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Crystal growth kinetics of Piracetam polymorphs in ethanol and isopropanol

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Abstract

The crystal growth kinetics of two different polymorphs of Piracetam have been investigated in ethanol and isopropanol. Isothermal seeded desupersaturation experiments were carried out at supersaturation ratios below 1.2 within the range of temperature 283-308 K. Liquid concentration was determined by in-situ ATR-FTIR spectroscopy by a calibration free method using Principal Component Analysis. The power law equation, the BCF and the B+S models were fitted to the experimental desupersaturation data by non-linear optimization. The growth rates ranged $10^{-7}$-$10^{-8}$ m/s, the growth rate order is clearly higher than unity, and the activation energies are in the range 39-66 kJ/mol for all the systems studied suggesting surface integration control. The growth of the metastable polymorph is faster than that of the stable form in both solvents. The crystal growth proceeds faster in ethanol than in isopropanol for both polymorphs. The solid-liquid interfacial energy is lower for the metastable form, and is for both forms lower in ethanol than in isopropanol. The surface diffusion mass transfer rate is higher for the metastable form compared to the stable form and higher in ethanol than in isopropanol.

Keywords: Crystal growth, Piracetam polymorphs, kinetic modelling, interfacial energy

1. Introduction

70% of compounds produced globally in the chemical process industry appear as solids, and many are crystalline. Crystallization from solution as unit operation in chemical and pharmaceutical engineering is of utmost importance since the performance of crystallizers determine the required up- and downstream handling and processing operations. Often the crystallization process allows for obtaining of pure products (up to 99%) in a single step and it can be operated at moderate temperatures. From a mechanistic standpoint, crystallization is envisaged as a two-step process composed of crystal nucleation followed by crystal growth. These mechanisms are still insufficiently understood and as a consequence, the development of crystallization processes of an active
pharmaceutical ingredient (API) is usually based on trial and error experiments in laboratory and pilot scale.

Polymorphism has been the focus of continuous research because of its influence on the drugs physicochemical properties, process robustness and intellectual property rights. The stability of the different polymorphs of a compound directly influences their rate of dissolution, bioavailability and the ease of manufacturing and purification of the API. The organic solvent used in crystallization of an API influences the polymorphic outcome, and therefore, bioavailability, morphology and crystal size distribution of the product. The polymorphic outcome is the result of the nucleation and growth behavior of the different polymorphs of the compound. Several studies have been devoted to understand the nucleation properties and kinetics, but much less work has been done concerning the difference in growth behavior of polymorphs. In crystal nucleation, because of the lower interfacial energy it is expected that the metastable polymorph will nucleate preferentially over a more stable form in spite of the fact that the supersaturation with respect to the stable form is higher. Recently, Black et al. reported that the polymorphic outcome of a process can be due to differences in the growth behavior rather than simply reflecting differences in nucleation behavior. Interfacial energy is a key parameter also in surface integration growth theories like the BCF and the B+S. From that point of view, we may have reason to expect that not only the nucleation rate but also the growth rate of a metastable form is higher, even though a direct comparison of growth rates may suffer from that the governing faces are not the same. In spite of the importance of growth rate data for the understanding of polymorphic systems, there are with very few exceptions, no such data is reported in the literature. Determination of accurate growth rate data is difficult and for a metastable polymorph, the tendency for transformation into the stable one makes such determination particularly challenging.

Piracetam (PCM) or 2-oxo-1-pyrrolidine acetamide (Fig. 1) is a so-called ‘smart drug’ used as a nootropic agent for the enhancement of memory in human beings. Its effectiveness in the treatment of ischemia, cognitive impairment, stroke, and dementia without causing sedation or stimulation is recognized widely. Piracetam is a low molecular weight compound (M=142 g/mol) with acid/base neutrality. Hitherto, five polymorphs of PCM have been reported: FI (6.747), FII(6.403), FIII(6.525), FIV(8.954) and FV(6.390). The numbers within parentheses refers to the unit cell dimension along the A-axis measured in Å. Among them, FIII is stable at room temperature and FII is a metastable form.
Figure 1. Representation of 2D and 3D molecular structures of Piracetam (PCM).

The solubility of FII and FIII forms and their stability have been determined in a range of organic solvents \(^3,^{15}\). These two polymorphs constitute a monotropic system in the range 278-323 K, viz., their solubility curves do not cross. The solid state \(^{14}\), solution mediated \(^{16,17}\) and wet granulation induced \(^{18}\) polymorphic transformations of PCM have been investigated using various analytical techniques like in situ Raman spectroscopy, infrared spectroscopy (IR), powder X-ray diffraction (PXRD) and near infrared spectroscopy \(^{13,19}\). The metastable zone width of PCM in ethanol has been studied \(^{19}\) as well as the formation of PCM co-crystals with hydroxyl group functionalized carboxylic acids \(^{12}\). To the best of our knowledge, there is scanty information on crystal growth kinetics of polymorphic systems in general \(^{9,20}\), and no determination whatsoever of the crystal growth behaviour of PCM polymorphs.

This work provides a detailed study on the overall crystal growth kinetics of a metastable (FII) and the stable (FIII) polymorphs of Piracetam in two organic solvents. The main aim is to find out and assess quantitatively the factors influencing the overall crystal growth rate: solvent, temperature, supersaturation and polymorphic form, and to establish whether the metastable polymorph has a higher growth rate. The results are analysed by fitting of empirical power law– and mechanistic–based models, in order to rationalise the differences in growth behaviour between the two polymorphs, and the influence of solvent and temperature.

2. Theoretical background

The crystal growth process is normally assumed to be a process involving two steps in series: (i) transport of molecules from the liquid phase through the boundary layer surrounding the crystal – sometimes called the volume diffusion step, and (ii) the surface integration step. Surface integration includes i) the gradual desolvation of the molecule, ii) the transfer of the molecule from the point of arrival over the crystal surface (surface diffusion) and, iii) its lattice integration into a favourable location. The rate of surface integration depends on the presence of surface dislocations. According to the Burton, Cabrera, Franck (BCF) model (Eq. 1) \(^{21}\), believed to be dominating at moderate supersaturation, screw dislocations that form hillocks near equilibrium provide for a constant supply of growth steps whose rate of propagation determines the overall growth rate (spiral growth) \(^{22}\). The dislocation propagation depends on the step height, surface diffusion and the presence of surface
defects. The linear displacement of a growing face according to the BCF theory, \( G_{\text{BCF}} \), [m/s] is described by:

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

where \( S \) is the supersaturation ratio, \( c/c^* \) (being \( c \) the solute concentration and \( c^* \) the solubility at the crystal growth temperature). The parameter \( A \) (temperature-dependent) accounts for the crystal surface status (Eq. 2) and the parameter \( B \) (temperature-independent) incorporates physical properties of the crystal growth system (Eq. 3). In these equations: \( \Gamma^* \) is the solute molecular adsorption coverage, \( V_m \) is the solute molecular volume, \( \gamma_{sl} \) is the solid–liquid interfacial energy, \( x_s \) is the mean displacement of the adsorbed units over the surface, \( k \) is the Boltzmann constant, and \( D_{\text{surf}} \) is the surface diffusion coefficient of solute, which in turn is expressed by an Arrhenius type relation (Eq. 4).

\[
A = \frac{\Gamma^* D_{\text{surf}} V_m}{x_s^2}
\]  

(2)

\[
B = \frac{19V_m \gamma_{sl}}{2kx_s}
\]  

(3)

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

(4)

At higher levels of supersaturation, surface nucleation (two-dimensional) can occur at the edges, corners and on the faces, forming terraces that create new growth steps on the crystal surface. The outgrowth of new crystalline layers generated by this nucleation, which determines the growth rate of the face, is described by e.g. the birth and spread model (B+S) \(^{23}\), see Eq. 5.

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

(5)

where \( v_{\text{step}} \) is the rate of step advancement and \( B_{\text{step}} \) is the rate of two-dimensional nucleation. Analogously to the BCF model, the parameter \( C \) (Eq. 6) is considered as temperature-dependent through the inclusion of \( D_{\text{surf}} \) (Eq. 4), whereas the parameter \( D \) (Eq. 7) is temperature-independent. In these equations, \( h \) denotes the step height, \( \beta^* \) is a correction factor (\( \beta^* \leq 1 \)), and \( N_A \) is Avogadro’s number.

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

(6)
\[
D = \frac{\pi}{3} V_m h \left( \frac{\gamma_{sl}}{k} \right)^2
\]  

(7)

Growth mechanisms can occur simultaneously on a crystal face, may differ for different faces of the crystal, and can change over time depending on the conditions. Because of this complexity, often more simple empirical power law equations are used where the growth rate \(G\) is expressed as the rate of change with time of a characteristic linear dimension of the whole crystal \(L\); \(G=\frac{dL}{dt}\). Eq. 8 gives the typical functional form with the growth order parameter \(g\) and the kinetic constant \(k_g\), the former often assumed to be independent of temperature and the latter expected to follow an Arrhenius dependence (see Eq. 9). Generally, it is accepted that a \(g\) value clearly higher than unity indicates that the surface integration step is comparatively slow and even governing the crystal growth rate. The driving force will be represented by \((S-1)\) in the present work.

\[
G = \frac{dL}{dt} = k_g (S-1)^g
\]  

(8)

\[
k_g = k_{g0} \exp \left( \frac{-E_g}{RT} \right)
\]  

(9)

When nucleation, growth rate dispersion, agglomeration and breakage are all assumed to be negligible and the crystal shape is assumed to be constant (Haüy’s law), a mass balance can be applied for expressing how the desupersaturation in a batch crystallizer\textsuperscript{24,25} relates to size change of seed crystals \((\bar{L})\) (see Eq. 10). Thereby, from Eqs. 8-10 the variation of the average crystal length in a batch crystalliser during an isothermal seeded desupersaturation experiment can be described by an ordinary differential equation of the type of Eq. 11.

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

(10)

\[
\frac{dL}{dt} = k_{g0} \exp \left( \frac{-E_g}{RT} \right) \left[ \Delta c_0 - \left( \frac{\bar{L}}{L_0} \right)^3 - 1 \right] \left( \frac{W_0}{M} / c^* \right) \]  

(11)

where the units of concentration are \(g_{\text{solute}}/g_{\text{solvent}}\), \(W_0\) is the mass of seeded crystals, \(M\) is the mass of solvent and \(\bar{L}_0\) is the mean initial size of seed crystals.

Eq. 11 is developed by the use of an empirical power law equation to describe the growth rate \(G\). However, other growth rate expressions can be used such as the BCF or the B+S. The involved kinetic parameters in either mechanistic or empirical models can be determined by solving the corresponding differential equation analogous to Eq. 11 and subsequent optimization by non-linear regression.
of these cases, the crystal length at any instant ($\bar{L}$) is obtained through integration of the corresponding growth rate equation by:

$$\bar{L} = \bar{L}_0 + \int_0^t G((S-1)(t)) dt \quad (12)$$

3. Experimental Section

Seeded isothermal desupersaturation experiments have been performed for two Piracetam polymorphs, FII and FIII, in ethanol and isopropanol at six different temperatures. The solubility of FIII and FII of PCM in the studied solvents can be found elsewhere $^{3,15}$.

3.1. Solute and solvents used

Piracetam (PCM, 99.9% wt., CAS Number: 7491-74-9) was supplied by Baoji Guokang Bio-Technology Co., Ltd. (Baoji, China) complying with European Pharmacopoeia standards EP 6.0. PCM as shipped was characterized by optical microscopy (Olympus IX53), PXRD (PANalytical-Empyrean X-ray Diffractometer) and DSC (PerkinElmer Pyris 1 differential scanning calorimeter). As for the solvents used: methanol (MeOH, 99.99% GC, CAS Number: 67-56-1), ethanol (EtOH, 99.99% GC, CAS Number: 64-17-5), isopropanol (IPrOH, 99.98% GC, CAS Number: 67-63-0), and 1,4-dioxane (99.9% GC, CAS Number: 123-91-1) were all supplied by Fisher Scientific Ltd.

3.2. Preparation and characterization of seed material

Seed crystals were prepared in several batches that were carefully mixed as explained below, and the polymorphic purity was verified before their use as a source for seed material for the experiments. Pure FIII crystals were synthesized by cooling crystallization of commercial PCM dissolved in MeOH by adapting the procedure described elsewhere $^{19}$: 100 g of pure PCM were dissolved in 208.5 g of MeOH at 333 K and 250 rpm during 2 h using a 300 mL glass jacketed batch crystallizer. The solution was cooled to 293 K at 0.1 K/min and agitated for 4 h. Then, it was cooled further to 278 K at 0.1 K/min and agitated for 4 h. FII crystals were prepared by cooling crystallisation of commercial PCM dissolved in 1,4-dioxane following the procedure described elsewhere $^{14}$. The crystalliser temperature and the cooling rate were controlled by a chiller (Ecosilver RE-145, Lauda) filled with silicon oil. The obtained solids were isolated by vacuum filtration and dried overnight in an oven at 318 K.

The pure polymorphic FII and FIII seeds obtained were characterized by optical microscopy, DSC and PXRD. In order to isolate the desired seed size, the pure dried polymorphic seeds were sieved twice by five stainless steel woven wire cloth sieves, with square apertures of nominal sizes 25-50 µm, 50-100 µm, 100-180 µm, 180-250 µm and 250-400 µm. After sieving, the seeds were characterized
by SEM (SU-70 Hitachi) and the final particle size distribution and shape were determined (G3 morphology, Malvern Instruments, Ltd.). Guided by the result of some trial and error experiments, the seed size, amount of seeds and agitation rate in the growth experiments were set to avoid crystals growing more than 30% of the initial seed size and to ensure crystals being properly suspended from the bottom without excessive agitation. A more substantial size increase could lead to changes in the crystals shape violating the assumption of constant particle shape of Eq. 10. Thereby, a seed size fraction 100-180 µm was selected as the most suitable.

Fig. 2 plots the PXRD diffractograms and DSC scans of PCM as commercially shipped along with those of the pure polymorphic (FII and FIII) seeds prepared. As can be seen, commercial PCM was mostly composed of FIII. Reference PXRD diffractograms in Fig. 2a were generated through the .cif files BISMEV (FII) and BISMEV01 (FIII) from the Cambridge Crystallographic Data Centre (CCDC) using the software Mercury 3.9. FIII presents regions with well-resolved diffraction peaks with no overlapping over FII peaks at 17.5, 20.5 and 25.5 2θ, whereas FII presents characteristic diffraction peaks around 18.8 and 23.5 2θ. All the DSC scans in Fig. 2b followed the same sequence of endothermal events: the corresponding transformation of FII (onset at 109 °C) or FIII (onset at 120 °C) into FI, and the subsequent melting of FI (average onset of 152.8 °C). The derived enthalpy changes of these transformations were 3.0 and 3.3 kJ/mol for the solid transformations of FII and FIII into FI, respectively, and an average (over three values) ΔH for the FI melting of 25.8 kJ/mol. These results are in good agreement with the literature 14,26, where further detail related to the PXRD and DSC characterization of FII and FIII can be found. Based on this outcome, the recrystallization of the pure FII and FIII polymorphs was deemed successful.

Figure 2. (a) PXRD diffractograms for pure PCM FII and FIII from CCDC files and those obtained for commercial PCM and prepared FII and FIII seeds. (b) DSC scan of commercial PCM and synthesized FII and FIII seeds. Heating rate: 5 °C/min.

Fig. 3 shows the crystals size distribution (CSD) and optical microscope and SEM images give examples of prepared FII and FIII seeds. The size distribution (Figs. 3a and 3b) is unimodal for both polymorphs and the number average particle sizes (longest dimension measured for over more than...
75000 particles) were 127 and 145 μm for FII and FIII seeds, respectively. These values are close to the average of the nominal sieve openings of the upper and the lower sieve of the fraction used: 140 μm. It could be argued that the area average size or the mass averaged size27 would be a more appropriate representation of the mean. However, for these distributions, the difference to the number mean is less than 5%, which result in negligible differences in the estimation of kinetic parameters and growth rates. As shown, fairly similar size distributions were obtained for the FII and FIII seed particles after sieving. The photographs show the typical hexagonal habit of FIII and the rod-shape of FII, and that there is no significant agglomeration.

![Figure 3](image)

**Figure 3.** Crystal size distribution and shape images of (a) FIII and (b) FII seeds. Images from optical microscope of FIII (c) and FII (d) seeds. SEM images of single crystals of FIII (e) and FII (f) seeds.

### 3.3. Crystal growth experiments

All the experiments were carried out in a 500 mL jacketed glass crystallizer (OPTIMAX 1001, Mettler Toledo) equipped with overhead agitation and a high accuracy temperature control system. In-situ IR (ReactIR15, Mettler Toledo) and FBRM (Particle Track G400, Mettler Toledo) probes were connected to the crystallizer in order to monitor the liquid concentration, and the number of particles and their distribution, respectively, during the runs. Examples of recorded IR spectra are depicted in Fig. 4. The absence of overlapping between the characteristic absorbing IR carbonyl band of PCM (~1700 cm⁻¹) and those of each solvent, made the tracking of solute concentration by IR possible. In an attempt to use acetone as solvent, such overlapping made the tracking of solute concentration unfeasible.
As first step in the experimental procedure, a 250 mL saturated solution of PCM was prepared and filled into the crystalliser. The stirrer was switched on (190 rpm and upward flow), and the solution was heated 10 K above the saturation temperature for at least 60 mins. Preliminary experiments on the metastable zone width advised to limit the initial supersaturation ratio to 1.20 corresponding to a supercooling temperature of ~3 K. Once the solute was perfectly dissolved (constant and almost nil signal of the FBRM probe), the supersaturation was generated by cooling the solution rapidly to the desired crystal growth temperature (283, 288, 293, 298, 303 or 308 K). When the temperature was stable (constant intensity of the characteristic peak of PCM in the IR spectra; typically after 30 min), a previously weighed amount of seed crystals of the desired polymorph was added to the solution. This instant was considered zero time for all the runs. The experiments were monitored until a stable signal (a plateau) was obtained from IR, indicating that solubility had been reached. Fig. 5 plots typical FBRM and IR signals produced during a run. After seeding (Fig. 5a), no significant increase in the counts of different chord lengths validated that neither significant secondary nucleation nor agglomeration took place in any of the experiments. In addition, the chord length distribution shape was found to be maintained after seeding during the runs (Fig. 5b), indicating that growth of the seed crystals was the prevalent mechanism of supersaturation consumption.
After each experiment, the solution was filtered, and the harvested solids rapidly dried, weighed and characterized by optical microscope and PXRD to assure that no polymorphic transformation had occurred during the experiments. Repeatability was examined by running experiments on growth of FIII at 298 K in IPrOH in triplicate (see Supporting Information S1). A maximum experimental uncertainty of 2% was estimated under a 95% of probability level in terms of the calculated supersaturation ratio $S$.

Experimental conditions were selected to minimize the risk for polymorphic transformation from FII to FIII by limiting the upper temperature to 308 K and performing the experiments for a reasonably short time (less than 10 h at the lowest temperature and less than 2 h at the highest one). For comparison, the stability of FII in IPrOH and in EtOH at 323 K has been reported as 30 h and 2.5 h, respectively. PXRD diffraction patterns of the product crystals obtained for all the experiments conducted with FII seeds in EtOH and IPrOH are given in the Supporting Information S2. None of the PXRD patterns of the crystals harvested after growth experiments of FII in either EtOH or IPrOH exhibited characteristic diffraction peaks of FIII. Examples for comparison of the CSD of seed and harvested crystals are provided in the Supporting Information S2. The unimodal distribution was maintained during growth.

### 3.4. Data treatment and model fitting

Due to the relatively low solubility of PCM, the IR signals obtained presented some scattering, especially at low temperatures and in the case of IPrOH. Rather than using the absorbance at a given wavenumber, the information of the whole spectrum within a selected region (1600-1800 cm$^{-1}$) was used. For this purpose, the MATLAB function `pca` was used to apply principal component analysis (PCA) to the raw experimental IR data aiming to reduce the data dimensionality and scattering, and to express the inherent variation pattern. Typically, the first principal component was able to explain more than 95% of the system variance, but in some cases, the second principal component was needed to achieve such level of variability description. Once the IR absorbance signals had been expressed through the principal component scores, the data transformation into concentration was carried out by a calibration free method, as described elsewhere. This was possible due to the isothermal character of the growth experiments that allows for assuming linear relationship between measured IR absorbance and liquid concentration. It was preferred to use the data directly after PCA analysis instead of applying mobile averaging treatment to smooth the signals because that may lead to a bias analysis of the residuals caused by removing the signals natural noise.

A dedicated MATLAB script carried out the fitting to experimental desupersaturation data. The ordinary differential equations obtained for each model (power law, BCF, B+S) were solved using the
ode23tb function. Thereby, values of \( L = f(t) \) were generated, which in turn were used to calculate the estimated driving forces by Eq. 10. The minimization of the differences between estimated and experimental driving forces vs time was performed by the MATLAB function `lsqcurvefit`. The convergence into a global minimum was ensured by changing the initial values of the estimates by several orders of magnitude and confirming that the same result was produced. The uncertainty associated with the estimation of kinetic parameters for each model were estimated through the function `nlinparci` for a 95% of confidence interval. The correlation matrix for the estimates was calculated through the covariance matrix, which in turn was computed by the Jacobian matrix and its transpose.

4. Results

4.1. Evaluation using the power law equations

Fig. 6 shows the solution PCM concentration as obtained through the PCA analysis and the simple power law equation fits (Eq. 8) for the two polymorphs in EtOH and IPrOH, respectively. The power law equation fits the whole set of experiments very well. Owing to the relatively low solubility of PCM in the explored solvents (ranging 9.1-31.2 g_{PCM}/kg_{IPrOH} and 20.5-63.1 g_{PCM}/kg_{EtOH}), some level of scattering remained even after PCA treatment of the data, especially in IPrOH at lower temperatures, which made the evaluation of the IR signals more challenging.
**Figure 6.** Fitting of Eq. 8 to experimental desupersaturation data in terms of ($S$-$1$) for all the solvents and polymorphs studied at different temperatures. (a) EtOH-FII, (b) EtOH-FIII, (c) IPrOH-FII and, (d) IPrOH-FIII. Hollow circles correspond to the experimental data and solid lines to the fitting of Eq. 8.

The estimated parameters from Eq. 8 by non-linear regression are collected in Table 1 along with the uncertainties and the correlation coefficients associated with their estimation. Values of the rate constant, $k_g$, and of the growth exponent, $g$, are reasonable. $g$ values ranged from 1.32 to 1.70, suggesting that the crystal growth is at least partially controlled by the surface integration. This is supported by the well faceted observed crystal habits since diffusion controlled growth usually leads to rougher structures formed by adhesive growth, e.g. dendritic morphology. $k_g$ values are in the order of magnitude of $10^{-6}$-$10^{-7}$ and in general increase with temperature even though in some cases, it is difficult to ascertain a clear temperature dependence. The fairly high correlation coefficients reveal a significant correlation between $k_g$ and $g$ values that reduce the relevance and confidence of the particular parameter values and that of the activation energies that could be derived from them (Supporting Information S3).

**Table 1.** Estimated kinetic parameters, associated error under a 95% of confidence interval and correlation coefficient for FII and FIII PCM polymorphs in EtOH and IPrOH by fitting of Eq. 11.

<table>
<thead>
<tr>
<th>T K</th>
<th>$k_g\times10^6$ [m/s]</th>
<th>$g$</th>
<th>Corr.</th>
<th>$k_g\times10^6$ [m/s]</th>
<th>$g$</th>
<th>Corr.</th>
<th>$k_g\times10^6$ [m/s]</th>
<th>$g$</th>
<th>Corr.</th>
<th>$k_g\times10^6$ [m/s]</th>
<th>$g$</th>
<th>Corr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>283.15</td>
<td>1.19 ± 0.21</td>
<td>1.49 ± 0.05</td>
<td>0.99</td>
<td>0.28 ± 0.03</td>
<td>1.32 ± 0.05</td>
<td>0.98</td>
<td>0.15 ± 0.03</td>
<td>1.34 ± 0.05</td>
<td>0.99</td>
<td>0.97 ± 0.17</td>
<td>1.41 ± 0.07</td>
<td>0.99</td>
</tr>
<tr>
<td>288.15</td>
<td>2.10 ± 0.52</td>
<td>1.45 ± 0.06</td>
<td>0.99</td>
<td>0.73 ± 0.08</td>
<td>1.51 ± 0.04</td>
<td>0.98</td>
<td>0.61 ± 0.12</td>
<td>1.53 ± 0.05</td>
<td>0.99</td>
<td>4.11 ± 0.55</td>
<td>1.70 ± 0.05</td>
<td>0.98</td>
</tr>
<tr>
<td>293.15</td>
<td>5.34 ± 0.95</td>
<td>1.64 ± 0.05</td>
<td>0.99</td>
<td>1.49 ± 0.23</td>
<td>1.56 ± 0.06</td>
<td>0.98</td>
<td>0.42 ± 0.09</td>
<td>1.36 ± 0.06</td>
<td>0.99</td>
<td>3.93 ± 0.79</td>
<td>1.60 ± 0.08</td>
<td>0.99</td>
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<tr>
<td>298.15</td>
<td>3.73 ± 0.89</td>
<td>1.53 ± 0.07</td>
<td>0.99</td>
<td>2.82 ± 0.47</td>
<td>1.61 ± 0.06</td>
<td>0.98</td>
<td>1.40 ± 0.37</td>
<td>1.63 ± 0.08</td>
<td>0.99</td>
<td>4.84 ± 1.08</td>
<td>1.48 ± 0.08</td>
<td>0.99</td>
</tr>
<tr>
<td>303.15</td>
<td>2.94 ± 0.87</td>
<td>1.35 ± 0.09</td>
<td>0.99</td>
<td>2.63 ± 0.37</td>
<td>1.46 ± 0.05</td>
<td>0.98</td>
<td>2.14 ± 0.52</td>
<td>1.54 ± 0.07</td>
<td>0.99</td>
<td>4.66 ± 0.9</td>
<td>1.35 ± 0.07</td>
<td>0.99</td>
</tr>
<tr>
<td>308.15</td>
<td>6.25 ± 1.3</td>
<td>1.48 ± 0.07</td>
<td>0.99</td>
<td>4.12 ± 0.77</td>
<td>1.41 ± 0.07</td>
<td>0.98</td>
<td>2.01 ± 0.42</td>
<td>1.47 ± 0.07</td>
<td>0.99</td>
<td>13.84 ± 2.52</td>
<td>1.55 ± 0.07</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Accordingly, to extract activation energies and $g$ values of increased confidence, we fit Eq. 11 to the experiments at different temperatures for each polymorph/solvent system, simultaneously. The parameters obtained by the non-linear regression of Eq. 11, $k_{g0}$, $E_a$ and $g$, and the uncertainties associated with their estimation are given in Table 2. The corresponding correlation matrices between the estimates can be found in the Supporting Information S3. The correlation between $g$, and $k_{g0}$ or $E_a$ is remarkably low, but the correlation between $k_{g0}$ and $E_a$ is still significant. Different combinations of $k_{g0}$ and $E_a$ values can provide very similar objective function values. Since the activation energy is within an exponential term, small changes in activation energy correspond to massive changes in $k_{g0}$, which makes the reliability of $k_{g0}$ much less. This correlation known as compensation effect is often observed in the fitting of Arrhenius-like expressions and the problem is perhaps even bigger in the investigation of crystal growth rates since the experimental supersaturation and temperature ranges have to be quite narrow. Because of this uncertainty in the $k_{g0}$ values we should not read too much into these numbers.
Fig. 7 shows the result for each system, where solid lines are calculated from the model representation, and the data points represent a horizontal projection of the difference between the experimental supersaturation and the model fit. The functional form of the model provides an adequate representation of the influence of supersaturation and temperature on the growth rate for all four systems. The corresponding parity plots and residual analysis are included in the Supporting Information S3. The residuals are reasonably random and evenly distributed and the values are low. The growth rates are of the order $10^{-7}$-$10^{-8}$ m/s, being close to those typically reported in crystallisation $^{36}$ (please refer to Table S4 in Supporting Information for a compilation of growth rate values reported for several organic and inorganic crystallising systems). Such growth rates must be envisaged as averaged values for the seed particles CSD. At equal temperature and driving force, the growth rate for PCM in EtOH and IPrOH is significantly lower than those reported for the growth of salicylic acid $^4$ and salicylamide $^{37}$ (one order of magnitude) and paracetamol $^{24,38,39}$ (about the half) in organic solvents.

**Figure 7.** Crystal growth rate curves at different temperatures vs. supersaturation for the main four systems studied. (a) EtOH-FII, (b) EtOH-FIII, (c) IPrOH-FII and, (d) IPrOH-FIII. Hollow circles refer to experimental data and solid lines to the fitting of Eq. 11.
Table 2. Estimates obtained by fitting of Eq. 11 and associated error with their estimation within a 95% confidence interval for the two polymorphs studied in EtOH and IPrOH. $k_g$ denotes the average of the rate constants calculated for the interval 283-308 K. SSR refers to the sum of squared residuals.

<table>
<thead>
<tr>
<th>System</th>
<th>$k_{g0}$ [m/s]</th>
<th>$E_a$ [kJ/mol]</th>
<th>$g$</th>
<th>$k_g$ [m/s]</th>
<th>SSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOH-FII</td>
<td>15 ± 8</td>
<td>39.28 ± 1.37</td>
<td>1.35 ± 0.02</td>
<td>1.92·10^{-6}</td>
<td>0.0013</td>
</tr>
<tr>
<td>EtOH-FIII</td>
<td>259915 ± 85370</td>
<td>65.08 ± 0.79</td>
<td>1.40 ± 0.03</td>
<td>1.05·10^{-6}</td>
<td>0.0078</td>
</tr>
<tr>
<td>IPrOH-FII</td>
<td>12453 ± 4522</td>
<td>58.40 ± 0.94</td>
<td>1.41 ± 0.03</td>
<td>7.25·10^{-7}</td>
<td>0.0063</td>
</tr>
<tr>
<td>IPrOH-FIII</td>
<td>30777 ± 14854</td>
<td>62.25 ± 1.13</td>
<td>1.50 ± 0.03</td>
<td>3.84·10^{-7}</td>
<td>0.0707</td>
</tr>
</tbody>
</table>

Typical activation energies for diffusion controlled growth are ~10-20 kJ/mol, whereas those for surface integration are at ~40-60 kJ/mol \(^{40}\). Accordingly, the $E_a$ values estimated in this work suggest that growth of both PCM polymorphs in EtOH and IPrOH is surface integration controlled, which agrees with the interpretation of the $g$ values. The values determined for FIII are somewhat high, but considering that $E_a$ for the growth of sucrose crystals in water has been reported to range 70-80 kJ/mol \(^{41}\), and that for the growth of salicylic acid in ethyl acetate as 74.9 kJ/mol \(^4\), the values appear to be reasonable.

4.2. Evaluation by the BCF and B+S models

The Classical BCF and B+S growth rate models are developed based on a physicochemical interpretation of the detailed growth process, and as such when fitted to experimental data can provide some deeper understanding into the mechanisms. However, they are developed for growth of individual faces, while in this work experimental data refer to the overall growth of all crystal faces of a population of crystals having rather similar though not identical size and shape. As a consequence, the kinetic information derived from the application of these theories to the present experimental data should be envisaged as the average values of relevance to an industrial like situation. Eqs. 1-4 (BCF) or 5-7 (B+S), where adopted in the growth model, and examples of the fitting of the desupersaturation profiles are illustrated in Fig. 8. Both models fitted experimental data very well.
For the estimation of parameters in BCF and B+S models, non-linear regression was performed to obtain either $A$ or $C$ values at each temperature and the temperature-independent parameters $B$ or $D$ respectively. The seven parameters estimated in each optimization and their associated uncertainty are presented in Tables 3 and 4. The correlation coefficients for the estimation of either $A$ and $B$, or $C$ and $D$ were below 0.6 in all the cases (see Supporting Information S5), which increase the reliability of the estimated values. As for the fitting goodness, Fig. 9 shows the parity plots and in Supporting Information (Fig. S5) the corresponding residual distributions for each system at different temperatures are shown. Although overall the residuals are rather low and reasonably distributed, there are systematic deviations between each model and experimental data, i.e. a tendency to overestimate experimental driving forces at high supersaturation, and slightly underestimate the same at low supersaturation. The difference between the models is essentially negligible, and the fit is comparable to the performance of the power-law equation (Eq. 11).

Table 3. Estimated parameters and associated errors within a 95% confidence interval for the BCF model and all the systems studied. SSR refers to the sum of squared residuals.

<table>
<thead>
<tr>
<th>$A \cdot 10^6 \text{[K m/s]}$</th>
<th>EtOH-FII</th>
<th>EtOH-FIII</th>
<th>IPrOH-FII</th>
<th>IPrOH-FIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>283 K</td>
<td>0.239 ± 0.009</td>
<td>0.140 ± 0.003</td>
<td>0.054 ± 0.001</td>
<td>0.044 ± 0.0013</td>
</tr>
<tr>
<td>288 K</td>
<td>0.461 ± 0.024</td>
<td>0.224 ± 0.005</td>
<td>0.110 ± 0.003</td>
<td>0.089 ± 0.0030</td>
</tr>
<tr>
<td>293 K</td>
<td>0.607 ± 0.024</td>
<td>0.384 ± 0.011</td>
<td>0.137 ± 0.005</td>
<td>0.112 ± 0.0044</td>
</tr>
<tr>
<td>298 K</td>
<td>0.695 ± 0.020</td>
<td>0.613 ± 0.022</td>
<td>0.215 ± 0.005</td>
<td>0.168 ± 0.0075</td>
</tr>
<tr>
<td>303 K</td>
<td>0.931 ± 0.026</td>
<td>0.814 ± 0.031</td>
<td>0.388 ± 0.014</td>
<td>0.245 ± 0.0136</td>
</tr>
<tr>
<td>308 K</td>
<td>1.251 ± 0.031</td>
<td>1.298 ± 0.052</td>
<td>0.487 ± 0.015</td>
<td>0.416 ± 0.0267</td>
</tr>
<tr>
<td>$B \text{[K]}$</td>
<td>4.88 ±0.39</td>
<td>10.85 ± 0.67</td>
<td>4.71 ± 0.32</td>
<td>16.72 ± 1.22</td>
</tr>
<tr>
<td>$SSR$</td>
<td>0.0010</td>
<td>0.0091</td>
<td>0.0071</td>
<td>0.0800</td>
</tr>
</tbody>
</table>

Table 4. Estimated parameters and associated errors within a 95% confidence interval for the B+S model and all the system studied. SSR refers to the sum of squared residuals.

<table>
<thead>
<tr>
<th>$C \cdot 10^6 \text{[m/s]}$</th>
<th>EtOH-FII</th>
<th>EtOH-FIII</th>
<th>IPrOH-FII</th>
<th>IPrOH-FIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>283 K</td>
<td>0.139 ± 0.006</td>
<td>0.105 ± 0.002</td>
<td>0.033 ± 0.001</td>
<td>0.032 ± 0.001</td>
</tr>
<tr>
<td>288 K</td>
<td>0.259 ± 0.016</td>
<td>0.162 ± 0.005</td>
<td>0.068 ± 0.002</td>
<td>0.064 ± 0.002</td>
</tr>
<tr>
<td>293 K</td>
<td>0.369 ± 0.018</td>
<td>0.278 ± 0.010</td>
<td>0.084 ± 0.003</td>
<td>0.079 ± 0.003</td>
</tr>
<tr>
<td>298 K</td>
<td>0.447 ± 0.016</td>
<td>0.444 ± 0.019</td>
<td>0.142 ± 0.004</td>
<td>0.115 ± 0.005</td>
</tr>
<tr>
<td>303 K</td>
<td>0.611 ± 0.021</td>
<td>0.591 ± 0.027</td>
<td>0.251 ± 0.010</td>
<td>0.164 ± 0.009</td>
</tr>
<tr>
<td>308 K</td>
<td>0.873 ± 0.028</td>
<td>0.977 ± 0.048</td>
<td>0.326 ± 0.011</td>
<td>0.288 ± 0.019</td>
</tr>
<tr>
<td>$D \text{[K^2]}$</td>
<td>474.2 ± 44.9</td>
<td>1178.2 ± 83.0</td>
<td>526.5 ± 37.3</td>
<td>1659.6 ± 124.4</td>
</tr>
<tr>
<td>$SSR$</td>
<td>0.0018</td>
<td>0.0135</td>
<td>0.0089</td>
<td>0.0980</td>
</tr>
</tbody>
</table>
Figure 9. Parity plots for desupersaturation data obtained from (a) BCF and (b) B+S modelling for the whole set of experiments.

Using the $A$ and $C$ values of Tables 3 and 4, the activation energy of surface diffusion ($E_{a,\text{surf}}$) can be determined from the slope of the corresponding Arrhenius plots, see Fig. 10 and Table 5. The good linear relation between the values estimated from independent experiments support the reliability of the data and the robustness for capturing the temperature dependence in the parameter estimation. $E_{a,\text{surf}}$ values from BCF and B+S models are quite similar for each system and agree reasonably well with values given in Table 2, based on the power law equation, suggesting that the surface diffusion step is an important growth step. Only $E_{a,\text{surf}}$ for EtOH-FII is somehow lower than those reported for the rest of the systems (different slope) but there is also a bigger uncertainty. In addition, the intercepts obtained from both models are comparable in terms of relative order and magnitude. If $E_{a,\text{surf}}$ values in BCF and B+S models are obtained directly from non-linear regression (values, the associated uncertainty and their correlation are shown in the Supporting Information S5, Tables S5.3-S5.6), the $B$ and $D$ values, and $E_{a,\text{surf}}$ values are very similar to those reported in Tables 3, 4 and 5.

Figure 10. Arrhenius plot of the temperature dependent parameters of (a) BCF and (b) B+S models for the main system studied.

The solid-liquid interfacial energy $\gamma_{sl}$ can be estimated from the parameter $D$ in the B+S model, Eq. 7, by assuming the height of the growth step $h$ equal to the cubic root of the molecular volume $V_m$ of
PCM. The molecular volume of FII and FIII, respectively, were estimated as 134.24 and 136.27 Å³ by the Materials Studio 7.0 software using the .cif files BISMEV and BISMEV01 from the CCDC, respectively. Moreover, the mean diffusion distance over the surface \(x_s\) can be estimated from the parameter \(B\) in the BCF model (Eq. 3) using the previously determined \(\gamma_{sl}\). Finally, although \(D_{surf}\) cannot be determined from this analysis, the value of \(\Gamma^*D_{surf}\) can be calculated at different temperatures since \(\Gamma^*A_{surf}\) can be isolated by substituting Eq. 4 in Eq. 2 and using the intercept values \(I_{BCF}\) in Fig. 10a that equal to \(ln(\Gamma^*A_{surf}V_m/x_s^2)\). All computed data is given in Table 5. Please notice that the determination of the mean diffusion distance, \(x_s\), and the parameter \(\Gamma^*D_{surf}\) must be taken as crude approximations since the interfacial energy needed for these calculations is obtained from the B+S model, and it is not conceivable that both models are governing at the same time. However, (i) detailed data over the processes on the surface are very scarce, especially for crystals growing at industrial-like conditions, (ii) the interfacial energies obtained from the B+S model are very reasonable and should thus give reasonable surface transport parameter values, and (iii) both models do fit the experimental results very well. For these reasons, we do believe that the analysis has value as long as the numbers are treated with caution.

### Table 5. Estimated parameters from regression and associated standard errors for BCF and B+S models, and calculated surface topological parameters.

<table>
<thead>
<tr>
<th></th>
<th>EtOH-FII</th>
<th>EtOH-FIII</th>
<th>IPrOH-FII</th>
<th>IPrOH-FIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E_{a,surf}) (BCF) [kJ/mol]</td>
<td>43.80 ± 4.77</td>
<td>64.24 ± 2.13</td>
<td>63.19 ± 4.16</td>
<td>61.05 ± 3.87</td>
</tr>
<tr>
<td>(R^2) (BCF)</td>
<td>0.955</td>
<td>0.996</td>
<td>0.983</td>
<td>0.984</td>
</tr>
<tr>
<td>(I_{BCF})</td>
<td>3.53 ± 1.94</td>
<td>11.53 ± 0.87</td>
<td>10.19 ± 1.69</td>
<td>9.08 ± 1.58</td>
</tr>
<tr>
<td>(E_{a,surf}) (B+S) [kJ/mol]</td>
<td>49.77 ± 3.94</td>
<td>64.32 ± 2.01</td>
<td>65.73 ± 4.14</td>
<td>59.22 ± 4.28</td>
</tr>
<tr>
<td>(R^2) (B+S)</td>
<td>0.976</td>
<td>0.996</td>
<td>0.984</td>
<td>0.980</td>
</tr>
<tr>
<td>(I_{B+S})</td>
<td>5.49 ± 1.61</td>
<td>11.25 ± 0.82</td>
<td>10.78 ± 1.69</td>
<td>7.97 ± 1.74</td>
</tr>
<tr>
<td>(\gamma_{sl}) [mJ/m²]</td>
<td>1.12 ± 0.05</td>
<td>1.75 ± 0.06</td>
<td>1.18 ± 0.04</td>
<td>2.08 ± 0.08</td>
</tr>
<tr>
<td>(x_s) [m]</td>
<td>2.1·10⁻⁸</td>
<td>1.5·10⁻⁸</td>
<td>2.3·10⁻⁸</td>
<td>1.2·10⁻⁸</td>
</tr>
<tr>
<td>(\Gamma^*D_{surf}) (288 K) [molec./s]</td>
<td>1.31·10⁶</td>
<td>3.82·10⁵</td>
<td>3.71·10⁵</td>
<td>0.73·10⁵</td>
</tr>
<tr>
<td>(\Gamma^*D_{surf}) (298 K) [molec./s]</td>
<td>2.41·10⁶</td>
<td>9.39·10⁵</td>
<td>8.99·10⁵</td>
<td>1.73·10⁵</td>
</tr>
<tr>
<td>(\Gamma^*D_{surf}) (308 K) [molec./s]</td>
<td>4.28·10⁶</td>
<td>2.18·10⁶</td>
<td>2.06·10⁶</td>
<td>3.84·10⁵</td>
</tr>
</tbody>
</table>

The estimated interfacial energy \(\gamma_{sl}\) ranges from 1.12 to 2.08 mJ/m². These values are higher (2-4 times fold) than those reported for the growth of salicylic acid \(^4\) and salicylamide \(^37\) in organic solvents. The interfacial energy for 2-D nucleation in the B+S model, is expected to be lower than that for 3-D nucleation in the bulk solution. Keeping that in mind we note that the present interfacial energies are of the same order of magnitude as those determined for the nucleation of Paracetamol (1-3 mJ/m²) in water acetone mixtures \(^38\) and of Ketaprofen (1.47 mJ/m²) in acetone \(^8\), and are about half of those determined for nucleation of Eflicumbine polymorphs in ethanol and n-heptane mixtures \(^7\).
The approximated mean surface diffusion displacement, $x_s$, is found to be in the order $10^{-8}$ m and longer for the metastable polymorph. Theoretically at low supersaturation, all the units reaching the surface within a distance $< x_s$ from a step or kink will eventually be integrated into the crystal lattice\cite{23}. Accordingly, longer $x_s$ can be interpreted as higher propensity of molecules to be integrated into the lattice, leading to faster growth rates. Generally, the surface mass transfer rate in terms of $\Gamma^* D_{\text{surf}}$ was found to increase with temperature for all the systems studied, and decrease in the order EtOH-FII > EtOH-FIII > IPrOH-FII > IPrOH-FIII, in agreement with that observed for the kinetic parameters $A$ (BCF) and $C$ (B+S), respectively. Faster surface mass transfer leads to faster crystal growth rate.

5. Discussion

In Fig. 11a the crystal growth rates versus supersaturation in the four systems at 303 K are compared. This diagram is representative for the outcome at all temperatures revealing that the growth rate is higher (approx. double) for the metastable form, in both solvents and is higher in ethanol for both polymorphs. A similar magnitude in the difference in growth between polymorphs has been reported for Indomethacin crystals grown from the amorphous solid state\cite{9,20}, and for the growth of L-glutamic acid polymorphs from solution\cite{11}, being as far as we know the only studies where the growth rate of two different forms have been measured before. The influence of the solvent corresponds to previous findings\cite{17}, where it has been demonstrated by molecular modelling that PCM molecules form stronger interactions with IPrOH than with EtOH. In addition, the viscosity of IPrOH is almost double that of EtOH, and this increases the volume diffusion mass transfer resistance, and may somewhat contribute to the lower growth rate (Fig. 11).

The influence of the polymorph and the solvent on the growth is consistent with the interfacial energies determined (Table 5) and the average kinetic constants (Table 2). The interfacial energy is lower for the metastable form regardless of the solvent, in agreement with expectation, and previously reported for a few systems (Supporting Information S6). However, we believe that the present work for the first time verifies this relation for crystal growth from solution. The lower interfacial energy for the metastable form reflects in the higher crystal growth rate. For both polymorphs the interfacial energy is higher in IPrOH than in EtOH. However, the difference in interfacial energy between the polymorphs in the same solvent is clearly larger than that for the same polymorph in the different solvents. This is perhaps partly because the two solvents are quite similar.
Figure 11. Estimated growth rates vs. supersaturation at 303 K in terms of: (a) m/s and, (b) [kg/(m$^2$s)]. Hollow symbols are calculated values and solid lines are guide to the eye.

In the evaluation of BCF and B+S parameters it is assumed that the growth is governed by the surface integration step. This assumption is supported by growth orders ($g$ in Table 1 and 2) clearly exceeding unity and activation energies being quite high (Table 2). To add additional support to this assumption, the growth rate completely governed by volume diffusion control is estimated, and is compared with the experimentally determined growth rate. When surface integration is much faster than bulk diffusion, the concentration difference between the bulk and the interface approximately equals to $(c-c^*)=\Delta c$ and the volume diffusion controlled growth rate ($G_d$) can be estimated by a mass transfer analysis leading to Eq. 13:

$$G_d = k_d \frac{f_s M_w}{3 f_v \rho_c} (S-1) c^*$$  \hspace{1cm} (13)

The mass transfer coefficient, $k_d$, is estimated by the Sherwood correlation$^{42}$ (see Supporting Information S7), and is assumed to be equal for the two polymorphs. $f_s$ and $f_v$ are surface and volume shape factors, respectively, and $\rho_c$ the crystal density. Their determination is detailed in the Supporting Information S8. For FII, $f_v$ and $f_s$ values estimate to 0.146 and 2.051, respectively, whereas those for FIII were 0.224 and 2.232. As representative examples of all the results, in Fig. 12a, $G_d$, for the experimental conditions of IPrOH-FII is compared with the actual growth rate ($G$) derived from the experimental data by non-linear regression of Eq. 8.

Usually it is assumed that the resistance to volume diffusion mass transfer and the resistance to surface integration are acting in series. In order to assess the rate limiting step in the present work the diffusion control index ($q_D$) defined by Nielsen and Toft (1984) (Eq. 14)$^{13}$ is used. Its inverse equals the ratio of the growth rate when volume diffusion is entirely rate limiting to the growth rate measured experimentally. Accordingly, the range for $1/q_D$ values is from unity to infinity. For $1/q_D \approx 1$ the growth is entirely volume diffusion controlled. For gradually increasing values the surface integration becomes gradually more rate limiting.
\[
\frac{1}{q_D} = \frac{G_d}{G}
\]  

(14)

Figs 12b and c depict the variation of \(1/q_D\) with supersaturation over an experiment at 298 K for the systems studied. Early during the experiment at high supersaturation, there is obviously an influence of volume diffusion resistance but it rapidly decreases as supersaturation decreases and it is very much negligible towards the end of the experiment. Accordingly, this supports that the growth process overall is dominated by the surface integration resistance, being consistent with the power law activation energies ranging 39–65 kJ/mol and the growth exponents ranging 1.4–1.5. The ratio \(G_d/G\) is dependent on temperature, solvent and polymorphic form. Generally, the lower the temperature the higher the ratio \(G_d/G\), which makes perfect sense since the surface integration step is expected to have a stronger temperature dependence.\(^{40}\)

**Figure 12.** (a) Comparison of estimated growth rates from Eq. 8 and diffusion growth rates vs. \((S-1)\) IPrOH-FII system at different temperatures. For the main four systems studied: (b) Variation of the ratio \(G_d/G\) with \((S-1)\) at 298 K, and (c) Evolution of the ratio \(G_d/G\) at 298 K.

In the evaluation of growth rates (m/s) it is assumed that the crystal shape is constant. In doing so, the shape factor value actually cancel out and it may appear as if the shape does not matter. However, for comparison of the growth rate of particles having different habits, the shape aspect cannot be ignored, i.e. the overall linear growth rate of the two polymorphs is not completely comparable. Accordingly, for further analysis also the rate of mass deposition per unit surface area of the growing crystals (Eq. 16) is compared:

\[
R_g \left[ \frac{kg}{m^2 s} \right] = \frac{3fv\rho_c \left[ \frac{kg}{m^3} \right]}{fs} G[m/s]
\]

(16)
The calculated growth rates in terms of kg/(m²s) are illustrated in Fig. 11b. Compared to the data in Fig. 11a, the overall picture remains the same in that: i) the growth rate of the metastable polymorph at equal driving force is higher than that of the stable, ii) the growth rate for both forms is higher in ethanol compared to isopropanol and, iii) the differences decrease with increasing temperature (not shown). A collection of important properties of the two Piracetam polymorphs is provided in the Supporting Information Table S9.

5. Conclusions

Power law equations, and the BCF and B+S growth models fit the experimental desupersaturation data very well. Estimated crystal growth rates are in the order 10⁻⁷–10⁻⁸ m/s for all the systems studied. Power-law equation activation energies (39 – 65 kJ/mol) and growth exponents (1.4–1.5) suggest that the growth rate is dominated by the surface integration resistance, and this is supported by a boundary layer mass transfer rate analysis. Apart from the inherent dependence on supersaturation and temperature, growth kinetics are clearly dependent on the polymorphic form and the solvent. The growth of the metastable polymorph is faster than that of the stable form in both solvents studied. The growth rate of both forms is higher in ethanol compared to isopropanol. The solid-liquid interfacial energy is in the range 1.1–2.1 mJ/m² and is higher for the stable polymorph and for growth in isopropanol. The mean surface diffusion distances are in the order of 10 nm being systematically longer for the metastable form, in agreement with the higher mass transfer rate over the surface.

Acknowledgement

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Supporting Information

FIII. Compilation of data and properties for the stable (FIII) and metastable (FII) polymorphs of Piracetam.

**Notation**

**Abbreviations**

API  Active Pharmaceutical ingredient

B+S  Birth and Spread

BCF  Burton Cabrera Frank

CSD  crystal size distribution

EtOH  ethanol

FII  polymorphic form II

FIII  polymorphic form III

$I_{BCF}$  intercept of the linearization of parameter $A$ in BCF equation

$I_{B+S}$  intercept of the linearization of parameter $C$ in B+S equation

IPrOH  isopropanol

PCM  Piracetam

**Nomenclature**

$A$  parameter in BCF model [K m s$^{-1}$]

$A_{surf}$  pre-exponential factor of surface diffusion equation [m$^2$s$^{-1}$]

$B$  parameter in the BCF model [K]

$C$  parameter in the B+S model [m s$^{-1}$]

$c$  solution concentration [g$_{solute}$ g$_{solvent}^{-1}$]

$c^*$  solubility at a given temperature [g$_{solute}$ g$_{solvent}^{-1}$]

$D$  temperature in the B+S model [K$^2$]

$D_{surf}$  surface diffusion coefficient [m$^2$ s$^{-1}$]
\( E_a \)  activation energy in power law equation [kJ mol\(^{-1}\)]

\( E_{a,\text{surf}} \)  activation energy of surface diffusion of adsorbed molecules [kJ mol\(^{-1}\)]

\( f_s \)  area shape factor [dimensionless]

\( f_v \)  volume shape factor [dimensionless]

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

\( g \)  growth exponent in power law equation [dimensionless]

\( G_d \)  crystal growth rate under diffusion control [m s\(^{-1}\)]

\( G_s \)  crystal growth rate under surface integration control [m s\(^{-1}\)]

\( h \)  height of the growth step [m]

\( k \)  Boltzmann constant [m\(^2\) kg s\(^{-2}\) K\(^{-1}\)]

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

\( k_g \)  rate constant in power law equation [m s\(^{-1}\)]

\( k_{g0} \)  pre-exponential factor of rate constant in power law equation [m s\(^{-1}\)]

\( L \)  average crystal length [m]

\( M_w \)  molecular weight [g mol\(^{-1}\)]

\( R \)  gas constant [J mol\(^{-1}\) K\(^{-1}\)]

\( R^2 \)  determination coefficient [dimensionless]

\( R_G \)  overall crystal growth rate [kg m\(^{-2}\) s\(^{-1}\)]

\( S \)  supersaturation ratio [dimensionless]

\( S-1 \)  relative supersaturation [dimensionless]

\( SSR \)  sum of squared residuals [dimensionless]

\( T \)  temperature [K]

\( t \)  time [s]

\( V_m \)  molecular volume [m\(^3\)]
\[ x_s \]
mean diffusion distance on the Surface [m]

**Greek letters**

\[ \Gamma \]
concentration of adsorbed molecules on the surface [mol m\(^{-2}\)]

\[ \Gamma^* \]
equilibrium concentration of adsorbed molecules on the surface [molecules m\(^{-2}\)]

\[ \gamma_{sl} \]
Solid-liquid interfacial energy [mJ m\(^{-2}\)]

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

**References**


Crystal growth kinetics of Piracetam polymorphs in ethanol and isopropanol

Rodrigo Soto and Åke C. Rasmuson

The growth kinetics of a metastable and the stable polymorphs of Piracetam have been studied in ethanol and isopropanol. The growth rates and solid-liquid interfacial energies are strongly dependent on the solvent used and on the polymorph studied. It is found that the higher the polymorph solubility, the lower the solid-liquid interfacial energy and the faster the growth rate.