersaturation do not necessarily have to be the same as those that govern the growth rate at high supersaturation.
Figure 4.9. Interfacial energies obtained from the fitted parameter $D$ of the B+S crystal growth model for growth data compared with values obtained using the classical nucleation theory from previously published nucleation data [16].
4.2.2 Comparison of Crystal Growth of Salicylamide versus Salicylic Acid

The same crystal growth method has been used previously to study salicylic acid [5]. Salicylic acid (SA) has an identical molecular structure except for the amide group in the meta-position being replaced by a carboxylic acid group. Various properties of the two solutes are shown in Table 4.5. The molecular weight is essentially the same, while the melting temperature of SA is about 20 K higher, and the crystal density of SA is somewhat higher and accordingly the molecular volume is a bit lower. The hydrogen bonding capability differs somewhat, contributing to differences in the crystal structures. Both salicylic acid and salicylamide molecules form dimers, but in addition to this motif the SAM molecules are also involved in other intramolecular hydrogen bond interactions. Ultimately, the differences in the hydrogen bonding are likely to play a significant role in the variances of growth rates obtained for the two solutes. The packing arrangements in the two structures differ considerably as illustrated in Figure 4.10. Because of the structural differences, the two compounds crystallize in completely different habits, as is further discussed below.

Table 4.5. Physical and crystal properties of the two solutes, salicylic acid versus salicylamide.

<table>
<thead>
<tr>
<th>Property</th>
<th>Salicylic Acid (SA)</th>
<th>Salicylamide (SAM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUPAC name</td>
<td>2-Hydroxybenzoic acid</td>
<td>2-Hydroxybenzamide</td>
</tr>
<tr>
<td>Formula</td>
<td>C$_7$H$_6$O$_3$</td>
<td>C$_7$H$_7$NO$_2$</td>
</tr>
<tr>
<td>Molecular Structure</td>
<td>![Structure of Salicylic Acid]</td>
<td>![Structure of Salicylamide]</td>
</tr>
<tr>
<td>Molar mass (g/mol)</td>
<td>138.12</td>
<td>137.14</td>
</tr>
<tr>
<td>Extrapolated Onset Melting Point (°C)</td>
<td>158.2[18]</td>
<td>138.7 [19]</td>
</tr>
<tr>
<td>Density (g/cm$^3$)</td>
<td>1.44</td>
<td>1.33</td>
</tr>
<tr>
<td>Crystal Habit</td>
<td>Hollow Needles</td>
<td>Rectangular Plates</td>
</tr>
</tbody>
</table>
Salicylic Acid (SA)

Salicylamide (SAM)

**Figure 4.10.** Unit cell representations showing hydrogen bonds (blue lines) the two solutes, salicylic acid versus salicylamide were obtained using the software Materials Studio for structures with CSD refcodes: SALIAC16 and SALMID01.

**Figure 4.11.** Crystal growth rate curves at (a) 10 °C and (b) 25 °C for salicylamide (present work; dashed lines) and salicylic acid [5] (solid lines) in four solvents at different driving forces obtained by fitting experimental results to the modified growth rate eq 16 with the driving force, $s$, represented by $\Delta\mu_T$.

In Figure 4.11, crystal growth rates of salicylamide are compared with salicylic acid in the same solvents at two temperatures. In both cases the driving force has been estimated according to eq 3 using the same approximation of the activity coefficient ratio [15]. At lower temperatures, the growth rates of the two compounds follow a similar solvent order, whereas at higher temperatures they follow a different order. For salicylamide, the growth rate at all temperatures decreases in the order: MeCN > MeOH > AC > EA, while for salicylic acid the solvent order changes with temperature: at 10 °C the order is MeCN > MeOH ≥ EA ≥ AC, while at 25 °C the order is EA > MeOH > MeCN ≥ AC. In summary acetonitrile provides the fastest growth...
kinetics for both solutes at 10 °C. Ethyl acetate provides the slowest growth rates for salicylamide, whereas acetone provides the slowest growth rates for salicylic acid consistently at both temperatures. Accordingly the order with respect to the solvent does not match perfectly for the two solutes. However it should be acknowledged that there is some uncertainty in the curves as shown in fitting; this could have a considerable effect on the solvent order in the case of salicylic acid for which the curves are close together. Salicylic acid exhibits a clearly faster growth than salicylamide in all solvents at the lower temperature (10 °C), whereas salicylamide has the faster growth in all solvents except EA at the higher temperature (25 °C) as illustrated in Figure 4.11. As regards the temperature dependence on the crystal growth rate, for salicylic acid in acetonitrile at $\Delta \mu_T$ of 10 Jmol$^{-1}$, the growth rate increases from $1.4 \times 10^{-8}$ ms$^{-1}$ up to $2.5 \times 10^{-8}$ ms$^{-1}$ with a 15 °C increase, which equates to a factor of 2. Under similar conditions, for salicylamide the growth rate increases from $1.1 \times 10^{-8}$ ms$^{-1}$ up to $7.0 \times 10^{-8}$ ms$^{-1}$, i.e. by a factor of 6. This shows that under the evaluated conditions the impact of increasing temperature has a significantly greater impact on the growth rate of salicylamide than salicylic acid. Comparing the activation energies obtained by fitting eq 16 using $\Delta \mu_T$ it is notable that $E_a$ values are significantly higher (from a factor 1.5 up to 4) for SAM in all the solvents. The $E_a$ value for salicylic acid is in the range 22 – 67 kJmol$^{-1}$ while for salicylamide the range is 58 – 91 kJmol$^{-1}$.

There appears to be no clear relationship between SAM and SA as regards the parameters $k_{g0}$ and $g$ with respect to the solvent. Significantly higher $k_{g0}$ values were obtained for salicylamide than salicylic acid. The values of the growth order parameter $g$ are for all solvent-solute combinations above unity with slightly higher values observed for salicylic acid in all solvents except ethyl acetate [5]. In comparing the activation energies for surface diffusion it may be noted that for SAM the value in MeOH is about 50 % higher compared to SA, while the values in AC are roughly the same, the value in MeCN is very much higher (by a factor 5 – 10), and the value in EA is slightly lower.
4.3 Conclusion

Out of four solvents, the crystal growth rate of salicylamide was found to be slowest in ethyl acetate under all conditions evaluated. For the remaining solvents, the order with respect to the growth rate of salicylamide depends on temperature, supersaturation and driving force representation. The growth kinetics are strongly affected by the temperature as reflected in the activation energy. The growth order parameter reveals that the crystal growth is at least partly controlled by surface integration, with the highest value being found in ethyl acetate where the growth rate is the lowest. Higher than expected activation energies and significant influence of the solvent indicate that desolvation is a governing process. The influence of the solvent on the growth rate of salicylamide is in good agreement with the corresponding growth rates obtained in primary nucleation experiments. The BCF model and the B&S model are both well fitted to the growth data, and the interfacial energies are estimated. As opposed to similar work on salicylic acid, interfacial energies from primary nucleation data have an opposite dependence on the solvent to that found for the present growth rate data. Compared with a similar study over the crystal growth rate of salicylic acid the influence of the solvent is essentially the same, with acetonitrile providing the fastest growth rate for both compounds. Salicylamide crystal growth has a stronger temperature dependence than salicylic acid crystal growth.
4.4 References for Chapter 4

CHAPTER 5

Face Indexing & Shape Analysis of Salicylamide
Crystal Grown In Different Solvents
5 Face Indexing & Shape Analysis of Salicylamide Crystal Grown In Different Solvents

The focus of this chapter was two-fold; to investigate how salicylamide crystals grew in different solvents at a molecular level including the solvent-solute interactions and also to face index experimentally grown crystals with different habits for the purpose of observing the correct faces during the growth process. SAM crystals grown experimentally in acetone, acetonitrile and methanol matched the attachment energy predicted rectangle plate vacuum habit. However, in ethyl acetate irregular hexagonal plate crystals form. Single crystal and powder x-ray diffraction was carried out to rule out the possibility of a new polymorph. Given no new polymorphs were discovered, instead this change in habit was found to be caused by the stunted growth of specific crystal faces during the crystallisation process. This alternative habit makes face indexing of experimentally grown crystals difficult. Precise face indexing is essential in order to measure the kinetics of crystal growth in a characteristic dimension accurately i.e. the correct faces [1, 2]. A combination of experimental and modelling prediction tools was employed for the face indexing process. The angle between faces combined with preferred orientation P-XRD was found to be the most accurate and reliable method leading to successful identification of each salicylamide crystal face. The surface chemistry of each face was examined on a molecular level with insights into the possible growth attachment sites being made. It was deduced that ethyl acetate could adsorb more strongly onto certain faces, the increased size of which, can explain the shape change.
5.1 Results

5.1.1 Salicylamide Crystal Habit Grown in Different Solvents

Salicylamide crystals were grown in each of the four solvents by slow solvent evaporation; typically one crystal habit dominated each solvent system. This is illustrated by representative crystals for each of the solvents in the micrographs in Figure 5.1. Acetone, acetonitrile and methanol mainly formed crystals with a rectangle habit. In ethyl acetate, the salicylamide crystals typically formed irregular hexagonal plates. In a few cases crystal habit did also change within each solvent system, for example ethyl acetate had the capabilities of forming crystals with a rectangle habit.

![Micrographs](a) AC (b) MeCN (c) EA (d) MeOH)

**Figure 5.1.** Micrographs of crystals grown by slow solvent evaporation in the different solvents: a) acetone, b) acetonitrile, c) ethyl acetate and d) methanol.
5.1.2 Salicylamide Crystal Morphology Prediction

According to the computational prediction by the attachment energy approach shown in Figure 5.2, the salicylamide crystal grown in vacuum forms a rectangular shaped particle containing 16 facets, with only 5 being unique. The modelling predicts flat sides (facets (200), (002) and (011)) and slanted top and bottom made by facets (11-2) and (110). Overall, the most dominant, thus the slowest growing are equivalent (002) and (00-2) faces which jointly take up 51.4% of the total surface area (see Table 5.2). Crystals grown in acetone, acetonitrile and methanol (Figure 5.1 a, b, d) gave similar habit to the predicted. However crystals grown in ethyl acetate (Figure 5.1 c) gave a different habit and so a check for polymorphism was performed.

![Figure 5.2](image)

**Figure 5.2.** The growth morphology (computational attachment energy prediction, COMPASS-II force-field) of salicylamide crystal. Miller indices are given for major faces.
5.1.3 Check for Polymorph

Although an altered crystal habit is not a sole indicator of polymorphism, it can be used as an initial test. To ensure the crystals with irregular hexagonal habit grown in our study were not a new polymorph, both P-XRD and SC-XRD data was collected. A powder sample of SAM was made by grinding SAM as supplied with a pestle and mortar and placing on sample holder. This powder sample was analysed by P-XRD and results were compared with a previously published P-XRD pattern of salicylamide [3]. Both patterns match as shown in Figure 5.3 indicating that SAM in this study forms the same polymorph as the previously reported stable Form I. In order to confirm for definite there are no minor changes in the crystallographic data we also determined the unit cell of SAM crystal grown in EA with irregular habit through SC-XRD and compared against previously reported crystallography data [3]. This confirmed for certain the same stable polymorph, Form I, was formed with the monoclinic I 2/a cell setting.

![Figure 5.3](image)

**Figure 5.3.** Powder XRD pattern of salicylamide sample as used in this work (2nd pattern is calculated from SC-XRD data obtained as part of this work and reported in [4], 3rd pattern is ground salicylamide sample as received) compared to previously published salicylamide XRD pattern [3].
5.1.4 Face Indexing

Step 1: Overlay of predicted habit onto experimental habit

As it has been shown that all crystals grown in the different solvents are of the same polymorph, it indicates the change in crystal habit is due to different growth rates of the same faces in the different solvents. The irregular habit makes face indexing difficult. Experimentally grown crystals which had a similar habit to the predicted can easily be subjectively indexed by simply overlaying the predicted habit to these micrographs and assigning the corresponding face index. The large flat face and the side face as shown in Figure 5.1a, b, d are likely to be the (002) and (200) respectively as predicted by the growth model in Figure 5.2. These can be confirmed experimentally by preferred orientation P-XRD in the next section. The end faces are more difficult to identify as the three end faces predicted do not always remain in the experimental crystals. In some crystals there are only one or two end faces. A more detailed analysis is required to identify these end faces correctly as will be discussed at a later stage in this chapter. As for crystals with the irregular habit, such as the ones grown in ethyl acetate as shown in Figure 5.1c, face indexing is not straightforward and so these crystals also require a more extensive approach.

Step 2: Preferred orientation P-XRD

In order to identify the faces of real crystals, separate P-XRD patterns were obtained for whole crystals grown in each of the four solvents which were rotated in a preferred orientation onto the disk as shown in Figure 5.4. All samples formed the same three peaks, comparing these peaks with the previously published salicylamide XRD indexed pattern [3] they infer the (002), (004) and (008) faces as shown in Figure 5.5. All are a part of the same (00l) indices family, representing different crystal planes. Hence all peaks observed from the preferred orientation XRD pattern confirm the presence of the large (002) face as predicted by the growth morphology in Figure 5.2. Interestingly, the two crystals grown in ethyl acetate which gave significantly different habits both gave the same XRD pattern. Accordingly, both crystals are dominated by a large (002) faces, but they differ in the side and or end faces.
Figure 5.4. Micrographs of each of the crystals to be examined by P-XRD, grown in each of the four solvents with two crystals for ethyl acetate due to different habit.

Figure 5.5. Previously published salicylamide XRD pattern [3] compared against preferred orientation XRD patterns of whole salicylamide crystals grown in acetone, acetonitrile, ethyl acetate (1), ethyl acetate (2) and methanol. Miller indices assigned to peaks of interest.

Additionally, one P-XRD pattern was obtained for multiple whole salicylamide crystals grown in methanol which were placed in a preferred orientation onto the disk as shown in Figure 5.6. The same three XRD peaks are observed again as were shown for the individual crystal scans. Predominantly (00l) face is observed in Figure 5.7 as expected from the modelled habit, again confirming the presence of predicted (002) face when compared against previously published salicylamide XRD pattern. However, this scan of multiple crystals at once gives an additional two peaks indicative of the (200) and (015) faces. The (200) face matches the predicted side face of the crystal in Figure 5.2. The (015) is part of the (0kl) family, which matches to the (011) end face of the predicted crystal habit. Scanning multiple crystals at once allowed for faces which had a small surface area ratio to be amplified and meant that their respective peak intensity could be increased and reach the minimum threshold and so not be overshadowed by the larger more intense peaks. These new peaks complement the predicted faces in the material studio model.
Figure 5.6. Image shows multiple whole salicylamide crystals grown in methanol – all crystals were oriented as shown on the disk and analysed by XRD.

Figure 5.7. Preferred orientation XRD patterns of multiple whole salicylamide crystals grown in methanol compared against published salicylamide pattern [3].

Although running multiple crystals in the preferred orientation led to the confirmation of the side (200) face and the end face (011), the large surface area of the (002) face still tend to outweigh the other peaks. In order to reduce the intensity of these (00l) peaks, and allow for other peaks to be observed, the crystal was cut using a blade and orientated differently so that the faces on the end of the crystal were facing upwards as demonstrated with the growth habit in Figure 5.8.

P-XRD patterns were obtained for two cut individual crystals grown in different solvents to account for differences in habits observed from the experimental crystals. The two crystals tested gave different peaks as shown in Figure 5.9 which indicates different dominate end faces on the samples. Only one peak formed for each of the samples, indicating that one face dominates the end of the crystals in both cases. Crystal 1 one which was grown in acetone had a peak representing the (110) face confirming one predicted end face. Whereas Crystal 2 which was grown in acetonitrile has a peak signifying the (024), this represents the (0kl) indices family which confirms the (011) end face as predicted in the growth morphology habit in Figure 5.2.
This further confirms that the dominate end faces change between salicylamide crystals, and that predicted habit alone cannot just be utilised for accurate face indexing of real crystals.

Figure 5.8. Growth morphology (computational prediction, COMPASS-II force-field) of salicylamide crystal; oriented same way as real crystal samples on P-XRD disk so that end faces are facing upwards. Miller indices are given for major faces.

Figure 5.9. Preferred orientation XRD patterns of cut & oriented salicylamide crystals grown in different solvents compared against published salicylamide pattern [3].

The use of preferred orientation P-XRD was instrumental in the face indexing process. This technique combined with predicted habit allowed for confirmation of specific faces from real salicylamide crystals, ultimately resulting in accurate face indexing of the crystal faces with relatively large surface area ratios. P-XRD confirmed the presence of the large flat (002) face, the main side (200) face and also some end faces (011) and (110). Experimental confirmation of four of the five unique facets predicted was achieved except for the small (11-2) end face. However, due to the fact that smaller peaks can be masked by the more dominating peaks it is not a suitable technique for identifying the smaller crystal faces. Instead experimentally measured interfacial angles will be compared against predicted angles in order to assign accurate indices to all the end faces of the crystal.
Step 3: Interfacial Angle

Interfacial angles can easily be calculated from previously published unit cell data using Material Studio Morphology software. Calculated angles are shown in Table 5.1. Although a crystal does not always maintain geometric similarity during growth (change in crystal habit), the interfacial angles do not vary as they are characteristic of the substance which makes them a reliable tool for face indexing crystals that have a variable habit [5, 6].

Table 5.1. Interfacial angles calculated using Material Studio for SALMID crystal habit.

<table>
<thead>
<tr>
<th>(h k l)</th>
<th>(h k l)</th>
<th>Interfacial Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 0 0 2)</td>
<td>( 2 0 0)</td>
<td>79.43</td>
</tr>
<tr>
<td>( 2 0 0)</td>
<td>( 0 1 1)</td>
<td>87.38</td>
</tr>
<tr>
<td>( 2 0 0)</td>
<td>( 1 1 0)</td>
<td>67.01</td>
</tr>
<tr>
<td>( 1 1 0)</td>
<td>( 0 1 1)</td>
<td>24.57</td>
</tr>
<tr>
<td>( 1 1 0)</td>
<td>(-1 1 0)</td>
<td>45.98</td>
</tr>
<tr>
<td>( 2 0 0)</td>
<td>( 1 1 -2)</td>
<td>73.59</td>
</tr>
<tr>
<td>(-1 1 2)</td>
<td>( 0 1 1)</td>
<td>22.75</td>
</tr>
<tr>
<td>( 1 1 0)</td>
<td>(-1 1 2)</td>
<td>47.32</td>
</tr>
<tr>
<td>(-1 1 2)</td>
<td>( 1 1 -2)</td>
<td>62.21</td>
</tr>
</tbody>
</table>

Typically a goniometer would have been used to measure the interfacial angles directly from real crystal samples. Nowadays, interfacial angles can be measured directly from micrographs using three point angle measuring tool on Olympus Stream Essentials software. It should be noted for the angle to be accurate the crystal needs to be laid flat. Experimentally measured angles shown in micrographs below (Figure 5.10) compared well with calculated angles as listed in Table 5.1. Figure 5.10a represents crystals with the regular rectangle habit; as acetone, acetonitrile and methanol all formed crystals of similar shape only one grown in acetone was reported. In order to successfully determine the miller indices of the end faces of the crystal, specific interfacial angles were measured; for example the 45.45° angle was calculated to be between the (110) and (-110) planes, and 69.74° angle was calculated to be between the (200) and (110) planes. Figure 5.10b represents crystals with the irregular hexagonal habit as formed in ethyl acetate. Measured
interfacial angles of 47.17° was calculated to be between the (110) and (-112) planes, and 66.91° was calculated to be between the (200) and (110) planes. Using this information, in both cases the Miller indicies can be assigned successfully to the end and side faces of the crystals.

Figure 5.10. Micrographs of individual salicylamide crystals grown experimentally in a) acetone and b) ethyl acetate with measured interfacial angles in red text/lines and assigned indices overlaid in black text.

Step 4: Assigning miller indices to real crystals

Combining all of the experimental and modelling results from the previous steps, salicylamide crystals of both regular rectangle habit and also irregular hexagonal habit were successfully fully face indexed as shown in Figure 5.11.

Figure 5.11. SEM images show individual salicylamide crystals grown experimentally in a) acetone and b) ethyl acetate with assigned miller indices overlaid.
5.2 Discussion

5.2.1 Molecular Analysis of Particle Interactions

Uninfluenced by the surroundings, the crystal shape is determined by the crystal structure and the solid state molecular interactions. In its crystal structure, each salicylamide molecule creates H-bonding with three neighbouring salicylamide molecules through the hydroxyl (-OH), amine (-NH$_2$) and carbonyl (-C=O) polar groups as shown in Figure 5.12. A centrosymmetric dimer present in the crystal lattice is stabilised by H-bonding with adjacent molecules. In molecular crystals, strong intermolecular interactions (such as H-bonding) tend to determine the growth directions [3, 7-9]. Thus, it can be expected that the growth rate may be higher in hydrogen bonding directions leading to the corresponding faces becomes small.

![Figure 5.12](image)

Figure 5.12. An arrangement of H-bonds (black dots) in the crystal structure of salicylamide projected along the crystallographic c-axis. Highlighted is the salicylamide dimer. Hydrogen – white, carbon – grey, oxygen – red, nitrogen – blue.

The crystal shape predicted by the attachment energy method is shown in Figure 5.2 and Figure 5.8. The crystal is dominated by the (002) faces and bound by (200) side faces. The attachment energy of the five slowest growing faces are given in Table 5.2. The attachment energy of the (002) face is -170.4 kJ/mol, being only half of the value for the second slowest growing side face (200), having the attachment energy of -357.0 kJ/mol. The difference to the following three faces is clear but not exceedingly big.
Table 5.2. Calculated attachment energy and total area for stable configurations of major facets predicted with the growth morphology method using the COMPASS II force-field.

<table>
<thead>
<tr>
<th>Facet (h k l)</th>
<th>$E_{\text{att}}$ (kJ/mol)</th>
<th>Area (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0 0 2)</td>
<td>-170.4</td>
<td>51.4</td>
</tr>
<tr>
<td>(2 0 0)</td>
<td>-357.0</td>
<td>24.2</td>
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<tr>
<td>(0 1 1)</td>
<td>-415.7</td>
<td>18.0</td>
</tr>
<tr>
<td>(1 1 −2)</td>
<td>-466.2</td>
<td>3.3</td>
</tr>
<tr>
<td>(1 1 0)</td>
<td>-487.2</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Figure 5.13 Molecular representations of crystal faces of salicylamide. Both 3D and 2D representations are shown for each surface.
In Figure 5.13, the molecular chemistry of the five slowest growing faces is shown. The slowest growing (002) faces feature protruding non-polar phenyl rings, where the contribution of van der Waals and \( \pi \)-interactions are likely to dominate (Figure 5.13e). The contribution from hydrogen bonding is low and thus the face is non-capable of making strong hydrogen bonding interactions with the solvents. Accordingly, the growth rates of these faces are not expected to be strongly influenced by the solvent. The (200) faces appears to be more polar, however the propensity for hydrogen bonding is reduced by the fact that it is the internally rotated hydrogen bonded alcohol group that dominates the surface and the amide groups are embedded deeper into the surface topology. The short side faces of the simulated crystal shape all have a more clear propensity for hydrogen bonding, which also explains why these are the smallest faces in Table 5.2, especially (110) and the (11-2).

The crystal grown in acetone (Figure 5.11) is not very different from that predicted by the attachment energy method. The crystal is clearly dominated by the (002) faces and the elongated (200) face is quite similar to that found in the predicted shape (Figure 5.2). Also, the (011) face is clearly seen on the short side of the crystal. In ethyl acetate, the salicylamide crystals form irregular hexagonal plates looking quite different from those in acetone. However, at closer inspection it is found that it is in fact the short side faces that has been slowed down by which the (200) faces become less dominating. The (110) and (11-2) faces have developed more than in the other solvents. However, it should be noted though that the attachment energies of these faces are not much higher than that of the (011) faces, indicating that just a modest slowing down of the growth rates for the (110) and (11-2) faces will result in the shape change as seen in ethyl acetate. As shown in Figure 5.13a and b, the (110) and (11-2) faces feature exposed amine groups (-NH\(_2\)), especially capable of hydrogen bond donation. However, we suspect that the change in shape, as observed in ethyl acetate, is not due to hydrogen bonding as both acetonitrile and acetone are also polar aprotic hydrogen bond accepting solvents. Thus we suspect that the size of the ethyl acetate molecule leading to higher propensity for van der Waals bonding, is an important factor in explaining that shape is more influenced in ethyl acetate.

Furthermore, the adsorption energy of the four solvent molecules on the salicylamide (110) surface was obtained by Monte Carlo simulations within Material Studio, as shown in Figure 5.14 [4]. In agreement with the discussion above, it was found that EA is adsorbed strongest on the (110) face with an adsorption energy of \(-48.78\) kJ/mol, and the adsorption energy decreases in the order EA > AC > MeCN > MeOH. The adsorption of solvent molecules onto the crystal surface (110) is either by hydrogen bonding and or van der Waals interaction. It was found that
EA molecules adsorb embedded in the salicylamide molecule landscape by van der Waals bonding. MeCN also absorbs onto the (110) surface by van der Waals interactions alone however the adsorption energy is 7.94 kJ/mol (approx. 16%) lower than for EA. EA’s molecular weight is over two times the weight of MeCN (88 g/mol versus 41.05 g/mol respectively) and EA accordingly covers a far larger surface area of the (110) face. On the other hand, AC adsorbs onto the (110) crystal face via van der Waals interaction and hydrogen bonding, and MeOH adsorption is dominated by hydrogen bonding. Hydrogen bonding is directional and leads to the molecule “sitting on top of” the surface rather than becoming embedded in the topology.

Figure 5.14. Adsorption of solvent molecules onto the (110) face of salicylamide growth morphology performed using the adsorption locator calculator on material studios. Solvents adsorbed in the respective images are EA (ethyl acetate) on top and MeOH (methanol) on the bottom. Note the images shown here are an enlarged representative area taken from the full adsorption output so findings could be seen clearly.
5.3 Conclusion

Salicylamide crystals grown experimentally were successfully face indexed using a combination of experimental and modelling techniques. Preferred orientation P-XRD combined with overlaying predicted habit allowed for experimental confirmation of the (002), (200), (011) and (110) faces from real salicylamide crystals. Due to the changing nature of salicylamide’s crystal habit grown under the same conditions in different solvents, comparing calculated interfacial angles against experimental angles was found to be the most reliable and consistent method for face indexing. The salicylamide crystal habit is most greatly affected by EA as compared to the habit of its crystals grown in AC, MeCN and MeOH. The underlying reduction of the growth of the salicylamide (110) face is likely due to stronger van der Waals interaction of EA molecules with the crystal surface. The adsorption energy of MeCN on the (110) face is lower because the molecule is smaller, as is the adsorption energy of AC and MeOH in spite of their greater propensity for hydrogen bonding.
5.4 References for Chapter 5


CHAPTER 6

Single Crystal Growth of Salicylamide
6 Single Crystal Growth of Salicylamide

This chapter examines the crystal growth of single salicylamide crystals directly using a microscope to improve our fundamental understanding of the crystal growth process. This chapter details the use of two different growth methods including a traditional single crystal growth method which uses a non-stirred cuvette and also puts forward an alternative multiple single crystal growth method which uses a rotating disk in an attempt to overcome some of the issues we face in the former and ultimately make a more robust method for examining the single crystal growth. Such issues have already been discussed in section 2.2.3.3; including its time consuming nature given the fact that each crystal can grow at different rates, also within each crystal each facet can have different growth rates and furthermore the experimental issues that arise when attempting to track the growth of a single crystal in a moving solution. In the growth cuvette the crystal growth rates were measured for both primary nucleated crystals and seed crystals manually inserted into the cuvette. Such measurements are helpful in that they provide baseline crystal growth kinetic data from which the impact of e.g. seeds and agitation can be assessed subsequently. In the rotating disk experiments 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). The impact of organic solvent, supersaturation, temperature, and hydrodynamic conditions on the crystal growth was studied. In all cases, the growth rate is considerably faster in the rotating disk experiments. Within the range of experimental conditions, the growth kinetics were strongly affected by the temperature and to a lesser degree by solvent choice. The influence of the supersaturation depended on the solvent. The crystal seed quality was found to have a substantial impact on the growth rate, with rougher crystals leading to quicker growth.
6.1 Results

6.1.1 Cuvette Growth Method

6.1.1.1 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 6.1. 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 the 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, were 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 and has been discussed in detail in the previous chapter 5. 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 6.1 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 ($\sigma = S-1$ which is 0.89 - 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.
6.1.1.2 Kinetics

6.1.1.2.1 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 6.2. 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 6.2 (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 is most strongly effected by change in driving force when EA was used as the solvent. The growth rate is 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 clearest example in EA at supersaturation 0.48: from 0.1 μm/s up to 4.3 μm/s among the 5 crystals, see Figure 6.2 (a). The growth rate distribution appears to increase with supersaturation in most of the solvents, and also within the studies that use spontaneously nucleated 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 and the solvent choice as illustrated in Figure 6.2. In the experiments with spontaneously nucleated crystals, the driving forces are higher and different for the different solvents since nucleation is to be induced. The approximate crystal growth difficulty order is as follows MeOH>AC>EA>MeCN. In previous work, the nucleation difficulty order for salicylamide was found to be MeOH>AC>MeCN>EA [1]. The solvent appears to be effecting the nucleation and crystal growth of spontaneously nucleated crystals in a similar order.

In the seeded experiments, the same initial supersaturation (S-1) of 0.12 and 0.06 was used regardless of the solvent. 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 is the highest in acetone and the lowest in acetonitrile, with methanol and ethyl acetate in between, in both length and width direction. At the lower supersaturation (0.06) the growth rate is still the highest in acetone in both directions, but the order among the other three is less systematic as shown in Figure 6.2 (c) and (d). As the cuvette growth method uses a non-stirred solution the growth rate is likely to be effected 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 (0.54mPa.s at 25°C), compared to acetone which has the lowest viscosity of the four solvents (0.31mPa.s at 25°C) [2]. Using the Wilke and Chang method for estimating the diffusivity ranks the solvents in the order AC> EA> MeCN> MeOH. Growth order of seed crystals follows similar order as solubility (mol/L) AC>EA>MeOH>MeCN. This states that acetone has the highest amount of solute in the total solution compared with other solvent-solute solutions with acetonitrile having the lowest which follows the same order as the growth order of the seed crystals.
Figure 6.2. 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. 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 the previous chapter we have face indexed experimentally grown salicylamide crystals using experimental and prediction techniques [3]. 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 this face is viewed from an aerial perspective. A mix of three end faces (-112), (011), and (110) represent the length direction, however all three faces may not appear in all crystals and so are difficult to track between crystals. The width typically represents the growth of the (200) and (-200) face; and as the (200) face is consistent between crystals, Figure 6.3 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 $AC \geq MeOH > MeCN > EA$ at 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 in ethyl acetate is faster than 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 [4].

![Figure 6.3](image_url)

**Figure 6.3.** 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.
6.1.2 Rotating Disk Method

6.1.2.1 Habit

Micrographs taken before and after the growth of salicylamide crystals in the rotating disk experiments are shown in Figure 6.4. 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 6.4. 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 hour. Only one representative crystal out of the total 32 crystals for each condition are shown for each in this image.
6.1.2.2 Kinetics

6.1.2.2.1 Effect of Solvent

There is little difference between the average growth rates of the seed crystals in the different solvents except for EA when using a crystal growth temperature of 15 °C and supersaturation (S-1) of 0.03 as illustrated in Figure 6.5. In both the length and width directions ethyl acetate provides the slowest growth rates of salicylamide compared to the other solvents.

![Figure 6.5](image)

**Figure 6.5.** 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 6.6. 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 6.7. 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.
Figure 6.6. 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 hour, S-1 of 0.03). Error bars are used to illustrate the standard deviation of the data.
Figure 6.7. SEM images of salicylamide crystals after growth via the rotating disk method at 15°C for 1 hour 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.
6.1.2.2.2 Effect of Supersaturation

In general, increasing the driving force i.e. supersaturation leads to an increase in the average crystal growth rates in the length and width dimensions as shown in Figure 6.8. The extent of the increase in growth rate is dependent on the solvent; increasing supersaturation (S-1) by 0.02 results in an increase in average growth of both length and width directions by factor of 2.0, 1.6, 1.5, and 3.5 for 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 6.9) under these conditions it is clear to see that a growth process has occurred, primarily repairing morphological defects i.e. the crystal will initially repair any defects prior to beginning outward growth of the facets.
Figure 6.8. 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 6.9. Micrographs show a salicylamide crystal before and after growth via the rotating disk method in acetonitrile at 15°C for 1 hour at supersaturation (S-1) of 0.012.
6.1.2.2.3 Effect of Temperature

The influence of temperature on the average crystal growth of salicylamide in acetonitrile is shown in Figure 6.10. 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, $E_a$; which can be obtained by fitting eq 19 (log of eq 16, where $C$ is a constant as experiments were performed at the same supersaturation) to the average growth rates at the three temperatures, simultaneously. $E_a$ values in the length and width directions are 93 kJ/mol and 96 kJ/mol, respectively.

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

In our previous work as outlined in chapter 4 [7], multiple salicylamide crystal seeds were grown simultaneously 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 also 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 ($5 – 20 \text{ kJmol}^{-1}$), and nearer those reported for surface integration ($40 – 60 \text{ kJmol}^{-1}$) [8].

![Figure 6.10](image)

**Figure 6.10.** Average crystal growth rate ($\mu$m/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 hour.
6.1.2.2.4 Effect of the Crystal Seed Properties (Quality)

As a retrospective analysis, the effect of the initial seed crystal quality on the salicylamide crystal growth rate was examined. For the purposes of this inquiry 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 6.11. 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.

![Graph](image)

**Figure 6.11.** 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.
6.2 Discussion

6.2.1 Comparison of the Two Single Crystal Growth Methods

Salicylamide seed crystal growth rates obtained from the cuvette and the rotating disk experiments at 15 °C are compared in Figure 6.12. 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 disk 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) [8-12]. 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 disk growth rates. 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 in the rotating disk experiments has been evaluated in the solvent which had the highest viscosity (Table 3.1) as the rate of diffusion is inversely proportional to the viscosity of the solution. Five stirring rates from 50 rpm up to 350 rpm has been evaluated for crystal growth in acetonitrile and the result is illustrated in Figure 6.13. Above 150 rpm the growth rate no longer increases with increasing rotation rate. Accordingly, a stirring speed of 150 rpm was 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 6.12. Average crystal growth rate 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 6.13. Average crystal growth rate of the (200) face of salicylamide seed crystals grown using the rotating disk growth method at different stirring rates (50 up to 350 rpm) in acetonitrile with supersaturation (S-1) of 0.03 at 15 °C.
6.2.2 Comparison of Single Crystal Growth with the Multiple Crystal Growth Study

In chapter 4, a batch agitated reactor was used to grow multiple salicylamide seed crystals via a seeded isothermal desupersaturation crystal growth method [7]. 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 6.14, these results are compared with the present rotating disk results were the crystal growth rate which is reported is representative of the average growth of the length and width dimensions as this accounts for the overall growth of the crystal and so acts as the best comparison with the MCG data which obtain overall crystal growth rates for the system. 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 chapter 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 6.14. 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 chapter 4 [7].
6.3 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.
6.4 References for Chapter 6

CHAPTER 7

Single Crystal Growth of Two Piracetam Polymorphs
7 Single Crystal Growth of Two Piracetam Polymorphs

This chapter studied the crystal growth process and associated kinetics of multiple single crystals of two polymorphs of piracetam within ethanol and isopropanol using the rotating disk method. 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. (011). The impact of polymorph form, organic solvent, supersaturation, and temperature on the crystal growth of piracetam was studied. The metastable FII form was found to have faster growth rates than the thermodynamically stable FIII form. Within the range of experimental conditions, the growth kinetics of both polymorphs were strongly affected by the temperature and to a lesser degree by solvent choice. Ethanol provided faster growth rates than isopropanol for both polymorphs. The influence of the supersaturation depended on the polymorph form, though for both forms the growth rate approximately doubled with a +0.10 (S-1) increase in supersaturation.
7.1 Results

7.1.1 Habit

Micrographs taken before and after the growth of piracetam FIII and FII crystals in ethanol and isopropanol are shown in Figure 7.1. Under certain conditions, the seed crystal could grow to a maximum length of 1850 µm and width of 900 µm i.e. seed crystals doubled in size. FIII appears to have consistent growth in all directions as supported by the shape maintenance, on the other hand the needle FII form, especially in ETOH, appears to have enhanced growth rates in its width dimension which is resulting in the shape altering to a rectangle habit. This change in habit was due to the fact that the seed crystals were produced in a different solvent to the growth solvent and so the “natural” shape of the crystal was not the shape of the seed.
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**Figure 7.1.** Micrographs of piracetam crystals of both polymorphs FII and FIII before and after growth in ETOH and IPrOH at 20 °C under supersaturation (S-1) of 0.1 for 1 hour. Only one representative crystal out of the total 32 crystals for each condition are shown for each in this image.
7.1.2 Kinetics

7.1.2.1 Effect of Polymorph and Solvent

The crystal growth rate was found to vary not only from one condition to another, but also among the crystals grown under the same condition, as illustrated by the error bars within Figure 7.2 which represent the error of standard deviation of the data. This phenomenon is commonly referred to as growth rate dispersion (GRD) and was observed within all conditions herein and also for salicylamide as discussed previously in the thesis [14]. The widest GRD was obtained when PCM FII crystals were grown in ethanol, crystal growth rate of the length ranged from 0.020 μm/s up to 0.164 μm/s among the 32 crystals examined. For both polymorphs, the growth rates of the length and width direction were very similar. The FII crystals which were manufactured in 1,4-dioxane had a needle habit which was caused by the stunted growth of the facets present along the width direction but when these seed crystals were grown further in ETOH and IPrOH the growth of the width was no longer stunted illustrating a strong effect of the solvent on the crystal habit. The growth rates were found to be dependent on the polymorph form and also on the choice of solvent as shown in Figure 7.2. The average growth rate of the length direction of PCM FII was 0.088 μm/s and 0.016 μm/s in ETOH and IPrOH respectively, whereas the growth rates for FIII in the same solvents were 0.042 μm/s and 0.005 μm/s respectively. In both solvents, the metastable FII form had faster growth rates over the stable FIII form, 3 times faster in IPrOH and 2 times faster in ETOH. A similar increase in the growth rate for the metastable form versus the stable polymorph has previously been reported for a few other compounds [1-3] and was also found for PCM when grown using an isothermal seeded desupersaturation method under similar conditions [4]. Solvent choice was found to have a greater impact on the growth rate of piracetam than the polymorphic form, with the growth rates of both polymorphs being approximately 7 times faster in ETOH than IPrOH. PCM has previously been shown to have stronger interaction with IPrOH than ETOH which can explain the slower growth rates observed [15]. In chapter 5, it was shown that slower growth rates of salicylamide in ethyl acetate were also due to the relatively stronger interactions of the solvent with the solute compared to the other solvent-solute interactions [5].
Figure 7.2. Average crystal growth rate of (a) length and (b) width (µm/s) of piracetam FII and FIII polymorphs grown in two solvents (ETOH and IPrOH) at temperature of 20 °C and supersaturation (S-1) of 0.10. Error bars are used to illustrate the error of standard deviation of the data.
7.1.2.2 Effect of Supersaturation

For both polymorphs, increasing the supersaturation i.e. driving force led to an increase in the crystal growth rates in both the length and width directions of the crystal as shown in Figure 7.3. Growth rates were very similar in the length and width direction for both forms, with the FII form having slightly faster growth rates in the width direction particularly at the higher supersaturations. The extent of the increase on the crystal growth rate with increasing driving force was slightly dependant on the polymorph; increasing supersaturation (S-1) by +0.10 resulted in a 2.5 increase in the growth rate for FIII whereas the increase was only by a factor of 2.0 for FII under the same increase in supersaturation. In the case of FIII, increasing the driving force also resulted in a wider growth rate dispersion. Whereas the growth rate dispersion remained relatively similar for FII when grown at the different supersaturations.

Figure 7.3. Average crystal growth rate (µm/s) of both length (filled) and width (unfilled) of FIII and FII polymorphs in ETOH with respect to supersaturation at 20 °C under supersaturation (S-1) of 0.1 for 1 hour. Error bars are used to illustrate the error of standard deviation of the data.
### 7.1.2.3 Effect of Temperature

The influence of temperature on the crystal growth of the two piracetam polymorphs grown in ethanol is shown in Figure 7.4. A 10 °C increase in the growth temperature resulted in an increase in the growth rate by a factor of 3.5 for FIII but only by a factor of 2.0 for FII. This strong dependence is of course reflected in the activation energies, $E_a$, which can be obtained by fitting eq 19 to the average growth rates at the three temperatures, simultaneously. $E_a$ values in the length and width directions for piracetam FIII were found to be 88 kJ/mol for both directions and for FII were found to be 52 kJ/mol and 36 kJ/mol respectively. In previous work [4], multiple PCM FIII and FII crystal seeds were grown simultaneously in a batch reactor using an isothermal seeded desupersaturation (ISD) crystal growth method. Increasing temperature within the same range from 20 °C to 30 °C in ETOH also led to an increase in the growth rate by a factor of 2.0 for FII but only by a factor of 2.4 for FIII. This work also estimated the activation energy values for both polymorphs after growth in ethanol over a slightly larger temperature range of 10 to 35 °C and gave values of 65 kJ/mol and 39 kJ/mol for FIII and FII respectively. The ISD method assumes the growth values and thus the activation energy values are representative of the width direction as the original crystal size was determined by sieving and so represents the second largest dimension, $E_a$ values for FII in the width direction are very similar from the two methods. Slightly lower activation energy value was calculated for FIII when using the ISD method, though both growth methods successfully calculate that the metastable form will have a lower activation energy. These activation energies are clearly higher than the values expected for simple molecular diffusion ($5 – 20 \text{kJmol}^{-1}$), and nearer those reported for surface integration ($40 – 60 \text{kJmol}^{-1}$) [8].

![Figure 7.4](image_url)

*Figure 7.4.* Average crystal growth rate (µm/s) of both length (filled) and width (unfilled) of FIII and FII polymorphs in ETOH with respect to the crystal growth temperature under supersaturation (S-1) of 0.1 for 1 hour. Error bars are used to illustrate the error of standard deviation of the data.
7.1.2.4 **Effect of the Crystal Seed Properties (Size)**

This work also examined the influence of the crystal seed properties on the crystal growth rate, in particular the effect of the seed size and also whether or not re-growing a seed crystal would result in a change of the crystal growth rate. Particle size has been shown to have an effect on the crystal growth kinetics. Two crystal seed sizes have been investigated in this work, including a smaller seed fraction of 100-180 µm and a larger seed fraction of 250-400 µm. Both seed sizes gave growth rates of the same order of magnitude, though it is clear to see from Figure 7.5 that the smaller seed size have a lower average crystal growth rate which would begin to suggest a size dependant crystal growth model (SDG). However when all the crystals which were grown were examined, it was clear that to see that the phenomenon of growth rate dispersion (GRD), i.e. different crystals within a population (under uniform conditions) exhibit a range of growth rates, is the more dominant model occurring for both seed groups as indicated by the overlap of the two crystal data sets. These findings are in agreement with the literature that the SDG is likely to be an artefact of GRD which in turn is attributed in part to the surface effects induced by the crystals growth history. This surface effect can be investigated by re-growing the crystals for a second time in a new supersaturated solution. As shown in Figure 7.6 the growth rates decreased upon re-growing despite the increase in the initial crystal seed size. These results support the idea that the initial growth process typically attempts to repair the defects within the crystal, thus leading to a smoother crystal surface which ultimately will result in slower growth rates during the second growth stage.
Figure 7.5. Crystal growth rate of length (µm/s) plotted against it’s respective crystal ID number, with respect to the crystal seed size (100-180 µm or 250-400 µm sieve fractions).

Figure 7.6. Crystal growth rate of length (µm/s) plotted against it’s respective crystal ID number. Crystals were grown initially for 1 hour (circle points) and then placed into a new supersaturated solution and regrown for another hour (triangle points).
7.1.2.5  Facet Growth Rates of Two Polymorphs

So far the crystal growth of the two polymorphs has been described in terms of the length and width directions which are of course indicative of the crystal facets present on these sides of the crystal. Fundamentally it is of greater interest to express the growth rates in terms of a specific facet, in order to do so we must first identify the faces of the two piracetam crystal forms through the combined use of experimental and prediction techniques [5]. The vacuum growth morphology of piracetam FII and FIII was predicted using the attachment energy method, habits for both polymorphs are shown in Figure 7.7. FII was predicted to form a rectangle habit whereas FIII forms a square habit. When grown through recrystallization in a solvent they did in fact form a needle and rectangle habit, respectively. The two polymorphs have a common (0 1 1) face which grows in the width direction for FII and in the length direction for FIII and so will be used to compare facet growth rates for the two polymorphs. The (0 1 1) facet of the experimentally grown crystals was confirmed by measuring the interfacial angle between the facets and comparing it with the interfacial angle calculated using material studio software.

Figure 7.8 shows the influence of the solvent on the growth rate of the (0 1 1) face of both polymorphs. The facet growth rate is taken as half of the corresponding rate of growth of the width (FII) and the length (FIII), respectively. Growth rate of the (0 1 1) face of both polymorphs was faster in ethanol than isopropanol. In both solvents the growth of FII (0 1 1) facet was faster than of the FIII (0 1 1) facet. In both polymorphs of piracetam, a centrosymmetric dimer present in the crystal lattice is attached with adjacent molecules by H-bonding. These strong intermolecular interactions, e.g. hydrogen bonding, are thought to determine the growth direction for molecular crystals with higher growth rates expected for the hydrogen bonding directions [9-11]. The molecular chemistry of the (0 1 1) facet for both polymorphs is shown in Figure 7.9 with both showing a capability to form hydrogen bonds. The carboxylate and amino groups which are involved in the dimer formation are embedded deeper into the surface topology of the stable polymorph form in comparison with the metastable form and so potentially reduce the propensity for hydrogen bonding. The attachment energy, $E_{\text{att}}$, of the (0 1 1) facet for FII and FIII was -115.14 kJ/mol and -220.29 kJ/mol respectively. This refers to the energy released on attachment of a growth slice to that growing crystal surface, were a lower attachment energy would result in a faster growth which is in line with the findings in this work.
Figure 7.7. The growth morphology (computational attachment energy prediction, COMPASS-II force-field) of piracetam (a) FII and (b) FIII crystal. Miller indices are given for major faces.

Figure 7.8. Average crystal growth rate of the (011) face (µm/s) piracetam FII and FIII polymorphs grown in two solvents, ETOH and IPrOH, at 20 °C under S-1 of 0.10. Error bars are used to illustrate the error of standard deviation of the data.
Figure 7.9. Molecular representations of the (011) crystal face of piracetam FII and FIII polymorphs. An arrangement of H-bonds (black dots) in the crystal structure of piracetam FII and FIII polymorphs. Highlighted is the piracetam dimer. Hydrogen – white, carbon – grey, oxygen – red, nitrogen – blue.
7.2 Discussion

7.2.1 Comparison of Single Crystal Growth with the Multiple Crystal Growth Study

In previous work [4], a batch agitated reactor was used to grow multiple PCM FII and FIII seed crystals via an isothermal seeded desupersaturation crystal growth method. This method used the smaller seed size (sieve fraction 100–180 µm). Aside of this all other experimental considerations (such as solvents, temperature and supersaturation range) were the same. The growth order parameter indicated that the growth process in the batch reactor was governed by surface integration. In Figure 7.10, these results are compared with the present rotating disk results. Overall, both growth methods in spite of significant differences in the hydrodynamics resulted in quite similar growth rates of the two piracetam polymorph crystals when grown under same conditions, the magnitude of growth was the same. In the previous work it was concluded that surface integration was the limiting step. In the present study, this could be experimentally verified by altering the rotation rate. With increasing relative velocity between the crystals and the fluid the volume diffusion resistance should decrease. The crystal growth rate increases and the crystal growth process becomes increasingly governed by the surface integration step. Four stirring rates from 50 rpm up to 300 rpm were evaluated for the crystal growth of the stable form in ethanol and the result is illustrated in Figure 7.11. Above 200 rpm the growth rate no longer increases with increasing rotation rate, the volume diffusion mass transfer resistance has been reduced to the extent where growth is governed by surface integration. The diagrams in Figure 7.10, indicate that there may be a mechanism transition occurring within the range of supersaturation. It is clearer for the FII form at about S-1 equal to ~0.08, but perhaps also occurring for the FIII form at S-1 equal to ~0.15, there is a change in the trend of the combined data.
Figure 7.10. Crystal growth rate of piracetam FIII & FII crystals grown by two methods in ethanol at 20 °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 a previous study [4].

Figure 7.11. Average crystal growth rate of width (µm/s) of PCM FIII grown using the rotating disk growth method at different stirring rates (50 to 300 rpm) in ETOH with supersaturation (S-1) of 0.1 at 20 °C.
7.3 Conclusion

Crystal growth of piracetam FII and FIII polymorphs was investigated under a surface integration controlled crystal growth process, and the associated growth rates were measured. The rotating disk growth method utilised in this work allowed for the hydrodynamic environment to be controlled, yet also track multiple single crystals for their specific facet growth rates at once. The growth rates obtained using this rotating disk method compared well with previously published growth data of the same compound which used a more traditional isothermal seeded desupersaturation growth method. The metastable polymorph, FII, was found to have growth rates which were double than the rates obtained for the stable form, FIII. The crystal growth rate of the (0 1 1) facet had growth rates which were 7 times faster when grown in ethanol than in isopropanol, as explained by piracetam having stronger interaction with the latter solvent. Increasing temperature by 10 °C led to an increase in growth rates of FIII and FII by a factor of 3.5 and 2 respectively. Increasing supersaturation by S-1 of 0.10 doubled the growth rates of the two polymorphs. The findings show that the two polymorph crystals grew at different rates under the same conditions and were also affected to different extents by the various experimental conditions tested which highlights the importance of investigating the crystal growth of different polymorphs.
7.4 References for Chapter 7

CHAPTER 8

General Conclusions


8 General Conclusions & Future Directions

The objective of this thesis was to attempt to rationalise the crystal growth process, in particular to understand the kinetics. The ultimate aim was to try to make the pharmaceutical crystallisation process more robust and reliable and in the future predictable. The crystal growth process, and associated kinetics, of salicylamide (SAM) and two polymorphs of piracetam (PCM FII/ FIII) was successfully investigated in this work. The multiple crystal growth study which used the isothermal seeded desupersaturation method studied the growth of thousands of SAM crystals at once under controlled hydrodynamic conditions and so provided a statistically relevant analysis of the growth process. The single crystal growth studies that used the cuvette method allowed the growth of SAM to be investigated at a fundamental level by observing the growth rate of specific crystal facets. The single crystal growth studies which used the alternative rotating disk growth method allowed the growth of 32 seed crystals of SAM and separately PCM FII/ FIII to be observed at a fundamental level but also under controlled hydrodynamics.

By comparing the growth data of salicylamide obtained from the two single crystal growth methods when grown under the same experimental conditions the hydrodynamics were found to have a significant impact on the crystal growth process. The growth rate of the (200) facet was increased by a factor of 20 when using the rotating disk method compared to the cuvette method, the addition of sufficient rotation was found to alter the growth process from volume diffusion resistance controlled growth to surface integration controlled growth. It should be highlighted that single crystal growth studies reported in the literature which used the cuvette method are thus likely to provide diffusion controlled kinetic data. As the rotating disk method was controlled by the surface integration step, the kinetic data obtained for both SAM and PCM was compared with the isothermal desupersaturation crystal growth method (multiple crystal growth) as this also provided surface integration controlled growth data. For both API, the rotating disk method delivered growth rates in good agreement with the data obtained by the multiple crystal growth experiments in spite of significant differences in the methodology which is very promising.

The effect of several process conditions on the crystal growth process of SAM and PCM FII/ FIII was resolved e.g. seed, temperature, supersaturation, and solvent. From the single crystal growth studies of SAM, cuvette method the use of seeds was found to control the crystal habit and also reduce the growth rate dispersion amongst the crystals in comparison to spontaneously
nucleated crystals. Within the seeded single crystal growth studies of SAM and PCM, which used the rotating disk method, a lower seed quality and larger seed size were found to increase the growth rate and the growth rate dispersion. Furthermore, the PCM studies concluded that the seed polymorph form impacted the resulting crystal growth rates with the metastable polymorph, FII, having growth rates which were double that of the rates obtained for the stable form, FIII. Increasing temperature by 10 °C was found to increase the growth rates of both SAM and PCM FII and FIII by a twofold increase in most cases, however a fourfold increase was found for SAM when grown in acetonitrile. Although the reason for this significantly higher increase in acetonitrile is still not understood, the effect of temperature on the growth of both API in the respective solvents was the same when grown using both the single crystal growth method (rotating disk) and multiple crystal growth method (isothermal seeded desupersaturation). Despite significant differences between the two growth methods, it is of great reassurance that both methods estimated similar activation energy values for SAM and PCM. Increasing supersaturation by S-1 of 0.10 led to a two-fold increase in the growth rates of both PCM polymorphs.

Although solvent choice was found to have one of the lower impacts on the crystal growth kinetics of SAM, it was found to have a large impact on the resulting crystal habit when SAM crystals were grown via slow solvent evaporation in different solvents. This experimental and supporting molecular modelling work concluded that solvents which were found to have a higher adsorption energy with specific crystal facets of salicylamide and also have a larger molecular weight, such as ethyl acetate, ultimately impeded the growth of such facets and thus has a greater effect on the habit compared to the other solvents. Similar conclusions were drawn for the effect of solvent on the growth of piracetam within this work also, where a stronger interaction of solvent molecules with piracetam lead to reduced growth rates by a factor of 7. Furthermore, the use of scanning electron microscopy to examine the crystal surface of salicylamide after growth in a number of solvents visually confirmed that growing a solute in different solvents created different topographical features on the surface which also accounted for the slower growth rate of salicylamide within ethyl acetate compared with methanol.

The initial step of the growth process, diffusion, is well understood in the literature, whereas the subsequent step, surface integration, is not. The novel single crystal rotating disk method developed in this thesis provides a cost effective experimental approach to study the growth of multiple single active pharmaceutical ingredient crystals directly using a microscope. This
method provides statistically valid kinetic data obtained under surface integration controlled conditions. So far this method has been used to successfully study the growth of seven API under surface integration conditions, two compounds of which have been discussed in this thesis. The research reported in this thesis has only scratched the surface in this area and has set out an experimental method which can be used to probe and attempt to understand the surface integration step in more detail. A key area for future work is the application of this rotating disk method to a range of other API, including their polymorphs, and process conditions. Within this thesis, two well-known surface integration facet growth models (BCF and B&S) were fitted to growth data obtained from the multiple crystal growth method which is an overall growth rate for thousands of crystals. It would be of far greater interest to be able to fit these models to surface integration controlled growth data obtained for specific facets, for example the data which can be obtained from the rotating disk approach.
Crystal Growth of Salicylamide in Organic Solvents

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ABSTRACT: Salicylamide was used as a model active pharmaceutical compound to investigate the crystal growth process and its associated kinetics. The impact of organic solvent, supersaturation, and temperature on the crystal growth was studied. The multiparticle crystal growth kinetics were determined using the seeded isothermal crystallization method and modeled using several growth rate equations, using different representations of the driving force. The results showed that crystal growth is significantly influenced by experimental conditions. Within the range of experimental conditions, the growth kinetics was affected strongly by the temperature and to a lesser degree by solvent choice. Comparison of the growth under parameter reveals a surface integration controlled growth. Higher than expected activation energies indicate desolvation as a governing process.

A comparison of the influence of the solvent on the crystal growth of salicylamide against previously published approximate data at much higher supersaturation shows good agreement, but the influence on the interfacial energy is opposite to that observed for crystal nucleation. In a detailed comparison with crystal growth data of salicylic acid, there is a consistency in the influence of the solvent on the crystal growth of the two compounds. Salicylamide growth kinetics is more strongly affected by increasing temperature than salicylic acid.

INTRODUCTION

Crystallization is a very important technique, especially in the pharmaceutical industry, as it is used in the formation, purification, and recovery of the crystalline active pharmaceutical ingredients (API).1-3 Despite this, crystallization fundamentals are still insufficiently understood. Efforts have previously been made to understand the kinetics of salicylamide nucleation.4 The present research focuses on advancing our knowledge of the crystal growth process of the same compound, in particular, the kinetics. Crystal growth is known to be significantly influenced by the crystallization environment. In this study, the crystal growth of salicylamide under multiparticle crystallization conditions is further investigated by using different environmental conditions, including solvent, supersaturation, and temperature, in order to determine which has the biggest impact on growth.4-10 The multiparticle crystal growth experiments provide overall growth rates for the entire crystal population in the crystallization reactor, which represents industrial process conditions.11-13 These studies were performed using mixing, i.e., a controlled hydrodynamic environment. Investigating this gives a good insight into the overall crystal growth kinetics and mechanism of the model API.

Salicylamide, C8H7NO2, molecular weight 137.14 g mol−1, was used as the model API. It is classified as a nonprescription drug with analgesic and antipyretic properties, and used as an over-the-counter pain remedy. Salicylamide is supplied as white, mainly blocky or plate-like crystals, with a melting point of 138.7 °C.14 Salicylamide has two polymorphs reported in the literature: FI and FII. FII, monoclinic 12/m, is the stable polymorph at ambient conditions, whereas FII, orthorhombic P21c, is only obtained under high pressure.15 For this reason, only FI will be used in this study. The solubility of salicylamide FI in acetone, acetonitrile, ethyl acetate, and methanol has already been determined between 10 and 50 °C by Nordström and Rasmuson.16

THEORY

In a supersaturated solution, crystal growth proceeds by bulk diffusion of growth units through the solution boundary layer surrounding the crystal, followed by stepwise desorption, surface diffusion over the crystal face, and integration into the crystal lattice, preferably at steps and kinks.3,5 These stages are essentially acting in series whereby the slowest one will be rate determining. By increasing the turbulence in the bulk solution around the crystal, the boundary layer mass transfer becomes faster, and the overall rate of growth becomes more surface integration controlled. The rate of growth of a crystal has a complex dependence on temperature, supersaturation, size,
Appendix I

Crystal Growth & Design

Crystal growth and design can be described by more or less empirical equations. Very commonly, a simple power law equation is used to govern the formation of the crystal, which only contains an explicit dependence on the supersaturation. This equation can be modified to also include an explicit temperature dependence as in Eq. 2.

Simple overall growth rate equation:

\[ G(s) = k_p s^6, \quad \text{where} \quad s = S - 1 \text{ or } \Delta u_f \]  

Modified overall growth rate equation:

\[ G(s) = k_p \exp\left(-\frac{E_a}{RT}\right) s^6, \quad \text{where} \quad s = S - 1 \text{ or } \Delta u_f \]  

Specifically for the surface integration step, two face growth rate models are commonly used. Burton, Cabrera, and Frank (BCF) described the screw dislocation mechanism, Eq. 3. The BCF model involves diffusion of solute molecules over the crystal face which then incorporate onto dislocations that are present on the surface. This leads to the formation of a stepped surface, which subsequently forms a spiral that acts as a permanent source of growth steps. As there is a permanent supply of growth, growth can continue at low supersaturation as nucleation is not required. In other words, parameter A (Eq 4, 5) describes the crystal surface, and parameter B (Eq 5) takes the physical properties of the crystal growth system into account. A has strong temperature dependence, whereas B is independent of temperature. The birth and spread (B&S) growth mechanism, Eq. 6, relies on crystal surface nucleation (birth), followed by the growth (spread) of the monolayers. This requires a higher supersaturation than the BCF model, as two-dimensional (2D) nucleation is essential when there are no surface steps present. This surface nucleation can develop at any location on a crystal surface, for example, edges, corners, and on the faces. Further surface nuclei can develop on the monolayer nuclei as they spread across the crystal face. The B&S model contains two parameters, C (Eq 7, 8) and D (Eq 8), which describe very similar properties of the crystal growth system as their respective counterparts (A and B) in the BCF model. Also, analogous to the BCF model, C and D are temperature dependent and independent, respectively.

The spiral growth model (BCF):

\[ G_{BCF} = A T \frac{(S - 1)}{(\ln S) \tan\left(\frac{B}{T \ln S}\right)} \]  

\[ A = \frac{V^b D_{diff}}{2 S}, \quad B = \frac{19 V^b u^b}{2 S c} \]  

The Birth and Spread model (B&S):

\[ G_{B&S} = h_{diff}^3 \frac{B_{d}^2}{2S} \]  

\[ C(S - 1)^{2/3} (ln S)^{1/6} \exp\left(-\frac{D}{T^2 \ln S}\right) \]  

\[ C = \left(\frac{114 V}{2}\right) \frac{1}{h_{diff}^3} \left(V_{in} / \Gamma N \right)^{1/6} \]  

\[ D = \frac{2 V_{in} u^b}{S c} \]  

The face growth models contain parameters A and C, respectively, which both rely heavily on a D_{diff} term:

\[ \Delta u_f = \Delta u_{crit} \exp\left(-\frac{E_{a, crit}}{RT}\right) \]  

This is simply an Arrhenius equation with emphasis on the activation energy of the surface diffusion of adsorbed molecules, E_{a, crit}. Both models also have a term for the interfacial energy between solid–liquid, \( \gamma_{SL} \), playing a key role in the B and D parameters. The solid–liquid interfacial energy in the B+S model in Eq 8 describes the radius of the 2D critical nuclei that form on the surface and are the source of new growth steps. B and D both incorporate physical properties of the crystal growth system, such as molecular volume, \( V_{in} \), of salicylamide, which is equal to 0.171 nm^3 as obtained from the crystal density, assuming the height of the growth step, h, is equal to the cubic root of \( V_{in} \), i.e., 0.56 nm. The parameter \( k \) denotes the Boltzmann constant and \( x \) is the diffusion mean free path over the surface.

Concentration decay can be related to the size change of the seed crystals through a mass balance, where the crystal length can be obtained by integration of the growth rate for \( G(\Delta u_f, T) = f(\alpha, \beta, \gamma, ...) \), where \( \alpha, \beta, \gamma, ... \) are parameters of the growth rate models to be determined by optimization. In the simple growth rate Eq 1, \( k_p \) and \( A \) are determined, in the modified growth rate Eq 2, \( B \) and \( E_a \) are determined, in the BCF model, Eq 3, and in the B&S model, Eq 6, C and D are determined. Optimization is performed with MATLAB, using the lsqcurvefit function and confidence intervals calculated using the nlparci function.

The true thermodynamic driving force for crystallization, \( \Delta \mu \) (J mol^{-1}), is the difference in chemical potential between the solute in the supersaturated solution and in the corresponding saturated solution (*):

\[ \Delta \mu = \mu_{crit} - \mu_{sol} = RT \ln \frac{a}{x^*} = RT \ln \frac{x^*}{x^* - \sigma} \]  

This expression is commonly simplified by neglecting the activity coefficient ratio entirely and is often represented simply by a concentration ratio, \( \Delta u \), or by using Eq 11 as an approximate representation of the logarithmic function of Eq 10.

\[ \sigma = S - 1 = \frac{x}{x^*} - 1 \]  

In a recently proposed method, an approximate representation of the activity coefficient ratio is obtained by neglecting only the temperature dependence, but not the concentration dependence, of the activity coefficient, resulting in the expression for the driving force given by Eq 12:

\[ \Delta \mu = RT \ln \frac{x^* (T^*)}{x^* - \sigma} \]  

where \( y \) for the supersaturated solution has been replaced by the corresponding value for the solution at its saturation temperature. For solutions that are not too dilute, i.e., in the Henry’s law region, this method is expected to be more accurate than neglecting the activity coefficient contribution to the driving force. However, the solubility of salicylamide in at least two of the evaluated solvents (methanol and acetonitrile) is low enough that it cannot be stated with certainty that the temperature dependence of the activity coefficient is negligible. In this study, both representations of the driving force given by
Figure 1. Graphs to the left show supersaturation decay curves (data are experimental values and lines are fits of eq 1), and graphs to the right show the corresponding growth rate curves, at four temperatures in four solvents.

eqs 11 and 12 are used and compared. Further details are given in the Supporting Information.

■ EXPERIMENTAL SECTION

Materials. Salicylamide (purity ≥99.9%) was purchased from Sigma-Aldrich (catalogue number 842330) and used as received without further purification. The solvents acetone (AC) 99.8%, acetonitrile (MeCN) ≥ 99.9%, ethyl acetate (EA) 99.7%, and methanol (MeOH) 99.9% were also purchased from Sigma-Aldrich and used as received.

Metastable Zone Width Determination. Metastable zone widths (MSZW) were determined in order to establish suitable levels of initial supersaturation in the crystal growth experiments. The MSZW studies involve cooling a saturated solution in an agitated jacketed 500 mL glass reactor with an inner diameter of 75 mm, using a 48 rpm 4-pitch 4-bladed PTFE-coated impeller with inclined blades rotating at 480 rpm, under a specific decreasing temperature rate, controlled by circulator (Lauda, RE305 series). A focused beam reflectance (FETRM) probe (Mettler-Toledo) was used to detect total counts of crystals in situ; i.e., this ensured that no unwanted nucleation was observed. The MSZW is quantified by taking note of the time when the experiment started, the time at which nucleation occurred and the temperature in vessel at this time. MSZW determination experiments were performed at four saturation temperatures (15 °C, 20 °C, 25 °C, and 30 °C) using two or three cooling rates (0.5 °C min⁻¹, 1 °C min⁻¹, and 1.5 °C min⁻¹) for each of the four solvents (AC, MeCN, EA, and MeOH). Acetone provides for the widest metastable zone for salicylamide, followed by ethyl acetate and methanol, and then acetonitrile. Details are given in the Supporting Information – Figure S1.

Crystal Growth Rate Determination. Seeded isothermal supersaturation experiments were performed according to a multiparticle crystal growth procedure. A known amount of sized seeds (300–315 μm) were suspended in a slightly supersaturated solution (200 mL) in the same reactor as was used for the MSZW studies, with inclined blades rotating at 500 rpm. The initial supersaturation was low to avoid nucleation (S < 1.05), and the solution was heated to temperature 6 °C above the saturation
temperature. The reactor was kept at a constant crystal growth temperature by using a circulator (Lauda, RE305 series), and the decay in supersaturation was recorded over time. An attenuated total reflectance Fourier transform infrared probe, ATR-FTIR (Mettler-Toledo ReactIR IC 10) was utilized to measure the solution concentration in situ. The system operates in the mid-IR region, from 1900 cm⁻¹ to 850 cm⁻¹, with 152 scans every minute. The decay in the solution concentration over time is proportional to the mass deposition on existing crystals, i.e., crystal growth. This concentration decay undergoes first-principles data treatment using the built-in feature within the IR software to extract the concentration information from the IR spectra. A FBRM probe was also utilized to detect unwanted nucleation. Experiments were performed at four crystal growth temperatures (10 °C, 15 °C, 20 °C, and 25 °C) for each of the four solvents (AC, MeCN, EA, and MeOH). More details are provided in our previous work.¹

**RESULTS**

Figure 1 shows the recorded supersaturation decay data as a function of time and the corresponding curve obtained in the fitting of the simple overall growth rate equation, eq 1, to the data. The corresponding crystal growth rate as a function of supersaturation in the four solvents at four different temperatures is given in the diagrams to the right. The growth rates increase with increasing temperature in all four solvents as expected, but the increase is not entirely even. The growth rates increase with supersaturation and range up to 0.4 μm s⁻¹, which is in agreement with growth rates previously reported in...
Figure 4. Solubility of salicylamide: scatter plot obtained from experimental data and solid line obtained from regression curves (a); activity coefficients in saturated solution (b); molar ratio of solvent to solute (c) and molar fraction of solute (d).

Table 1. Parameters of eq 2, Given with 95% Confidence Limit for De-Supersaturation Experiments in Four Solvents

<table>
<thead>
<tr>
<th>Solvents</th>
<th>k_g × 10^9 m/s</th>
<th>g</th>
<th>E_g kJ/mol</th>
<th>(RT/Δμ*) (S - 1)</th>
<th>G = k_g exp(-RT/Δμ*)</th>
<th>g</th>
<th>E_g kJ/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH</td>
<td>1.12 ± 0.94</td>
<td>1.12 ± 0.03</td>
<td>60.26 ± 2.1</td>
<td>(1.50 ± 1.73) × 10^7</td>
<td>1.13 ± 0.01</td>
<td>88.4 ± 2.9</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>1.28 ± 3.3</td>
<td>1.37 ± 0.04</td>
<td>58.78 ± 4.0</td>
<td>1.15 ± 0.01</td>
<td>88.4 ± 4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeCN</td>
<td>4.57 ± 3.65</td>
<td>1.28 ± 0.03</td>
<td>90.9 ± 2.0</td>
<td>(3.15 ± 1.28) × 10^7</td>
<td>1.32 ± 0.02</td>
<td>91.2 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>1.83 ± 2.68</td>
<td>1.60 ± 0.04</td>
<td>55.9 ± 3.3</td>
<td>(2.72 ± 2.65) × 10^4</td>
<td>1.69 ± 0.04</td>
<td>80.7 ± 1.5</td>
<td></td>
</tr>
</tbody>
</table>

The maximum growth rate depends on the solvent and the temperature, but this is mostly governed by experimental conditions and limitations (e.g., assuming that nucleation does not occur). Parameters of eq 1 are given in the Supporting Information - Table S1. The growth order parameter g is in all cases above unity, indicating that crystal growth is at least partly controlled by the surface integration as was also found for salicylic acid.\(^{10}\) No clear trend can be found in how the parameters, g and k_g, change with temperature or with solvent, since a significant parameter correlation is likely to exist between the g and the k_g values for each case.\(^{10}\)

The modified overall growth rate equation, eq 2, has been fitted to the experimental de-supersaturation data using the two driving force representations given by eq 11 and eq 12, S-1 and Δμ*. As shown in Figures 3 (Δμ*) and S2 (S-1), regardless of the driving force approximation used, the temperature dependence becomes more even compared to eq 1. This is expected since the temperature dependence is built into the growth rate equation and is determined by fitting to all data at all temperatures for each solvent. As is shown in Figure 3, with respect to the influence of the solvent, there is a difference between the two driving force representations, originating from the fact that the correction for the activity coefficient ratio is solvent and temperature dependent. Notably, using Δμ*, leads to a less temperature dependent influence of the solvent, i.e., at both temperatures shown in Figure 3, the order of growth rates at equal driving force essentially is MeCN > MeOH > AC > EA. When representing the driving force in terms of relative supersaturation (S-1), the order between the solvents changes with temperature: at 25 °C, the order is the same as when using Δμ*, whereas at 10 °C the order is MeOH > AC > MeCN > EA. The growth model, eq 2, takes temperature effects on kinetics into account. Δμ* also takes temperature effects on the driving force into account, which is not the case using S-1 as a driving force representation. The results stress the importance of the choice of representation of the driving force when growth rates in different solvents and at different temperatures are compared, as previously found for salicylic acid.\(^{10}\)

Figure 4 shows the saturated solution properties of salicylamide in acetonitrile, ethyl acetate, and methanol. The mass ratio solubility shown in Figure 4a is calculated from the molar fraction solubility. In mass ratio terms, the solubility of salicylamide is relatively high in acetonitrile and lower in methanol, ethyl acetate, and acetone. A value of the activity coefficient higher than unity implies that solute-solute interactions are more favorable than interactions between...
Crystal Growth & Design

Table 2. Fitted Kinetic Parameters of the BCF Crystal Growth Model with 95% Confidence Limits for De-Supersaturation Experiments

<table>
<thead>
<tr>
<th>solvent</th>
<th>25 °C</th>
<th>20 °C</th>
<th>15 °C</th>
<th>10 °C</th>
<th>R</th>
<th>k</th>
<th>E_a, kJ/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH</td>
<td>15.5 ± 0.1</td>
<td>10.3 ± 0.3</td>
<td>7.19 ± 0.24</td>
<td>4.84 ± 0.01</td>
<td>0.49 ± 0.10</td>
<td>61.78</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>12.2 ± 1.30</td>
<td>7.13 ± 0.73</td>
<td>4.94 ± 0.28</td>
<td>4.28 ± 0.13</td>
<td>0.77 ± 0.20</td>
<td>49.05</td>
<td></td>
</tr>
<tr>
<td>MeCN</td>
<td>16.3 ± 1.90</td>
<td>8.46 ± 0.39</td>
<td>5.79 ± 0.13</td>
<td>2.37 ± 0.01</td>
<td>0.79 ± 0.13</td>
<td>84.86</td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>7.71 ± 0.84</td>
<td>3.19 ± 0.33</td>
<td>2.85 ± 0.14</td>
<td>2.33 ± 0.01</td>
<td>3.15 ± 0.47</td>
<td>2495</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Fitted Kinetic Parameters of the B&G Crystal Growth Model with 95% Confidence Limits for De-Supersaturation Experiments

<table>
<thead>
<tr>
<th>solvent</th>
<th>25 °C</th>
<th>20 °C</th>
<th>15 °C</th>
<th>10 °C</th>
<th>D_i</th>
<th>k_i</th>
<th>E_a, kJ/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH</td>
<td>8.35 ± 0.57</td>
<td>5.71 ± 0.16</td>
<td>3.33 ± 0.18</td>
<td>2.18 ± 0.07</td>
<td>87 ± 14</td>
<td>61.39</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>6.59 ± 0.80</td>
<td>3.37 ± 0.48</td>
<td>2.70 ± 0.20</td>
<td>2.45 ± 0.10</td>
<td>151 ± 30</td>
<td>695.3</td>
<td></td>
</tr>
<tr>
<td>MeCN</td>
<td>8.41 ± 1.11</td>
<td>4.46 ± 0.24</td>
<td>3.09 ± 0.12</td>
<td>1.43 ± 0.04</td>
<td>125 ± 17</td>
<td>79.84</td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>3.91 ± 0.43</td>
<td>2.01 ± 0.21</td>
<td>1.76 ± 0.80</td>
<td>1.54 ± 0.07</td>
<td>315 ± 52</td>
<td>69.97</td>
<td></td>
</tr>
</tbody>
</table>

solute—solvent (acetonitrile or methanol); in contrast, relatively strong interactions between solute—solvent result in values of the activity coefficient below 1 (ethyl acetate and acetone). The comparatively strong solute—solute interactions predicted in acetonitrile and methanol are substantiated by experimental findings showing these solvents do in fact lead to faster growth rates compared with the other systems. With increasing temperature, the solution behavior approaches ideality, and values of the activity coefficient in all solvents tend toward unity. The molar ratio of solute to solute in saturated solution and mole fraction solubility are compared at different temperatures in Figure 9.c.d. Unsurprisingly, the molar ratio of acetonitrile to salicylamide is much higher compared with the values in other solvents due to the lower solubility of salicylamide in acetonitrile.

In Table 1 the parameters obtained by fitting eq 2 to the experimental data are given. Regardless of solvent and driving force representation used, the g value is above unity as was also found using eq 4, indicating again that the crystal growth is at least partly controlled by the surface integration. The g value changes with the solvent, overall corresponding to the influence on the growth rate. The lowest g value is found in methanol where the growth rate is the highest, and the highest 1 g value is found in ethyl acetate where the growth rate is the lowest. This relation is logical since a lower growth rate can be due to a slower surface integration for which we would expect a higher g value, and vice versa. The order between the solvents with respect to the value of g does not depend on the driving force representation, and in fact the numerical value is only moderately influenced by the driving force choice, with a tendency of being lower when using S-1. The rate constant value k_S when using S-1 has the units of m/s, and in all cases receives a numerical value of the expected order of magnitude. The corresponding rate constant when using S-2 has units of J/mol, and the variation depending on the solvent is several orders of magnitude. Again, it can be expected that much of the variation stems from numerical correlation between parameters.

As shown in Figure 2, the growth rate is strongly dependent on the temperature. In methanol, at a driving force of Δf_g = 20 J/mol, the growth rate increases by a factor 7 when the temperature is increased from 10 to 25 °C. The corresponding factor in acetone is 4. This strong dependence is of course reflected in the activation energies, E_a, with values given in Table 1. The activation energy order with respect to the solvent when using Δf_g is MeCN > MeOH > EA ≥ AC. When using S-1 the activation energy obtained in EA is lower than in AC. It is worth noting that while g does not depend strongly on the driving force representation, the activation energy, E_a, does, and the higher value obtained in methanol when using Δf_g is more in line with expectations. These activation energies are clearly higher than the values expected for simple molecular diffusion (3–20 kJ mol⁻¹) and near the values reported for surface integration (40–60 kJ mol⁻¹). The surface integration step contains different physicochemical processes like desorption, surface diffusion, and lattice integration. All data together suggest that the crystal growth depending on the solvent, and temperature is at least partly governed by the surface integration, and since there is a clear dependence of the solvent perhaps desorption plays an important role.

It should be stressed that the difference between the different driving force representations can be significant, and moreover, the difference is highly solvent-dependent. As explained in the Supporting Information, the largest difference observed between Δf_g calculated by including and neglecting the activity coefficient contribution, respectively, is 37% in acetone, while in methanol the difference is close to zero. This is because activity coefficients, and their influence on Δf_g, depend on the solvent. The difference between the two representations not only depends on solvent, however, but also on temperature; increasing temperature results in a decrease in the difference between the representations in MeOH (from 5% to ~3%) and EA (from 28% to 24%), while it remains virtually constant at all temperatures in AC (37%) and MeCN (22%). Δf_g accounts for the concentration dependence of the activity coefficient, which in many cases is expected to dominate the total influence of nonideality on the driving force. However, it should be noted that some solutions evaluated in this work are fairly dilute, and thus the temperature dependence of the activity coefficient is expected to be more important than assumed in the derivation of eq 12. For these cases, we cannot state with certainty that Δf_g is a better approximation than S-1.

In applying the BCF and the B&G equations, it should be noted that the crystal growth rate data obtained from seeded de-super saturation experiments represent an average over a
number of crystals growing simultaneously, as well as an average over the growth of different faces. Accordingly, in the application of face growth models to such data the physical parameters determined have to be understood as averages over the different faces. Both growth models provide a good fit to the experimental data, as shown in Figure S3 of the Supporting Information. The BCF model gives a slightly better fit at 10 and 25 °C according to the residual curves.

Table 2 and Table 3 list the fitted parameters of the BCF and B&S models, and the surface diffusion dependent parameters A and C for each solvent are plotted versus the inverse temperature in Figure 5. In all cases, the graphs show a reasonably linear increase in the parameter value with a decrease in the inverse temperature from which the surface diffusion activation energy, $E_{surf}$, is determined according to Eq. 9. The surface diffusion activation energies are given in Tables 2 and 3 and for both models follow the same order with respect to the solvent as obtained for the activation energy above for Eq. 2 using $\Delta_{HF}$: MeCN > MeOH > EA > AC.

## DISCUSSION

According to the results, the crystal growth rate of salicylamide in the four different solvents at equal driving force ($\Delta_{HF}$) decreases in the order: MeCN > MeOH > AC > EA. Regardless of temperature, the growth rate in EA is clearly lower than in the other solvents and the growth rate in MeCN and MeOH is quite similar. When the driving force is described by S-I, the order is more dependent on temperature, but at 15 °C the order is MeOH > AC > MeCN > EA. In Figure 6, the latter data are compared with data from a study over primary nucleation of salicylamide in the same solvents, from which also approximate crystal growth rates are estimated. These estimates assume that the crystals become visible when they reach a size of 1 μm, which of course is only an arbitrary value based on the findings of R. Devi, M. Svard et al. However, within this assumption, the crystal growth rates from the nucleation experiments are on the order of 20 times higher, as would be expected from the much higher supersaturation under which the crystals are grown in the nucleation experiments. However, the order of growth rates with respect to the solvent exactly matches the order found in the present study. Methanol provides the fastest growth for salicylamide crystals, both at the nucleus stage at high supersaturation and for the much larger seed crystals at lower supersaturation, whereas ethyl acetate leads to the slowest growth rates. This shows that the growth of salicylamide crystals of varying size (1 and 355 μm up to 1000 μm) and under different driving forces were influenced in the same way by the different solvents even though the growth mechanism may actually be different.

The B parameter in the spiral growth model is directly proportional to the interfacial energy (Eq. S), and the D parameter in the B&S model is proportional to the interfacial energy raised to the power 2 (Eq. S). Accordingly, based on the parameter values given in Table 2, the interfacial energy determined using the BCF model follows the order EA > MeCN > MeOH, while the order obtained using the B&S model is slightly different: EA > AC > MeCN > MeOH. According to Eqs. 5 and 8, a low interfacial energy leads to a high crystal growth rate, which is in agreement with the results from the growth rate experiments reported in this work. It is widely accepted that the solid–liquid interfacial energy appears as a governing parameter also in crystal nucleation. For this reason, values previously reported from nucleation experiments are compared with interfacial energies obtained from crystal growth data using the B&S model in Figure 7. The interfacial energies obtained from nucleation experiments follow an order exactly opposite to that of the B&S growth data: MeOH > MeCN > AC > EA. In the BCF theory the interfacial energy determines the radius of the growth spiral, while in the B&S theory the interfacial energy is based on the “birth” term of the B&S equation which can be considered as a 2D nucleation on a substrate surface, which explains why the interfacial energy...
Appendix I

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Figure 7. Interfacial energies obtained from the fitted parameter D of the B-S crystal growth model for growth data compared with values obtained using the classical nucleation theory from previously published nucleation data.

obtained from crystal growth data is expected to be significantly smaller than that obtained from nucleation data (three-dimensional (3D) nucleation). However, at present we have no clear explanation why the influence of the solvent on the interfacial energy as determined from crystal growth and nucleation experiments, respectively, show completely opposite trends, and this disagrees with our previous findings for salicylic acid. One possibility would be that the faces governing the crystal growth process do not have the same importance for the formation of nuclei. It is well understood that the supersaturation dependence of the growth rate of different faces can be different leading to that faces governing the growth at low supersaturation do not necessarily have to be the same as those that govern the growth rate at high supersaturation.

We have previously reported a similar crystal growth study on salicylic acid (SA). SA has an identical molecular structure except for the amide group in the meta-position being replaced by a carboxylic acid group. Various properties of the two solutes are shown in Table S4 in the Supporting Information. The molecular weight is essentially the same, while the melting temperature of SA is about 20 K higher, and the crystal density of SA is somewhat higher and accordingly the molecular volume is a bit lower. The hydrogen bonding capability differs somewhat, contributing to differences in the crystal structures. Both SA and salicylamide molecules form dimers, but in addition to this motif the SAM molecules are also involved in other intramolecular hydrogen bond interactions. Ultimately, the differences in the hydrogen bonding are likely to play a significant role in the variances of growth rates obtained for the two solutes; however, the details need to be investigated in further work. The packing arrangements in the two structures differ considerably as illustrated in Figure 8. Because of the structural differences, the two compounds crystallize in completely different habits, as is further discussed below.

In Figure 9, crystal growth rates of salicylamide are compared with salicylic acid in the same solvents at two temperatures. In both cases the driving force has been estimated according to eq 12 using the same approximation of the activity coefficient ratio. At lower temperatures, the growth rates of the two compounds follow a similar solvent order, whereas at higher temperatures they follow a different order. For salicylamide, the growth rate at all temperatures decreases in the order: McCN > MeOH > AC > EA, while for salicylic acid the solvent order changes with temperature: at 10 °C the order is McCN > MeOH > EA > AC, while at 25 °C the order is EA > MeOH > McCN > AC. In summary acetone provides the fastest growth kinetics for both solutes at 10 °C. Ethyl acetate provides the slowest growth rates for salicylamide, whereas acetone provides the slowest growth rates for salicylic acid consistently at both temperatures. Accordingly the order with respect to the solvent does not match perfectly for the two solutes. However, it should be acknowledged that there is some uncertainty in the curves as shown in fitting; this could have a considerable effect on the solvent order in the case of salicylic acid for which the curves are close together. SA exhibits a clearly faster growth than salicylamide in all solvents at the lower temperature (10 °C), whereas salicylamide has the faster growth in all solvents except EA at the higher temperature (25 °C) as illustrated in Figure 9. With regard to the temperature dependence of the crystal growth rate, for salicylic acid in acetone at ΔT = 10 J mol⁻¹ C⁻¹ increases from 1.4 × 10⁻⁷ m s⁻¹ up to 2.3 × 10⁻⁶ m

Figure 8. Unit cell representations showing hydrogen bonds (blue lines) the two solutes, SA versus salicylamide were obtained using the software Materials Studio for structures with CSD codes: SALLAC16 and SALMID.
Figure 9. Crystal growth rate curves at (a) 10 °C and (b) 25 °C for salicylamide (present work, dashed lines) and salicylic acid (solid lines) in four solvents at different driving forces obtained by fitting experimental results to the modified growth rate eq 2 with the driving force, $\Delta \mu$, represented by $\Delta \mu$. 

$s^{-1}$ when the temperature goes from 10 to 25 °C, which equates to a 78% increase. Under similar conditions, for salicylamide $G$ increases from $1.1 \times 10^{-3}$ m s$^{-1}$ up to $7.0 \times 10^{-3}$ m s$^{-1}$, i.e., a 536% increase. This shows that under the evaluated conditions the impact of increasing temperature has a significantly greater impact on the growth rate of salicylamide than salicylic acid. Comparing the activation energies obtained by fitting eq 2 using $\Delta \mu$, it is notable that $E_g$ values are significantly higher (from a factor 1.5 to 4) for SAM in all the solvents. The $E_g$ value for salicylic acid is in the range 22–67 kJ mol$^{-1}$, while for salicylamide the range is 58–91 kJ mol$^{-1}$.

There appears to be no clear relationship between $k_{eq}$ and $g$ with respect to the solvent. Significantly higher $E_g$ values were obtained for salicylamide than salicylic acid. The values of the growth order parameter $g$ are for all solvent–solvent combinations above unity with slightly higher values observed for salicylic acid in all solvents except ethyl acetate.$^{10}$ In comparing the activation energies for surface diffusion, it may be noted that for SAM the value in MeOH is about 50% higher compared to SA, while the values in AC are roughly the same, the value in MeCN is a much higher (by a factor 4–10), and the value in EA is slightly lower.

In Figure 10, the interface energies determined from the parameter $D$ in the B&S model are compared for the two solvents in the same four solvents. There is a clear tendency for an opposite dependence on the solvent, where for salicylamide the interfacial energy decreases in the order EA > AC > MeCN > MeOH, while for salicylic acid the corresponding order is MeOH > AC > MeCN > EA. Salicylic acid has higher interfacial energy values than salicylamide in all solvents except ethyl acetate. The influence of the solvent on the interfacial energy is of course due to the corresponding influence on the parameter $D$. Besides having a different order with respect to the solvent, the $D$ values are clearly higher for salicylic acid, except in ethyl acetate. The $C$ values are of a similar order of magnitude, but more different in MeCN and EA. For comparison, the $B$ parameter of the BCP theory is also clearly higher for salicylic acid than for salicylamide except in EA.

It may be argued that a comparison of linear growth rates is not trivial, especially not for two different compounds, since the morphologies are different and growth rates in one linear dimension are not really comparable. In the present case, for both compounds the seed crystal size has been determined by the same method: sieving, assumed to fractionate the crystals in terms of the second largest linear dimension. However, as shown in Figure 11 the shapes are quite different. In determining the crystal growth rate by the seeded de-supersaturation method it is assumed that the crystal shape is constant and thus that the de-supersaturation rate is directly related to the rate of increase of the linear dimension characterizing the size of the crystals:

$$\frac{dn}{dt} = 3N_p n_k L_t \frac{G}{L_t} \frac{G}{L_t}$$

Figure 10. Interfacial energies obtained from the fitted parameter $D$ of the B&S crystal growth model for salicylamide (SAM) and salicylic acid (SAH) crystals.

Figure 11. Micrographs of (a) salicylic acid and (b) salicylamide crystals used as model crystals for dimensions analysis in Table 4.
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In the evaluation of the linear growth rate $G$ the shape factor cancels out, i.e., as long as the morphology remains constant the actual shape is unimportant. For the same compound growing in different habits in different solvents the linear growth rates are not necessarily comparable. However, in the present study, the seed material used is the same regardless of the solvent and the extent of growth is fairly limited, which would reasonably enable comparison. On the other hand, if structures of two different compounds having different crystal shapes are compared, the linear growth rates are not directly comparable without recognizing the difference in the shape factor, i.e., equal linear growth rate does not mean equal mass consumption rate. By a recalibration, a comparison can be made in terms of mass deposition rates per unit surface area, $MD$:

$$MD = \frac{1}{SA} \frac{dn}{dt} = 3\left(\frac{k_2}{k_3}\right)G = 3\left(\frac{CV}{SA} L G \right)$$  \hspace{1cm} (14)

<table>
<thead>
<tr>
<th>Table 4. Parameter Values Used for Mass Deposition Rate Per Unit Surface Area Calculations for the Two Compounds Obtained from Representative Crystals as shown in Figure 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>salicylic acid</td>
</tr>
<tr>
<td>crystal size, $L$ (m)</td>
</tr>
<tr>
<td>crystal volume, CV (m$^3$)</td>
</tr>
<tr>
<td>surface area, SA (m$^2$)</td>
</tr>
<tr>
<td>density, $\rho$ (kg m$^{-3}$)</td>
</tr>
</tbody>
</table>

In Figure 11, mass deposition rates per unit area curves are shown for the two solutes in different solvents at two temperatures. Compared to the linear growth rate curves (Figure 9), there are no major qualitative changes. From Figure 12a, it is clear that SA has a significantly higher mass deposition rate per unit surface area in all the solvents compared to SAM at 10 $^\circ$C. However, at 25 $^\circ$C (Figure 12b), the mass deposition rate of SAM is clearly higher in two out of four solvents (MeOH and MeCN).

CONCLUSIONS

Out of four solvents, the crystal growth rate of salicylamide was found to be slowest in ethyl acetate under all conditions evaluated. For the remaining solvents, the order with respect to the growth rate of salicylamide depends on temperature, supersaturation, and driving force representation. The growth kinetics are strongly affected by the temperature as reflected in the activation energy. The growth order parameter reveals that the crystal growth is at least partially controlled by surface integration, with the highest value being found in ethyl acetate where the growth rate is the lowest. Higher than expected activation energies and significant influence of the solvent indicate that desolvation is a governing process. The influence of the solvent on the growth rate of salicylamide is in good agreement with the corresponding growth rates obtained in primary nucleation experiments. The BCF model and the B+S model are both well fitted to the growth data, and the interfacial energies are estimated. As opposed to similar work on salicylic acid, interfacial energies from primary nucleation data have an opposite dependence on the solvent to that found for the present growth rate data. Compared with a similar study over the crystal growth rate of salicylic acid the influence of the solvent is essentially the same, with acetonitrile providing the fastest growth rate for both compounds. Salicylamide crystal growth has a stronger temperature dependence than salicylic acid crystal growth.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.7b00977.

Experimentally determined metastable zone width of salicylamide. Simple rate equation kinetic parameters and modified growth rate equation kinetic curves, followed by BCF & B&S growth mechanisms fitted to kinetics. Solubility and estimation of thermodynamic driving force. Lastly properties of salicylic acid and salicylamide compared (PDF)

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- SYMBOLS AND NOMENCLATURE

a, activity, dimensionless; A, BCF model parameter, K m⁻¹ s⁻¹; B, BCF model parameter, K²; B_{step} two-dimensional nucleation rate; C, B+S model parameter, mol m⁻³; CV, crystal volume, m³; D, B+S model parameter, K¹; dm/dt, rate of increase of the linear dimension; E_a, apparent activation energy, kJ mol⁻¹; g, growth rate order; dim, dimensionless; G, rate of change of characteristic dimension of crystal, m s⁻¹; h, height of the growth step; ΔS_{surf}, surface area shape factor, dimensionless; k, parameter in modified growth rate equation (pre-exponential factor/frequency factor), unit depends on s. term of the driving force; ε_r, elastic shape factor, dimensionless; M, characteristic dimension of crystal, m; M_r, Molecular weight, g mol⁻¹; M_{1 stage} Mass deposition rates per unit surface area, kg m⁻² s⁻¹; M_{step}, total number of seed crystals, dimensionless; E, gas constant, J K⁻¹ mol⁻¹; s, driving force, unit changes with representation; S, supersaturation ratio, dimensionless; S_A, surface area, m²; S_{relative}, relative supersaturation, dimensionless; τ, time, s; T_{step}, temperature; K_{step}, step advancement rate in the B + S model; x, mole fraction, concentration, dimensionless.

- GREEK LETTERS

γ, activity coefficient, dimensionless; μ, chemical potential, J mol⁻¹; Δγ, chemical potential difference, J mol⁻¹; Δγ_{pot}, chemical potential difference, neglecting the temperature-dependence of the activity coefficient, J mol⁻¹; ρ, density, kg m⁻³.

- REFERENCES

Face indexing and shape analysis of salicylamide crystals grown in different solvents

Aisling Lynch, Vivek Verma, Jacek Zegiński,
Pauric Bannigan and Åke Rasmussen

The effect of solvent on salicylamide's crystal habit was investigated. Crystals grown experimentally in acetone, acetonitrile and methanol matched the attachment energy predicted rectangle plate vacuum habit. However, in ethyl acetate irregular hexagonal plate crystals form. This change in habit was found to be caused by the startled growth of specific crystal faces during the crystallization process. Single crystal and powder X-ray diffraction was carried out to rule out the possibility of a new polymorph. Given no new polymorphs were discovered, the changing habit makes face indexing of experimentally grown crystals difficult. A combination of experimental and modelling prediction tools was employed for the face indexing process. The interfacial angle between faces combined with preferred orientation (P-XRD) was found to be the most accurate and reliable method leading to successful identification of each salicylamide crystal face. The surface chemistry of each face was examined on a molecular level with insights into the possible growth attachment sites being made. It is deduced that ethyl acetate is adsorbed more strongly on the faces, the increased size of which, can explain the shape change.

Introduction
The focus of this study is two-fold; to understand how the crystal growth in different solvents and also face index experimentally grown crystals with different habits for the purpose of observing the correct faces during the growth process. The role of solvent on the crystallisation process is of great interest to the crystal engineering community, specifically the pharmaceutical industry which relies heavily on crystallisation for formation, purification and recovery of the active pharmaceutical ingredient (API). It is well known that the crystal growth process is significantly influenced by the solvent; some insights have been made when trying to understand the solvent effect on the crystallization kinetics of the faces and thus resulting crystal habit. Solvents may accelerate, retard or even stop the further growth of individual crystal faces, sometimes producing a habit change. Crocker et al. found that the solvent influenced the growth process of phenacetin crystals by various solute-solvent interactions and also alters the growth rates of specific crystal faces. Solvent can inhibit the growth of a crystal by adsorbing onto the fastest growing crystal surface, as found by studying the growth of sulfathiazole in both a hydrogen bond acceptor solvent and also solvents which are considered donor and acceptors. Specific adsorption of solvent molecules at the growing crystal surface can result in a lower growth rate despite a higher solubility, as has been experimentally observed for α-resorcinol with its polar faces, succinic acid (001) face containing carboxyl acid groups. Also Lahav reviewed the growth of a number of polar crystals and found their growth to be impeded by certain solvents with high binding compatibility and thus strong interaction. In recent times, computational and molecular dynamics simulations have started to be used to predict the crystal habit grown in solvent and are beginning to show interesting findings which are matching to experimental work. The exact effect of solvent on the crystal habit is still unknown, so more work needs to be done in this area before we can be able to fully predict its effect. This study tries to further improve our knowledge of these solute-solvent interactions by using salicylamide as the API grown in four different organic solvents with various properties. Salicylamide properties (chemical, uses, classification, and solubility) have already been described in detail. Also the single crystal structure of salicylamide has already been determined a number of times, CIF files available. P-XRD data for each of these CIF files has been compared and show matching patterns; for this reason only SALMID01 data will be utilised in this study for modelling input data and comparison.

Furthermore, as the different solvents may cause a change in the crystal habit but not necessarily create a new
polymer. It causes a knock-on issue on the face indexing process. Precise face indexing is essential in order to measure the kinetics of crystal growth in a characteristic dimension accurately. The correct faces are the faces of the sample that are parallel to the face of the original crystal. This paper aims to create a simple solution for face indexing of experimentally grown crystals of the same polymer but having different crystal habits by using a combination of experimental and prediction techniques already used in the field.37,39-42

**Experimental**

**Materials**

Salicylamide (purity ≥ 99.0%) was purchased from Sigma Aldrich (catalogue number 84230), and used as received without further purification. The solvents; acetone (AC) 99.8%, acetonitrile (MeCN) ≥99.9%, ethyl acetate (EA) 99.7%, and methanol (MeOH) 99.9% were also purchased from Sigma Aldrich and used as received.

**Growing crystals**

Crystals were grown via slow solvent evaporation under controlled room temperature from initially saturated solutions. Saturated solutions were prepared by dissolving sufficient amount of salicylamide in each of the four solvents, left mixing at room temperature (298 K) for 1 hour. 10 mls of solution was filtered and poured into new vial of width 27.5 mm and covered with parafilm with 3 pin holes with diameter 1.2 mm to control evaporation. Vials were left for 1 week to allow crystals to form, in the fastest system crystals appeared in two days.

**Microscopy**

Inverted light optical microscope (Olympus BX53) integrated with Olympus SC10 camera combined with a PC with image/video capture and analysis software (Olympus Stream Essentials) was used to capture micrographs of crystals grown experimentally. Crystal samples were gold coated crystal with 20 mA for 30 seconds prior to visualisation with SEM-Cary Scope JEOL JCM-5700.

**Single crystal X-ray diffraction (SC-XRD)**

SC-XRD measurements were collected at room temperature (293.86 K), on a Bruker Quest DS Mo sealed tube (β = 0.71073 Å), equipped with CMOS photon detector. Unit cell parameters were determined using APEX3 and compared against previously reported data.

**Powder X-ray diffraction (PXRD)**

PXRD was employed to characterize the preferred orientation of each form and also confirm correct polymorph was present. Powder sample was made by grinding salicylamide as received with a pestle and mortar. Whole individual crystals grown in each of the 4 solvents were oriented on separate disks with largest face facing upwards. Also cut crystals with end faces facing upwards on disk were analysed. PXRD data were collected in reflection mode with an Empyrean diffractometer (PANalytical, Philips) equipped with CuKα1,2 radiation (λ = 1.5406 Å) operating at 40 kV and 40 mA at room temperature. Samples were scanned between 2θ values of 5 and 30° at a step size of 0.079° 2θ/scan, 90.27 s per step.

**Interface angle**

Interface angles can be calculated using many different software tools. This study used BIOVIA Materials Studio Morphology Prediction. Experimental interface angles were measured directly from the micrographs using built in measurement tools on Olympus Stream Essentials software.

**Morphology prediction & molecular analysis**

BIOVIA Materials Studio Morphology was used to predict the vacuum growth morphology using the attachment energy method, in which the growth rate of each crystal face is assumed to be proportional to the attachment energy, viz. the energy released upon attachment of a growth slice to a given crystal face. All modelling was run using previously published salicylamide crystallographic data (ref: SALMID01).14,15 The COMPASS II force-field was used for the morphology prediction and the attachment energy calculations. BIOVIA Materials Studio Morphology was also used to model the surface chemistry of the dominating crystal faces.

The molecular dynamic simulation of the interaction between solvent and salicylamide (110) face was carried out in a simulation box (37.28 Å × 50.82 Å × 46.5 Å) with periodic boundary conditions to model a representative part of the interface devoid of any arbitrary boundary effect. The salicylamide (110) face (1.4 Å thickness) was first built using CIF file SALMID01. Then the face of salicylamide (110) was increased and its periodicity is changed by constructing a supercell, and then a vacuum slab with 40 Å thickness was built on the salicylamide (110) face. Molecular structure of various solvents (AC, EA, MeCN, MeOH) was built using sketching tool available in Material Studio and their geometry optimization was performed by Force module using COMPASS II force field. Finally, the adsorption locator module was used to perform Monte Carlo simulations to investigate the adsorption of solvent molecules on the (110) surface, for all four solvents; EA, AC, MeCN and MeOH. Each simulation includes five solvent molecules and a salicylamide (110) surface. The adsorption region was defined by the atom set and functional groups present on top of (110) face. COMPASS II force field was used for geometry optimization, the Ewald & group summation method was used for electrostatic term for more accurate non-bond energy calculation, and the atom based summation was used for Van der Waals terms. Maximum adsorption distance was fixed to 5.0 Å. The low-energy adsorption (local energy minima) site is identified by performing Monte Carlo search. Each solvent molecule is free to rotate and translate around the surface, but conformational changes of the solvent molecules are neglected.
Results and discussion

Salicylamide crystal habit

Salicylamide crystals grown in different solvents. Salicylamide crystals were grown in each of the four solvents by slow solvent evaporation; typically one crystal habit dominated each solvent system. This is illustrated by representative crystals for each of the solvents in the micrographs in Fig. 1. Acetone, acetonitrile and methanol mainly formed crystals with a rectangle habit. In ethyl acetate, the salicylamide crystals typically formed irregular hexagonal plates. In a few cases crystal habit did also change within each solvent system, for example ethyl acetate had the capabilities of forming crystals with a rectangle habit.

Salicylamide crystal morphology prediction. According to our computational prediction by the attachment energy approach shown in Fig. 2, the salicylamide crystal grown in vacuum forms a rectangular shaped particle containing 16 facets, with only 5 being unique. The modelling predicts flat sides (facets (200), (002) and (011)) and slanted top and bottom made by facets (11–2) and (110). Overall, the most dominant, thus the closest growing are equivalent (602) and (90–2) faces which jointly take up 51.4% of the total surface area (see Table 3). Crystals grown in acetone, acetonitrile and methanol (Fig. 1a, b and d) gave similar habit to the predicted. However crystals grown in ethyl acetate (Fig. 1c) gave a different habit and so a check for polymorphism was performed.

Check for polymorph

Although altered crystal habit is not a sole indicator of polymorphism, it can be used as an initial test. To ensure the crystals with irregular hexagonal habit grown in our study were not a new polymorph, both PXRD and SCXRD data was collected. A powder sample of salicylamide was made by grinding the salicylamide as supplied with a pestle and mortar and placing on sample holder. This powder sample was analysed by PXRD and results were compared with a previously published PXRD pattern of salicylamide (SALMID25) and also a PXRD pattern which was calculated from the SCXRD data obtained in this study. PXRD patterns for all are shown in Fig. 3. All three patterns match confirming salicylamide in this study forms the same polymorph as the previously reported stable form I. Peak intensity of experimental powder sample is significantly lower than the previously reported and calculated data; but major peaks are still present. In order to confirm for definite there are no minor changes in the crystallographic data we also determined the unit cell of salicylamide crystal grown in ethyl acetate with irregular habit through SCXRD and compared against previously reported crystallography data as shown in Table 1.25 This confirmed for certain the same stable polymorph, form I, was formed with the monoclinic P2₁/a cell setting.

Table 1. Crystallographic data for salicylamide grown in this study compared with previously reported salicylamide data (SALMID)25

<table>
<thead>
<tr>
<th>Current study</th>
<th>Previous work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal grown in EA</td>
<td>SALMID alcohol – H₂O</td>
</tr>
<tr>
<td>Crystal form/colour</td>
<td>Block, colourless</td>
</tr>
<tr>
<td>Cell setting</td>
<td>Monoclinic, P2₁/a</td>
</tr>
<tr>
<td>a/Å</td>
<td>12.89</td>
</tr>
<tr>
<td>b/Å</td>
<td>4.98</td>
</tr>
<tr>
<td>c/Å</td>
<td>20.09</td>
</tr>
<tr>
<td>α°</td>
<td>90.08</td>
</tr>
<tr>
<td>β°</td>
<td>91.52</td>
</tr>
<tr>
<td>γ°</td>
<td>90.08</td>
</tr>
<tr>
<td>V/Å³</td>
<td>1343.08</td>
</tr>
</tbody>
</table>

Face indexing

Step 1: overlay of predicted habit onto experimental habit.

As it has been shown that all crystals grown in different solvents are of the same polymorph, it indicates the change
Fig. 3 Powder XRD pattern of salicylamide sample as used in this work (2nd pattern is calculated from SC-XRD data obtained in this work (Table 1), 3rd pattern is ground salicylamide sample as received) compared to previously published salicylamide XRD pattern as obtained by M. Kikudo (ref. code: SALMID®).

Fig. 4 Micrographs of each of the crystals to be examined by P-XRD, grown in each of the four solvents with two crystals for ethyl acetate due to different habits.

Fig. 5 Previously published salicylamide XRD pattern (ref. code: SALMID®) compared against preferred orientation XRD patterns of whole salicylamide crystals grown in acetonitrile, ethyl acetate (1), ethyl acetate (2) and methanol. Miller indices assigned to peaks of interest.
in crystal habit is due to different growth rates of the same faces in the different solvents. The irregular habit makes face indexing difficult. Experimentally grown crystals which had a similar habit to the predicted can easily be subjectively indexed by simply overlaying the predicted habit to these micrographs and assigning the corresponding face index. The large flat face and the side face as shown in Fig. 1a, b and d are likely to be the (002) and (200) respectively as predicted by the growth model in Fig. 2. These can be confirmed experimentally by preferred orientation PXRD in the next section. The end faces are more difficult to identify as the three end faces predicted do not always form in the experimental crystals. In some crystals there are only one or two end faces. A more detailed analysis is required to identify these end faces correctly as will be discussed at a later stage in this paper. As for crystals with the irregular habit, such as the ones grown in ethyl acetate as shown in Fig. 1c, face indexing is not straightforward and so these crystals also require a more extensive approach.

Step 2: Preferred orientation PXRD. In order to identify the faces of real crystals, PXRD patterns were obtained for whole crystals grown in each of the four solvents which were rotated in a preferred orientation onto the disk as shown in Fig. 4. All samples formed the same three peaks, comparing these peaks with the previously published salicylamide XRD indexed pattern [SALMID\textsuperscript{31}] they infer the (002), (004) and (008) faces as shown in Fig. 5. All are apart of the same (00f) indices family, representing different crystal planes. Hence all peaks observed from the preferred orientation XRD pattern confirm the presence of the large (002) face as predicted by the growth morphology in Fig. 2. Interestingly, the two crystals grown in ethyl acetate which gave significantly different habits both gave the same XRD pattern. Accordingly, both crystals are dominated by a large (002) faces, but they differ in the side and end faces.

Additionally, one PXRD pattern was obtained for multiple whole salicylamide crystals grown in methanol which were placed in a preferred orientation onto the disk as shown in Fig. 6. The same three XRD peaks are observed again as were shown for the individual crystal scans. Predominantly (00f) face is observed in Fig. 7 as expected from the models habit, again confirming the presence of predicted (002) face when compared against previously published salicylamide XRD pattern. However, this scan of multiple crystals at once gives an additional two peaks indicative of the (200) and (015) faces. The (200) face matches the predicted side face of the crystal in Fig. 2. The (015) is part of the (01f) family, which matches to the (011) end face of the predicted crystal habit. Scanning multiple crystals at once allowed for faces which had a small surface area ratio to be amplified and meant that their respective peak intensity could be increased and reach the minimum threshold and so not be overshadowed by the larger more intense peaks. These new
peaks complement the predicted faces in the Material Studio model.

Although running multiple crystals in the preferred orientation led to the confirmation of the side (200) face and the end face (011), the large surface area of the (002) face still tend to outweigh the other peaks. In order to reduce the intensity of these (002) peaks, and allow for other peaks to be observed, the crystal was cut using a blade and orientated differently so that the faces on the end of the crystal were facing upwards as demonstrated with the growth habit in Fig. 8. PXRD patterns were obtained for two cut individual crystals grown in different solvents to account for differences in habits observed from the experimental crystals. The two crystals tested gave different peaks as shown in Fig. 9 which indicates different dominant end faces on the samples. Only one peak formed for each of the samples, indicating that one face dominates the end of the crystals in both cases. Crystal 1 one which was grown in acetone had a peak representing the (110) face confirming one predicted end face. Whereas crystal 2 which was grown in acetonitrile has a peak signifying the (024), this represents the (0kl) indices family which confirms the (011) end face as predicted in the growth morphological habit in Fig. 2. This further confirms that the dominant end faces change between salicylamide crystals, and that predicted habit alone cannot just be utilised for accurate face indexing of real crystals.

The use of preferred orientation PXRD was instrumental in the face indexing process. This technique combined with predicted habit allowed for confirmation of specific faces from real salicylamide crystals, ultimately resulting in accurate face indexing of the crystal faces with relatively large surface area ratios. PXRD confirmed the presence of the large flat (002) faces, the main side (200) face and also some end faces (011) and (110). Experimental confirmation of four of the five unique facets predicted was achieved except for the small (11-2) end face. However, due to the fact that smaller peaks can be masked by the more dominating peaks it is not a suitable technique for identifying the smaller crystal faces. Instead experimentally measured interfacial angles will be compared against predicted angles in order to assign accurate indices to the end faces of the crystal.

Step 3: interfacial angle. Interfacial angles can easily be calculated from previously published unit cell data using Material Studio Morphology software. Calculated angles are shown in Table 2. Although a crystal does not always maintain geometric similarity during growth (change in crystal habit), the interfacial angles do not vary as they are characteristic of the substance which makes them a reliable tool for face indexing crystals that have a variable habit.3,20

Typically a goniometer would have been used to measure the interfacial angles directly from real crystal samples. Nowadays, interfacial angles can be measured directly from micrographs using three point angle measuring tool on Olympus Stream Essentials software. It should be noted for the angle to be accurate the crystal needs to be laid flat. Experimentally measured angles shown in micrographs below (Fig. 10) compared well with calculated angles as listed in Table 2. Fig. 10a) represents crystals with the regular rectangle habit; as acetone, acetonitrile and methanol all formed crystals of similar shape only one grown in acetone was

**Fig. 9 Preferred orientation XRD patterns of cut & oriented salicylamide crystals grown in different solvents compared against published salicylamide pattern (SAL.MID).**

Counts

**Table 2** Interfacial angles calculated from previously published unit cell data using Material Studio Morphology software. Calculated angles are shown in Table 2. Although a crystal does not always maintain geometric similarity during growth (change in crystal habit), the interfacial angles do not vary as they are characteristic of the substance which makes them a reliable tool for face indexing crystals that have a variable habit.3,20

**Fig. 10** Preferred orientation XRD patterns of cut & oriented salicylamide crystals grown in different solvents compared against published salicylamide pattern (SAL.MID).20
Table 2: Interfacial angles calculated using Material Studio for SLMID crystal habit.

<table>
<thead>
<tr>
<th>hkl</th>
<th>hkl</th>
<th>Material Studio interface angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[0 0 2]</td>
<td>[2 0 0]</td>
<td>79.42</td>
</tr>
<tr>
<td>[2 0 0]</td>
<td>[0 1 1]</td>
<td>87.38</td>
</tr>
<tr>
<td>[1 1 0]</td>
<td>[1 1 0]</td>
<td>97.91</td>
</tr>
<tr>
<td>[1 1 0]</td>
<td>[1 1 0]</td>
<td>114.27</td>
</tr>
<tr>
<td>[2 0 0]</td>
<td>[2 1 1]</td>
<td>73.20</td>
</tr>
<tr>
<td>[1 1 2]</td>
<td>[1 1 2]</td>
<td>62.21</td>
</tr>
</tbody>
</table>

In order to successfully determine the Miller indices of the end faces of the crystal, specific interfacial angles were measured for example the 45.43° angle was calculated to be between the (110) and (−110) planes, and 69.74° angle was calculated to be between the (200) and (110) planes. Using this information, in both cases the Miller indices can be assigned successfully to the end and side faces of the crystals. Combining all of the experimental and modelling results from the previous steps, salicylamide crystals of both regular rectangle habit and also irregular hexagonal habit were successfully fully face indexed as shown in Fig. 11.

Molecular analysis of particle interactions

Uninfluenced by the surroundings, the crystal shape is determined by the crystal structure and the solid state molecular interactions. In its crystal structure, each salicylamide molecule creates H-bonding with three neighboring salicylamide molecules through the hydroxyl (-OH), amine (-NH₂) and carbonyl (-C=O) polar groups as shown in Fig. 12. A centrosymmetric dimer present in the crystal lattice is stabilised by H-bonding with adjacent molecules. In molecular crystals, strong intermolecular interactions (such as H-bonding) tend to determine the growth directions. Thus, it can be expected that the growth rate will be higher in hydrogen bonding directions leading to that the corresponding faces become small.

Fig. 11: SEM images show individual salicylamide crystals grown experimentally in a) acetone and b) ethyl acetate with assigned Miller indices overlaid.
The crystal shape predicted by the attachment energy method is shown in Fig. 2 and 8. The crystal is dominated by the (002) faces and bound by (200) side faces. The attachment energy of the five slowest growing faces are given in Table 3. The attachment energy of the (002) face is -170.4 kJ mol^{-1}, being only half of the value for the second slowest growing side face (200), having the attachment energy of -257.0 kJ mol^{-1}. The difference to the following three faces is clear but not exceedingly big.

In Fig. 13, the molecular chemistry of the five slowest growing faces is shown. The slowest growing (002) faces feature protruding non-polar phenyl rings, were the contribution of van der Waals and π-interactions are likely to dominate (Fig. 13e). The contribution from hydrogen bonding is low and thus the face is non-capable of making strong hydrogen bonding interactions with the solvents. Accordingly, the growth rates of these faces are not expected to be strongly influenced by the solvent. The (200) faces appears to be more polar, however the propensity for hydrogen bonding is reduced by the fact that it is the internally hydrogen bonded alcohol group that dominates the surface and the amide groups are embedded deeper into the surface topology. The short side faces of the simulated crystal shape all have a more clear propensity for hydrogen bonding, which also explains why these are the smallest faces in Table 3, especially (110) and the (11-2).

The crystal grown in acetone (Fig. 11) is not very different from that predicted by the attachment energy method. The crystal is clearly dominated by the (002) faces and the elongated (200) face is quite similar to that found in the predicted shape (Fig. 2). Also, the (011) face is clearly seen on the short side of the crystal. In ethyl acetate, the salicylamide crystals form irregular hexagonal plates looking quite different from those in acetone. However, at closer inspection it is found that it is in fact the short side faces that has been sloved down by which the (200) faces become less dominating. The (110) and (11-2) faces have developed more than in the other solvents. However, it should be noted though that the attachment energies of these faces are not very much higher than that of the (001) faces, indicating that just a modest slowing down of the growth rates for the (110) and (11-2) faces will result in the shape change as seen in ethyl acetate. As shown in Fig. 13(a) and (b), the (110) and (11-2) faces feature exposed amine groups (-NH₂), especially capable of hydrogen bond donation. However, we suspect that the change in shape, as observed in ethyl acetate, is not due to hydrogen bonding as both acetone and acetone are also aporic hydrogen bond accepting solvents. Thus we suspect that the size of the ethyl acetate molecule leading to higher propensity for van der Waals bonding, is an important factor in explaining that shape is more influenced in ethyl acetate.

The absorption energy of solvent molecules on the salicylamide (110) surface, as obtained by Monte Carlo simulations is presented in Table 4. In agreement with the discussion above, it was found that EA is adsorbed strongest on the...
Fig. 13 Molecular representations of each of the crystal faces of salicylamide. Both 3D and 2D representations are shown for each surface: (a) (110), (b) (11-2), (c) (011), (d) (200), and (e) (002).

Table 4 Adsorption energy (kJ mol⁻¹) of one solvent molecule with the functional groups present on the (110) face of salicylamide SALMIDE®. Solvents investigated were ethyl acetate (EA), acetone (AC), acetonitrile (MeCN) and methanol (MeOH).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Adsorption energy (kJ mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl acetate</td>
<td>-48.78</td>
</tr>
<tr>
<td>Acetone</td>
<td>-42.99</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>-46.84</td>
</tr>
<tr>
<td>Methanol</td>
<td>-38.82</td>
</tr>
</tbody>
</table>

The (110) face with an adsorption energy of -48.78 kJ mol⁻¹, and the adsorption energy decreases in the order EA > AC > MeCN > MeOH. The adsorption of solvent molecules onto the crystal surface (110) is either by hydrogen bonding and/or van der Waals interaction, and is illustrated in Fig. 14. It was found that EA molecules adsorb embedded in the salicylamide molecule landscape by van der Waals bonding. MeCN also absorbs onto the (110) surface by van der Waals interactions alone however the adsorption energy is 7.4 kJ
mol$^{-1}$ (approx. 164%) lower than for EA. EA's molecular weight is over two times the weight of MeCN (88 g mol$^{-1}$ versus 41.95 g mol$^{-1}$ respectively) and EA accordingly covers a far larger surface area of the (110) face. On the other hand, AC adsorbs onto the (110) crystal face via van der Waals interaction and hydrogen bonding, and MeOH adsorption is dominated by hydrogen bonding. Hydrogen bonding is directional and leads to the molecule "sitting on top of" the surface rather than becoming embedded in the topology.
APPENDIX II

Conclusion

Salicylamide crystals grown experimentally were successfully face indexed using a combination of experimental and modelling techniques. Preferred orientation PXRD combined with predicted habit allowed for experimental confirmation of the (002), (200), (011) and (110) faces from real salicylamide crystals. Due to the changing nature of salicylamide crystals habit grown under the same conditions in different solvents, comparing calculated interfacial angles against experimental angles was found to be the most reliable and consistent method for face indexing. The salicylamide crystal habit is most greatly affected by EA as compared to the habit of its crystals grown in AC, MeCN and MeOH. The underlying reduction of the growth of the salicylamide (110) face is likely due to stronger van der Waals interaction of EA molecules with the crystal surface. The adsorption energy of MeCN on the (110) face is lower because the molecule is smaller, as is the adsorption energy of AC and MeOH in spite of their greater propensity for hydrogen bonding.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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