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Crystal growth kinetics of a metastable polymorph of Tolbutamide in organic solvents

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Abstract

The crystal growth of tolbutamide (Form I1) in different solvents has been investigated by isothermal seeded desupersaturation experiments at different temperatures (268-283 K). Experimental data has been evaluated using empirical power law equations and the mechanistic based models: Burton-Cabrera-Frank (BCF) and Birth and Spread (B+S). The estimated activation energies and growth exponents suggest a surface integration controlled growth as confirmed separately by a mass transfer analysis. From the B+S model, the estimated solid-liquid interfacial energies and the mean diffusion distances on the surface ranged 1.23-1.90 mJ/m² and 1-16 nm, respectively. The growth rate is strongly dependent on the solvent, decreasing in the order: acetonitrile > ethanol > ethyl acetate > n-propanol > toluene. The crystal growth becomes slower as the overall strength of the solute-solvent binding increases. This influence of the solvent corresponds very well with that found for nucleation of tolbutamide in the same solvents, and further supports the hypothesis that desolvation is an important step in crystallization. The similarity in the influence of the solvent on the kinetics of nucleation and growth very strongly supports the hypothesis that the solvent-solute interactions play an important role in the kinetics of formation of crystalline phases.
1. Introduction

Many active pharmaceutical ingredients (API) exhibit polymorphism and thus several solid forms of the same chemical compound are possible. In the last two decades, the number of studies devoted to polymorphism has increased drastically. The right choice of a polymorph for a given application is a key step in the drug formulation design since polymorphs may differ significantly in essential properties like solubility and thus rate of dissolution, stability, particle size distribution, melting point, ease of tableting and processability. Frequently, the most stable polymorph does not provide the optimum properties for drug formulation and metastable forms are considered. However, polymorphic transformations can be induced by heat, stress or solvent mediated processes. Studies on the nucleation and growth kinetics of polymorphic systems are indispensable to improve our understanding of polymorphism as well as to provide the necessary tools for controlling the polymorphic outcome. Surprisingly, relevant kinetic data are very scarce for such systems. One of the major constraints is the difficulty of studying nucleation and growth kinetics of metastable forms due to their tendency to transform into stable ones.

Crystal growth and nucleation are the two main processes involved in crystallization and they interact in a crystallizer contributing to the crystal size distribution of the solid. Even though progress has been made, there is still a lack of fundamental understanding especially with respect to larger molecules with conformational flexibility. For instance, it has been corroborated that the ease of nucleation of risperidone, salicylic acid, tolbutamide can be directly related to the strength of the solute-solvent binding in solution and that the polymorphic outcome can be predicted for isonicotinamide and prasugrel hydrochloride. It was revealed that the stronger the solvent binds to the solute, the slower the nucleation becomes and that the nature of the interactions, Van der Waals or hydrogen bonding, plays a fundamental role in the polymorphic outcome. However, nucleation kinetics are also influenced by the solution conformation of solute molecules with high flexibility and multiple functional groups.
Crystal growth rates depend on supersaturation, macro and microstructure of the crystal surface, degree of deformation of the lattice, solvent used and the presence of adsorbed or included impurities, and differ for different faces of the crystal and vary among the crystals in a larger population leading to size and shape distributions. Considering the fundamental mechanisms of crystal nucleation and crystal growth, both involve transport of molecules from the solution and integration into either a crystalline structure or a crystalline structure to be formed. Accordingly, it may be suspected that in some cases the growth behavior of a compound would show similarities to the nucleation properties. To our knowledge, there are only a few recent papers addressing this aspect, in spite of that such comparisons could promote a deeper understanding of crystallization kinetics. Macroscopic results from nucleation experiments must comprise the effects of both nucleation and growth yet the contribution of the latter is often neglected. In fact, the crystallization outcome may owe at least as much to their nucleation as to the relative crystal growth rate of available surfaces previously formed. It is reasonable that the nucleation and growth behavior in solution should be influenced by the same nature of solute-solvent intra and intermolecular interactions. It is then rational to expect that molecules with a relative ease of nucleation in a given solvent may also show a higher growth rate and vice versa.

In this study, Tolbutamide (TBM) has been chosen as model compound to investigate the crystal growth properties in different solvents. There is a previously published nucleation investigation revealing the ease of nucleation in different solvents, and basically finding a relation to the strength of solvent – solute interaction as determined by molecular simulations. With toluene as a clear exception, it is found that the stronger the solvent binds to the solute the more difficult the nucleation becomes. In toluene, the solvent-solute interaction is weak but conversely the nucleation is found to be more difficult than in any of the other solvents investigated. Based on molecular simulation conformational analysis, it is suggested that in toluene the tolbutamide molecule forms a particular intramolecularly hydrogen bonded conformation. This conformation is clearly different from that prevailing in the solid
crystalline structure and the required conformational transformation accordingly presents an additional barrier to the formation of the solid phase. If this explanation is correct, it is to be expected that also the crystal growth rate should be particularly slow in toluene, and to test this is one particular objective of the present study. The experimental work is evaluated by empirical and mechanistic models to extract statistically averaged kinetic parameters over the crystal growth process. Previous MD and DFT molecular modelling calculations are used to rationalize the growth results obtained and support a discussion on the relation to the corresponding nucleation kinetics.

Tolbutamide (C₁₂H₁₈N₂O₃S, N-[(butylamino) carbonyl]-4-methyl- benzenesulfonamide; 1-butyl-3-(p-tolylsulfonyl)-urea), see Figure 1, is an antidiabetic potassium channel blocker useful in the treatment of type 2 diabetes when diet treatment is ineffective. It is a sulfonylurea oral hypoglycemic medication that stimulates the pancreatic secretion of insulin¹² and controls the blood sugar levels.¹³ Hitherto, up to six different Tolbutamide polymorphs (FI₁, FI₂, FII, FIII, FIV and FV) have been reported owing to its high conformational flexibility.¹⁴,¹⁵ Forms FI-FIII maintain their crystals structure at room conditions and can be crystallized from solvents.¹⁶ FII is the most stable polymorph at room conditions and it transforms into FI₂ at approximately 380 K. The thin fiber needle-shape habit of FII make the industrial production of this polymorph unsuitable due to the downstream processing difficulty, e.g. filtration, drying, etc.¹³ FI₁ is the second more stable form at room conditions, it presents desired processability characteristics, and it transforms into FI₂ at low temperature (311 K). The interconversion, kinetic reversibility and structural similarities of FI₁ and FI₂ are the reasons for their special nomenclature.¹² FIII also transforms to FI₂ at 375 K and the melting of FI₂ is reported to occur at 401 K. FIV is an unstable form difficult to crystallize from solvents that can be prepared by spray drying and transforms to FII at high humidity conditions.¹⁶ FV is 1-D isostructural with FIV and converts to FI₁ at room conditions.¹⁷


2. Experimental section

In this work, isothermal seeded desupersaturation experiments have been performed to determine the crystal growth kinetics of Tolbutamide form I\textsuperscript{I} in different solvents. Moreover, the solubility of this form has been determined in several different solvents.

2.1 Chemicals

Tolbutamide (\textgreater 99.3\% wt., CAS Number: 64-77-7) was supplied by Changzhou Extraordinary Pharmatech Co., Ltd. (Changzhou, China) complying with European Pharmacopoeia standards EP 6.0. The purity was confirmed by HPLC (\textgreater 99.7\%, Supporting Information S1) using a Agilent 1200 Infinity series II equipped with an Eclipse plus C18 column, 4.6 x150 mm, of 5 \( \mu \)m pores and by DSC (PerkinElmer Pyris 1 differential scanning calorimeter), and no further purification was done. The polymorphic form was determined by PXRD (PANalytical-Empyrean X-ray Diffractometer) as being the metastable FI\textsuperscript{I} form. Regarding the solvents used acetonitrile (ACN, \textgreater 99.9 \%GC, CAS Number: 75-05-8), ethanol (EtOH, \textgreater 99.9 \%GC, CAS Number: 64-17-5), ethyl acetate (EA, \textgreater 99.9 \%GC, CAS Number: 141-78-6), 1-propanol (1-PrOH, \textgreater 99.9 \%GC, CAS Number: 71-23-8) and toluene (TOL, \textgreater 99.9 \%GC, CAS Number: 108-88-3) were all supplied by Fischer Scientific. Ltd. (Ireland). Some properties of the solvents and the drug used are listed in Table S1, Supporting Information. Among used solvents, 1-propanol presents the highest viscosity whereas ACN the lowest. Hildebrand solubility parameters (\( \delta \)) provide an estimation of the degree of solvation, being better as more alike are \( \delta \) of solvent and solute.
2.2 Solubility of tolbutamide polymorphs

The solubility of FII (stable) in the organic solvents of interest in the range 273-413 K was determined by Svärd et al. Moreover, Zeglinski et al. reported the solubility of the metastable polymorph FI in these solvents yet in a quite narrow range of temperature (275-280 K). In the crystal growth experiments, we aimed for a wide range of temperature and supersaturation to reduce the correlation between parameter values and reach as much numerical confidence as possible in the kinetic data determined. Consequently, further solubility data of FI was determined in a wider range of temperature.

An Easymax reactor equipped with a rack of three 30 mL reactors was used at 600 rpm for solid-liquid equilibration and the equilibrium solution concentration was determined gravimetrically. Excess FI was placed in 20 mL of solvent and let to equilibrate for at least 24 h at constant temperature. Then, stirring was switched off for 3 hours and aliquots (~2 mL) of the supernatant were taken, filtered (0.2 µm PTFE syringe filter), and transported to previously weighed evaporation vials. Then, the vials were weighed again and finally again after evaporation to complete dryness. In addition, the solid phase, at equilibrium were sampled, and analyzed by PXRD to ensure that no polymorphic transformation occurred during the solubility determination. The solubility $c^* (\text{g}_\text{solute}/\text{g}_\text{solvent})$ at each temperature was calculated by means of Eq. 1. The values determined in this work, always with standard deviation <5%, are gathered in Supporting Information S2. For comparison purposes, they have been plotted in Figure 2 along with those previously reported at 275-280 K. Solubility values were obtained in the range 268-283 K. Determination above 283 K or below 268 K (-5 °C) failed due to either polymorphic transformation or because the solid mass remaining after evaporation was too low to be accurately determined. As seen in Figure 2, FI solubility in toluene is one order of magnitude lower than the solubility in the rest of solvents. The highest solubility is found in EtOH.

$$c^* (\text{g}_\text{solute}/\text{g}_\text{solvent}) = \frac{m_{\text{vial+cap+solid}} - m_{\text{vial+cap}}}{m_{\text{vial+cap+solution}} - m_{\text{vial+cap+solid}}}$$ (1)
Figure 2. Solubility of tolbutamide FI\textsuperscript{L} in a range of organic solvents vs. temperature. Hollow symbols refer to the experimental values determined in this work and solid ones to those reported by Zeglinski et al. (2018). Dashed lines are guides to the eye.

2.3 Seed preparation and characterization

The polymorph FI\textsuperscript{L} was used as received. The forms FII and FIII were prepared by cooling crystallization in EtOH following the procedures specified by Hasegawa et al.\textsuperscript{16} When sufficient amounts of each polymorph were prepared, each batch was sieved at least three times by five stainless steel woven wire cloth sieves, with squares apertures of nominal sizes 25-50 µm, 50-100 µm, 100-180 µm, 180-250 µm and 250-400 µm. After sieving, the different polymorphs were characterized by optical microscopy (Olympus IX53), SEM (SU-70 Hitachi), Raman (Kaiser Raman RXN2), DSC (PerkinElmer Pyris 1 differential scanning calorimeter) and PXRD (PANalytical-Empyrean X-ray Diffractometer). Figure 3 illustrates some SEM micrographs at different magnification and further information can be found in the optical microscope micrographs in Supporting Information S3. FI\textsuperscript{L} crystals were well defined, homogeneous in shape and size exhibiting hexagonal-like habit (Figure 3a and d). Conversely, FII (Figure 3b and e) and FIII (Figure 3c and f) crystals prepared exhibited fiber-like or needle-shape habits, respectively. In both cases, significant aggregation occurred, especially for the FII crystals for which fibers joined to form entities of bigger size (Figure 3b), which made sieving very arduous.
Figure 3. SEM images of prepared TBM polymorphs. (a,d) FI\textsubscript{L}, (b,e), FII and (c,f) FIII.

X-ray diffractograms in Figure 4a confirmed the structural purity of each polymorph prepared. The parameters used in the analysis are detailed in the Supporting Information S3. The Cambridge Crystallographic Data Centre (CCDC) cif files: ZZZPUS18, ZZZPUS17, ZZZPUS15, ZZZPUS13, ZZZPUS07 and ZZZPUS10, are used for the polymorphs FI\textsuperscript{L}, FI\textsuperscript{H}, FII, FIII, FIV and FV, respectively. The characteristic diffraction bands of the metastable polymorph FI\textsuperscript{L} are around 20 and 21°, around 7 and 10° for the stable FII, and around 12.5, 18 and 24° for the metastable form III. The Raman spectra collected for each polymorph differ noticeably mainly in the form of single/double absorption peaks and peak shifts as highlighted in Figure 4b. The main differences between polymorphs are found at Raman shifts of 325, 600, 800, 945-960, 1065, 1120 and 1313 cm\textsuperscript{-1}. 
**Figure 4.** (a) PXRD of prepared tolbutamide polymorphs and comparison with the Cambridge Crystallographic Data Centre (CCDC) files. (b) Solid state Raman spectra of prepared tolbutamide polymorphs. Grey bands and black lights are guides to highlight the differences in Raman shift between polymorphs.

Figure 5a plots typical DSC thermograms obtained for the polymorphs prepared. On heating FI it transforms to FI (onset at 310.9 K) with an associated enthalpy change (endothermic) of 1.9 kJ/mol. Further heating leads to the melting of FI (onset at 402.2 K) with an enthalpy of fusion of 24.8 kJ/mol. On heating form II, it transforms to FI (onset at 387 K) with a related enthalpy change (endothermic) of 2.9 kJ/mol and subsequently FI melts (onset at 400.8 K and $\Delta H=22.4$ kJ/mol). Upon heating FII, an unexpected endothermic event occurred (onset at 310.5 K) with an associated endothermic enthalpy change of 0.25 kJ/mol followed by its transformation into FI (onset at 378.2 K, $\Delta H=0.44$ kJ/mol) and eventually the melting of FI (onset at 401.3 K, $\Delta H=24.1$ kJ/mol). According to literature, the unexpected endotherm at 310.5 K can be related to the rearrangement of hydrogen bonds in the molecule. A final melting temperature of 401.4 K of the form FI was estimated over 10 scans. The thermal events and values reported are in close agreement with previous studies.

The attempt of using the prepared FII and FIII seed material in growth experiments failed because of secondary nucleation immediately triggered as soon as the seeds were added to the crystallizer. Not even by tweaking experimental conditions, i.e. reducing the initial supersaturation and the amount of seeds, could avoid this behavior. This restricted the choice of seed polymorph to FI only.

The measured particle size distribution in terms of length and width for the FI seed material used in the seeded isothermal desupersaturation experiments is plotted in Figure 5b, where the background images illustrate examples of the crystals characterized in the G3 morphology system. As it can be seen, quite narrow and unimodal distributions were obtained, being also the particles homogenous in shape. An average length of 335.2 µm and width of 219.7 µm were determined over more than 14000 particles measured for six different
population/distributions of particles, and the width value is very close to the arithmetic mean of the upper and lower sieve opening nominal sizes (215 μm). Using the mass, area, and mean length obtained for the six distributions analyzed, the volume \( f_v \) and area \( f_s \) shape factors were estimated as \( 0.239 \pm 0.005 \) and \( 1.893 \pm 0.003 \), respectively. A crystallographic density \( \rho_c \) of 1.252 g/cm\(^3\) obtained by the corresponding CCDC reference was used. Supporting Information S4 shows the calculations performed, where excellent linear trends can be observed validating the procedure followed that is detailed elsewhere\(^{18}\).

![Figure 5](image)

**Figure 5.** (a) DSC scans of prepared TBM polymorphs. Heating rate: 10 K/min. (b) Particle size distribution and shape (background images) of the Tolbutamide FI crystals used as seed.

### 2.4 Isothermal seeded desupersaturation experiments

Supersaturated solutions (250 mL, i.d. = 77 mm) of TBM in ACN, EtOH, EA, 1-PrOH and TOL were prepared in a glass jacketed stirred tank reactor (Optimax 1001, Mettler Toledo) equipped with an accurate control of temperature. The initial supersaturation generated by cooling was carefully set to avoid the risk of secondary nucleation and the range of temperature studied was 268-283 K. In situ FBRM (Particle Track G400, Mettler Toledo) and IR (ReactIR15, Mettler Toledo) were connected to the crystallizer to track respectively the distribution of particles and the liquid concentration during the runs. When the crystallizer was at the growth temperature and the probe signals were stable, a previously weighed amount of seed material was added through one of the reactor head openings. This was considered as \( t = 0 \) of the growth experiments. The suspension was kept isothermal and agitated (270 rpm, upward flow and using a four bladed stainless steel 45° impeller of i.d.=40...
mm) until a plateau in the IR signal was observed, indicating that the solubility at the crystal growth temperature had been reached. Further details about the experimental procedure can be found elsewhere. Examples of the IR and FBRM signals collected are illustrated in the Supporting Information S5. After seeding, the constant number of counts indicated that neither significant agglomeration or breakage nor significant secondary nucleation occurred during the runs.

For the relation of IR signals with liquid concentration, the MATLAB function pca was used to apply principal component analysis (PCA) and thereby using information about the whole spectra rather than using a particular wavenumber peak value or a corresponding peak area. Finally, the liquid concentration was related to the PCA scores by a calibration free method since each experiment is carried out at constant temperature. Repeatability was evaluated by replication of the experiment in EtOH at 275 K. The supersaturation decay curves obtained after PCA overlapped almost perfectly, see Supporting Information S6. A maximum experimental uncertainty of 2% was estimated for a 95% probability level in terms of the calculated supersaturation ratio S. Therefore, the experiments and applied methodology were deemed reproducible and reliable.

It is to be noted that there are experimental challenges to the work performed. In example, the solubility in toluene is very low and only in-situ IR could track the progress in the experiments; in situ UV-VIS and Raman were not useful. Secondly, the tendency for polymorphic transformation limits solubility determination. Except for toluene and 1-propanol, solubility determination for the metastable polymorph above 283 K was not possible due to its transformation into the stable form in less than 7 h. Finally, in some of the solvents at 280 K, solution mediated polymorphic transformations from FI to FII were detected after few hours of experiments, which forced us to design less lasting experiments by adjusting the experimental conditions, i.e. initial supersaturation and seed loading. Such particular circumstances along with the secondary nucleation that occurred when using FII
and FIII seeds extremely narrowed the range of possible experimental conditions and restricted the framework of our investigation.

2.5 Evaluation of crystal growth rates

Crystal growth in supersaturated solutions is usually regarded as a process occurring in two steps in series: mass transfer through the fluid boundary layer sometimes referred to as volume diffusion, and integration into the crystal lattice called surface integration. However, besides the volume diffusion step, there are detailed phenomena like i) volume diffusion of solvated molecules through the adsorption layer, ii) surface diffusion of partially solvated and unsolvated molecules, iii) gradual desolvation of molecules, iv) integration of molecules into the crystal lattice, v) counter diffusion of released solvent molecules to the adsorption layer, and vi) counter diffusion of solvent molecules through the boundary layer.

Crystal growth kinetics can be described using different empirical and model based approaches. Empirical power law equations (Eqs. 2-3) are simple and applicable in a wide range of supersaturations but provide limited information about the growth mechanism and crystal surface features. Mechanistic models such as the Burton Cabrera Frank (BCF) and Birth and Spread (B+S) provide more information but their range of applicability is more restricted. The BCF (Eq. 4) or spiral growth model applies at moderate supersaturations whereas the B+S (Eq. 5) or two-dimensional nucleation model becomes more admissible at higher supersaturations. At much higher supersaturation, the crystal growth is controlled by the volume diffusion step (Eq. 6).

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

\[ G = k_s \exp\left(\frac{-E_g}{RT}\right)(S-1)^g \]
\[ G_{\text{BCF}} = \frac{AT}{B} (S-1)(\ln S) \tanh\left( \frac{B}{T \ln S} \right) \]  

(4)

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

(5)

\[ G_d = k_d \frac{f_s M_w}{3 f_v \rho_c} (S-1) c^* \]  

(6)

In eqs 2-6: \( k_{g0} \) is a rate constant pre-exponential factor; \( E_a \) is the activation energy; \( g \) is the growth exponent; \( A \) (Eq. 7) and \( C \) (Eq 9) are temperature dependent parameters; \( B \) (Eq. 8) and \( D \) (eq. 10) are temperature independent parameters; \( S \) is the supersaturation ratio \( (c/c^*) \); \( h \) is the step height; \( v_{\text{step}} \) is the step advancement rate; \( B_{\text{step}} \) is the two-dimensional nucleation rate; \( V_m \) is the molecular volume; \( \gamma_s \) is the solid-liquid interfacial energy; \( x_s \) is the mean diffusion displacement on the surface; \( \beta^* \) is a correction factor \( (\beta^*-1) \); \( \Gamma^* \) is the equilibrium concentration of surface adsorbed molecules; \( \Gamma \) is the concentration of surface adsorbed molecules; \( k \) is the Boltzmann constant; \( N_A \) is the Avogadro’s number; \( k_d \) is the mass transfer coefficient; \( f_s \) and \( f_v \) are respectively surface and volume shape factors; \( \rho_c \) is the crystallographic density; and \( D_{\text{surf}} \) is the surface diffusivity that is expressed by an Arrhenius like form (Eq.11).

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

(7)

\[ B = \frac{19V_m \gamma_s}{k x_s} \]  

(8)

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

(9)

\[ D = \frac{\pi}{3} V_m h \left( \frac{\Gamma^*}{k} \right)^2 \]  

(10)
\[ D_{\text{surf}} = A_{\text{surf}} \exp \left( \frac{-E_{a,\text{surf}}}{RT} \right) \]  

(11)

If nucleation, growth rate dispersion, agglomeration and breakage are assumed negligible and crystal shape is maintained constant (Haüy’s law), a mass balance can be used (Eq. 12) to express the decrease in supersaturation in a batch crystallizer as a function of the increase in size \( \langle L \rangle \) of seeded crystals.\(^{30}\)

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

(12)

The crystal length at any instant \( \langle L \rangle \) can be obtained by integration of the corresponding growth rate expression as:

\[ \langle L \rangle = L_0 + \int_0^t G((S-1)(t)) \, dt \]  

(13)

One of the Eqs. 2-5, is substituted into Eq. 13 and solved together with Eq. 12 in the fitting to the experimental desupersaturation data for determination of the growth kinetic parameters. The ordinary differential equation \( (dL/dt) \) can be solved using a proper computational method and allow for the estimation of the involved kinetic parameters in each of the models considered.

In order to reduce the correlation between estimated Arrhenius equation parameters\(^{31}\) equation 14 is adopted. The equivalence between rate constant expression in Eq. 3 and Eq. 14 is that the pre-exponential factor \( k_{g0} \) equals to \( \exp(k_{g1}E_a/R\bar{T}) \), whereas \( E_a \) has exactly the same meaning as in Eq. 3. \( \bar{T} \) is the mean temperature of the range explored.

\[ k_g = \exp \left( k_{g1} - \frac{E_a}{RT} \left( \frac{1}{T} - \frac{1}{\bar{T}} \right) \right) \]  

(14)

In this study, the ordinary differential equations were solved by scripts designed in MATLAB using the function \textit{ode23tb}. The minimization of the differences between experimental and
calculated driving forces was performed using the function *lsqcurvefit* and the errors
associated with the estimation of parameters were computed by the function *nlparci* for a 95%
of confidence interval. The correlation between estimates was estimated through the
covariance matrix. To ensure the convergence in a global minimum, the initial estimates
values were varied by several orders of magnitude.

### 2.6 Molecular modelling

The density functional theory (DFT) binding energies for the 1:1 API-solvent pair interactions
has been previously determined\(^6\) for all the solvents but ethanol. For tolbutamide-ethanol, the
corresponding calculation has been done in a similar way in this work. An API molecule was
extracted from the crystal lattice of its stable form crystal structure and optimized with a B97-
D3 Grimme’s functional,\(^{32}\) and a Gaussian-type 6-31G(d,p) basis set.\(^{33}\) The molecular
geometries changed only slightly upon gas-phase optimization, preserving the original
crystal-like conformation. The binding energy of the 1:1 API-ethanol dimer was calculated
for the lowest energy configuration, after probing molecular interactions. Single point
energies were calculated using a double hybrid B2PLYP-D3\(^{34}\) functional combined with an
exact Hartree Fock exchange with an MP2-like correlation and long-range dispersion
corrections with a basis set of quadruple-\(\zeta\) valence quality (def2-QZVPP).\(^{35}\) This
methodology has previously been successfully applied for small and medium-sized API
molecules.\(^5,36\) The binding energy was calculated as follows:

\[
\Delta E_{\text{bind}} = E_{A:B} - (E_A + E_B)
\]

(15)

where, \(E_{A:B}\) is the single point energy of the given API-ethanol dimer, while \(E_A\) and \(E_B\) are the
respective single point energies of the isolated monomers, A and B, in the gas phase.

### 3. Results and discussion

After each experiment, the PXRD of the grown Fl\(^1\) crystals showed that no polymorphic
transformation occurred during the runs, see *Supporting Information* S7. Figure 6 shows the
experimental desupersaturation profiles obtained along with the fitting of simple power law equation (Eq. 2). The obtained experimental desupersaturation curves have low scattering, and the power law equation provides an excellent fit. Estimated rate constants ($k_g$), growth exponents ($g$) and their correlation can be found in the Supporting Information S8. With the exception of toluene, the growth exponents were always above the unity in all the solvents suggesting that surface integration is at least partly the limiting step. $k_g$ values ranges $1.03 \cdot 10^{-8}$–$1.48 \cdot 10^{-6}$ m/s and decrease in the order ACN>EtOH>EA>1-PrOH>TOL. Except for the notably low values reported in toluene, estimated $k_g$ are about one order of magnitude lower than those determined for the growth of salicylic acid\textsuperscript{19} and salicylamide\textsuperscript{37} in organic solvents and comparable to those reported for the growth of Piracetam polymorphs\textsuperscript{18} in ethanol and isopropanol. The $k_g$ values generally increase with temperature but there are exceptions, which is ascribed to the high correlation in the estimation of $k_g$ and $g$, leading to uncertainty in the actual values.

**Figure 6.** Experimental and calculated desupersaturation data vs. time. (a) ACN, (b) EtOH, (c) EA, (d) 1-PrOH and (e) TOL. Hollow symbols refer to the experimental data and solid lines to the fitting of simple power law equation (Eq. 2).
By adoption of Eq. 3 and including the results of all temperatures simultaneously for
determination of three different parameters ($k_{gb}$, $E_a$ and $g$), the correlation problem can be
partly reduced. The results are given in Table 1 and the fitting goodness is illustrated in
Figure 7. In this graph, the deviations are represented as horizontal projection of the
differences between experimental and calculated driving forces for the same value of growth
rate calculated using the model estimated parameters. Further information about the fitting
can be found in Supporting Information S9 as the corresponding parity plots. The growth
rates are in the order $10^{-8}$ m/s, being comparable to those determined for the growth of
paracetamol in water/acetone mixtures, in acetone/toluene mixtures, in water/methanol mixes
and in ethanol. For a similar range of supersaturation, these values are also close to
the growth rates of piracetam in isopropanol and about one-two order of magnitude lower
than those estimated for the growth of piracetam in ethanol, the growth of salicylic acid and
salicylamide in organic solvents.

Figure 7. Crystal growth rate curves at different temperatures vs supersaturation for FI crystals
in the different solvents studied: (a) ACN, (b) EtOH, (c) EA, (d) 1-PrOH and (e) TOL. Hollow
symbols refer to experimental data and solid lines to the fitting of eq. 3 to the data at all
temperatures for each system.
In spite of the high uncertainty usually associated with the estimation of pre-exponential factors, $k_{g1}$ estimated values were quite reasonable being within the range $(-13.78)$ - $(-18.04)$ m/s and decreasing in roughly the same order to that observed for rate constants in Table S8. The activation energies are quite high being comparable to the typical values for a surface integration controlled growth (40-60 kJ/mol). Unavoidably, still high correlation coefficients remained for the estimation between $k_{g1}$ and $E_a$ in all the cases. In comparison to Eq. 2, the use of Eq. 14 allowed for some reduction of the correlation (from 0.99 to 0.67-0.98 depending on the system). The activation energies and the growth exponents estimated from both rate constant equations were almost identical, being only significant the differences of values estimated in toluene. The growth exponents were well above the unity, suggesting surface integration controlled growth in coherence with $E_a$ values. However, the growth exponent of 0.66 estimated for toluene was an outlier suggesting significant contribution of external mass transfer to the overall growth rates. Accordingly, further analysis is advisable to clarify the rate-limiting step in toluene. The ranking of average rate constants ($k_g$) derived from the estimated parameters decreased in the order ACN>EtOH>EA>1-PrOH>TOL, being very similar to that reported in Table S8 for the fitting of simple power law equation and coinciding with that of $k_{g1}$ values. The main difference is the position switch between EA and EtOH.

**Table 1.** Estimates obtained from fitting of complete power law equation of the form $G=k_{go}\exp(-E_a/RT)\cdot(S-1)^g$ or of the form $G=\exp(k_{g1}\cdot E_{a1}/R(1/T-1/T_{mean}))\cdot(S-1)^{g_1}$. Errors refer to a 95% probability level and SSR refers to the sum of squared residuals.

<table>
<thead>
<tr>
<th></th>
<th>ACN</th>
<th>EtOH</th>
<th>EA</th>
<th>1-PrOH</th>
<th>TOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{g0}$ [m/s]</td>
<td>-13.78 ± 0.07</td>
<td>-14.65 ± 0.05</td>
<td>-14.28 ± 0.04</td>
<td>-15.19 ± 0.03</td>
<td>-18.04 ± 0.01</td>
</tr>
<tr>
<td>$k_{g1}$ [m/s]</td>
<td>13.32 ± 0.92</td>
<td>(4.49 ± 0.22)·10^5</td>
<td>(6.14 ± 0.26)·10^5</td>
<td>41.93 ± 1.32</td>
<td>(6.05 ± 0.06)·10^4</td>
</tr>
<tr>
<td>$E_a$ [kJ/mol]</td>
<td>37.5 ± 2.0</td>
<td>63.0 ± 1.6</td>
<td>72.7 ± 1.4</td>
<td>45.2 ± 0.08</td>
<td>83.1 ± 9.8</td>
</tr>
<tr>
<td>$E_{a1}$ [kJ/mol]</td>
<td>37.4 ± 2.0</td>
<td>63.3 ± 1.6</td>
<td>73.7 ± 1.5</td>
<td>43.6 ± 0.8</td>
<td>67.7 ± 2.7</td>
</tr>
<tr>
<td>$g$ [-]</td>
<td>1.47 ± 0.03</td>
<td>1.53 ± 0.02</td>
<td>1.66 ± 0.02</td>
<td>1.42 ± 0.01</td>
<td>0.74 ± 0.04</td>
</tr>
<tr>
<td>$g_1$ [-]</td>
<td>1.47 ± 0.03</td>
<td>1.54 ± 0.02</td>
<td>1.66 ± 0.02</td>
<td>1.42 ± 0.01</td>
<td>0.66 ± 0.01</td>
</tr>
<tr>
<td>$k_g$·10^6[m/s]</td>
<td>1.061</td>
<td>0.463</td>
<td>0.720</td>
<td>0.263</td>
<td>0.015</td>
</tr>
<tr>
<td>SSR</td>
<td>0.008</td>
<td>0.068</td>
<td>0.059</td>
<td>0.048</td>
<td>0.148</td>
</tr>
<tr>
<td>SSR$_t$</td>
<td>0.008</td>
<td>0.068</td>
<td>0.059</td>
<td>0.048</td>
<td>0.045</td>
</tr>
</tbody>
</table>

*a* $k_g$ refers to the average rate constant calculated for the range of temperature studied for each solvent using the equation $k_g=k_{g0}\exp(-E_a/RT)$. 

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Parameters estimated by fitting the BCF (Eq. 4) and B+S (Eq. 5) equations are given in Table 2 along with the error associated with their estimation. The parity plots can be found in the Supporting Information S9. The correlation coefficients between the estimates were always below 0.80, which increases the reliability of the estimated values. The temperature dependent parameters $A$ and $C$ decreased in the same order as the rate constants previously presented, in agreement with their direct proportionality with growth rates. The activation energies of the surface diffusion ($E_{a,surf}$) determined by plot of either $\ln A$ or $\ln C$ vs. $1/T$ are gathered in Table 3. Good linear relations were obtained in all the cases, please refer to Supporting Information S9, confirming the ability of both mechanistic models to account for the kinetic effect induced by changes in temperature. Comparable $E_{a,surf}$ values were estimated from both models, being also in agreement with those determined from the power law equation modeling and suggesting that surface diffusion is an important step in the growth process. For toluene, $E_{a,surf}$ values are apparently high, since the influence of temperature is very strong.

**Table 2.** Estimated parameters and associated errors within a 95% confidence interval for the BCF and B+S models and all the systems studied. $SSR$ refers to the sum of squared residuals.

<table>
<thead>
<tr>
<th></th>
<th>ACN</th>
<th>EtOH</th>
<th>EA</th>
<th>1-ProOH</th>
<th>TOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A \cdot 10^6$ ([K·m/s])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>268 K</td>
<td>0.278 ± 0.010</td>
<td>0.086 ± 0.002</td>
<td>0.100 ± 0.002</td>
<td>0.092 ± 0.005</td>
<td>–</td>
</tr>
<tr>
<td>275 K</td>
<td>0.347 ± 0.012</td>
<td>0.143 ± 0.004</td>
<td>0.186 ± 0.012</td>
<td>0.147 ± 0.007</td>
<td>–</td>
</tr>
<tr>
<td>277 K</td>
<td>0.483 ± 0.018</td>
<td>0.243 ± 0.011</td>
<td>0.297 ± 0.019</td>
<td>0.176 ± 0.012</td>
<td>0.014 ± 0.001</td>
</tr>
<tr>
<td>280 K</td>
<td>0.540 ± 0.034</td>
<td>0.277 ± 0.011</td>
<td>0.303 ± 0.013</td>
<td>0.180 ± 0.006</td>
<td>0.028 ± 0.002</td>
</tr>
<tr>
<td>283 K</td>
<td>–</td>
<td>–</td>
<td>0.248 ± 0.011</td>
<td>0.043 ± 0.005</td>
<td></td>
</tr>
<tr>
<td>$B$ [K]</td>
<td>13.25 ± 1.17</td>
<td>18.64 ± 0.99</td>
<td>26.31 ± 2.32</td>
<td>30.77 ± 1.83</td>
<td>316.4 ± 6.31</td>
</tr>
<tr>
<td>$SSR$</td>
<td>0.011</td>
<td>0.070</td>
<td>0.103</td>
<td>0.079</td>
<td>0.083</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ACN</th>
<th>EtOH</th>
<th>EA</th>
<th>1-ProOH</th>
<th>TOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C \cdot 10^6$ [m/s]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>268 K</td>
<td>0.198 ± 0.009</td>
<td>0.064 ± 0.002</td>
<td>0.082 ± 0.002</td>
<td>0.049 ± 0.001</td>
<td>–</td>
</tr>
<tr>
<td>275 K</td>
<td>0.245 ± 0.009</td>
<td>0.098 ± 0.003</td>
<td>0.099 ± 0.005</td>
<td>0.076 ± 0.002</td>
<td>–</td>
</tr>
<tr>
<td>277 K</td>
<td>0.337 ± 0.015</td>
<td>0.153 ± 0.006</td>
<td>0.163 ± 0.010</td>
<td>0.110 ± 0.006</td>
<td>0.014 ± 0.001</td>
</tr>
<tr>
<td>280 K</td>
<td>0.333 ± 0.022</td>
<td>0.187 ± 0.008</td>
<td>0.202 ± 0.007</td>
<td>0.113 ± 0.003</td>
<td>0.029 ± 0.002</td>
</tr>
<tr>
<td>283 K</td>
<td>–</td>
<td>–</td>
<td>0.150 ± 0.004</td>
<td>0.0511 ± 0.008</td>
<td></td>
</tr>
<tr>
<td>$D$ [K²]</td>
<td>1258.3 ± 124.6</td>
<td>1574.1 ± 85.8</td>
<td>1806.0 ± 85.5</td>
<td>2102.6 ± 74.3</td>
<td>2994.9 ± 94.3</td>
</tr>
<tr>
<td>$SSR$</td>
<td>0.016</td>
<td>0.103</td>
<td>0.156</td>
<td>0.100</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Note: the data for EtOH at 275 K corresponds to the average of the replicated experiments.
The solid-liquid interfacial energy ($\gamma_{sl}$) can be calculated by Eq. 10 using the estimated $D$ values, see Table 3. In doing so, the molecular volume ($V_m$) and surface area of FI$^1$ were estimated to 242.56 Å$^3$ and 303.67 Å$^2$, respectively, using the software Materials Studio 7.0 and the corresponding .cif file (ZZZPUS18). Further details on the molecular geometry optimization and $V_m$ calculations can be found in the Supporting Information S12. The height of the growth step $h$ was assumed to be ($V_m$)$^{1/3}$. The estimated $\gamma_{sl}$ ranged 1.23(ACN)–1.9(TOL) and increased in the opposite order to that determined for rate constants in Table 1. This makes perfect sense since the higher the solid-liquid interfacial energy the slower the expected crystal growth kinetics according to the models. In comparison, $\gamma_{sl}$ values are higher (2-4 fold) than those estimated for the growth of salicylic acid$^{19}$ and salicylamide$^{37}$ in organic solvents and similar to those estimated for the growth of Piracetam polymorphs$^{18}$ in ethanol and isopropanol.

### Table 3. 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>ACN</th>
<th>EtOH</th>
<th>EA</th>
<th>1-PrOH</th>
<th>TOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{a,\text{surf}}$ (BCF) [kJ/mol]</td>
<td>35.31 ± 8.33</td>
<td>63.34 ± 5.72</td>
<td>61.86 ± 10.93</td>
<td>39.53 ± 4.06</td>
<td>121.9 ± 18.2</td>
</tr>
<tr>
<td>$E_{a,\text{surf}}$ (B+S) [kJ/mol]</td>
<td>29.34 ± 9.42</td>
<td>56.92 ± 10.71</td>
<td>47.06 ± 15.14</td>
<td>46.5 ± 5.34</td>
<td>138.8 ± 7.2</td>
</tr>
<tr>
<td>$\gamma_{sl}$ [mJ/m$^2$]</td>
<td>1.23 ± 0.06</td>
<td>1.38 ± 0.04</td>
<td>1.47 ± 0.03</td>
<td>1.59 ± 0.03</td>
<td>1.90 ± 0.30</td>
</tr>
<tr>
<td>$x_s$ [m]</td>
<td>1.55·10$^{-8}$</td>
<td>1.23·10$^{-8}$</td>
<td>9.35·10$^{-9}$</td>
<td>8.63·10$^{-9}$</td>
<td>1.01·10$^{-9}$</td>
</tr>
<tr>
<td>$\Gamma^*_{\text{surf}}$ (268 K) [molec./s]</td>
<td>2.75·10$^5$</td>
<td>5.36·10$^4$</td>
<td>3.60·10$^4$</td>
<td>2.83·10$^4$</td>
<td>–</td>
</tr>
<tr>
<td>$\Gamma^*_{\text{surf}}$ (275 K) [molec./s]</td>
<td>3.44·10$^5$</td>
<td>8.93·10$^4$</td>
<td>6.72·10$^4$</td>
<td>4.51·10$^4$</td>
<td>–</td>
</tr>
<tr>
<td>$\Gamma^*_{\text{surf}}$ (277 K) [molec./s]</td>
<td>4.79·10$^5$</td>
<td>1.52·10$^5$</td>
<td>1.07·10$^5$</td>
<td>5.41·10$^4$</td>
<td>5.77·10$^1$</td>
</tr>
<tr>
<td>$\Gamma^*_{\text{surf}}$ (280 K) [molec./s]</td>
<td>5.35·10$^5$</td>
<td>1.73·10$^5$</td>
<td>1.09·10$^5$</td>
<td>5.51·10$^4$</td>
<td>1.18·10$^2$</td>
</tr>
<tr>
<td>$\Gamma^*_{\text{surf}}$ (283 K) [molec./s]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>7.62·10$^4$</td>
<td>1.77·10$^2$</td>
</tr>
</tbody>
</table>

In a previous study about the nucleation of FI$^1$ in the same solvents$^6$ (excepting EtOH), $\gamma_{sl}$ values were extracted using the classical nucleation theory. These values follow essentially the same order as those herein obtained for crystal growth, see Figure 8. As observed in other studies,$^{19,37}$ the interfacial energies from crystal growth experiments are lower than those derived from nucleation experiments. This is very much what is to be expected. In growth by the Birth and Spread mechanism new growth layers are initiated by a 2-D nucleation on the
surface, while primary nucleation in solution involves a 3-D nucleation. In growth, the nucleation is facilitated by the presence of the crystal surface, and that is the reason why it occurs at a lower driving force than that required for primary nucleation in solution.

![Interfacial energy comparison](image.png)

**Figure 8.** Comparison of interfacial energies determined from nucleation and growth for Tolbutamide FI in organic solvents. Nucleation data from Zeglinsky et al. (2018). Note that $\gamma_d$ data in EtOH from nucleation was not available.

Estimated $x_s$ values vary between 1-16 nm and decreased in the order ACN > EtOH > EA > 1-PrOH > TOL, which coincides with that determined for growth rate constants. This is coherent since longer $x_s$ indicate a higher probability of molecules to become surface integrated, which in turn leads to faster growth rates. The mass transport parameter $\Gamma*D_{surf}$ was found to increase with temperature and to decrease in the same order as $x_s$, which also makes sense since it is known that surface diffusion is enhanced with temperature and that faster surface mass transfer is reflected into faster crystal growth rates. As discussed elsewhere, the values of $\Gamma*D_{surf}$ and $x_s$ (Table 3) have to be regarded as overall averages, since the growth rate concerns the overall increase in crystal size, not the growth rate of a particular face. They should also be treated with caution since we do make use of data from both theories simultaneously.

Although in most of the cases the estimated growth exponents and activation energies suggest surface integration controlled growth, there are some cases, e.g. toluene, for which a separated mass transfer analysis is advisable to confirm the rate-limiting step. The diffusion control index ($q_0=G/G_d$) defined by Nielsen is useful for assessing the governing mechanism during a growth experiment in which volume diffusion and surface integration are
assumed to proceed in series. It is defined as the ratio of the experimentally derived growth rate to that derived from a fully volume diffusion controlled growth (Eq. 5). $1/q_D$ approaches unity for a volume diffusion governed growth, and increases as the growth is controlled by surface integration. The procedure followed for the estimation of mass transfer coefficients is detailed in Supporting Information S13. As an example, Figure 9 plots how $1/q_D$ at 280 K changes over the experiments. $1/q_D$ was always higher than unity and increased with time in all the solvents, confirming that surface integration is controlling also in toluene. Such confirmation increase the reliability in the estimated values in BCF and B+S models and ensures that a comparison of the growth rates obtained in each solvent is rigorous since the same mechanism is in control.

![Figure 9](image_url)

**Figure 9.** Evolution of the ratio $G_d/G$ during the runs at 280 K for all the solvents studied.

Figure 10 compares the F1 growth rates obtained in the range of supersaturation studied at 277 K, being in agreement with the rest of temperatures at which data is available for all the solvents, see Supporting Information S11. The growth rates decrease in the order ACN>EtOH>EA>1-PrOH>TOL, in agreement with the order of the rate constants determined for the power law equation and that of the surface mass transport parameter $\Gamma D_{surf}$ and that of the solid-liquid interfacial energies. Mass transfer coefficients are expected to increase with decreasing solvents viscosity, and notably the rank of growth rates differs from that of solvent viscosity (Table S1) and $k_d$ estimated values (see Supporting Information S13), further
reinforcing that the growth is not mass transfer controlled. In addition, the growth rate order with respect to the solvent differ from the solubility order (Figure 2).

![Graph showing growth rates vs supersaturation for different solvents at 277 K and 280 K.](image)

**Figure 10.** Comparison of the growth rates obtained by fitting of Eq. 2 vs supersaturation for the solvents studied at (a) 277 K and (b) 280 K.

The tolbutamide molecule has an amphiphilic character where the center of the molecule features a hydrophilic sulfonylurea comprising two sulfone oxygens and one carbonyl oxygen. The carbonyl, sulfanyl and amide groups of tolbutamide provide both hydrogen bond donor and acceptor capacity. In fact, each tolbutamide molecule in the optimized unit cell of Fi can interact with neighboring molecules by six hydrogen bonds, as presented in Figure S12. The toluene and n-butane end groups of the tolbutamide molecule are predominantly hydrophobic and non-polar, and hence expected to render much weaker interactions. Both polar aprotic solvents, acetonitrile and ethyl acetate, with the former being more polar than the latter due to larger dipole moment, possess only hydrogen bond accepting functionality. On the other hand, ethanol and n-propanol are polar protic solvents possessing both hydrogen bond donor and acceptor capacity, whereas toluene is a non-polar solvent without hydrogen bonding capability. Acetonitrile and ethyl acetate are weak electron donors but the latter presents a stronger chemical similarity with tolbutamide by a centric polar group surrounded by non-polar regions. The aromatic ring of toluene is also a weak electron donor and can form a comparatively weak bond with a hydrogen of an electron acceptor through H-π (π) interaction.
The 1:1 binding between the solute and the solvent has been analysed for three different specific sites on the tolbutamide molecule surface as illustrated in Fig 11. Site 1 exposes the hydrogen bond donating functionality of the amide groups. Site 2 has the hydrogen bond accepting functionality in the two sulfone oxygens and the carbonyl oxygen. Site 3 is the nonpolar aromatic end group. For four of the solvents the binding energies have been estimated by DFT calculations in previous work. For ethanol the binding energies have been determined in the present work. The results are given in Table 4 - the solvents arranged in the order of increasing interfacial energy as determined in the present growth work. For all solvents the binding is the strongest to Site 1, at the amide groups and in particular the bonding to acetonitrile and ethyl acetate is strong. For Site 2 the protic alcohol solvents clearly have the strongest bonding.

![Figure 11](image.png)

**Figure 11.** Tolbutamide molecule sites to which solvents binding energy of molecular interactions (1:1) are evaluated (top). Resulting interactions with optimized geometry of EtOH molecule with each site (bottom).

**Table 4.** Binding energies calculated by DFT for optimized geometry of tolbutamide-solvent systems at different molecule sites.

<table>
<thead>
<tr>
<th></th>
<th>Site 1</th>
<th>Site 2</th>
<th>Site 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>-38.5</td>
<td>-15.2</td>
<td>-17.4</td>
</tr>
<tr>
<td>Ethanol</td>
<td>-31.9</td>
<td>-25.3</td>
<td>-16.2</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>-41.1</td>
<td>-18.0</td>
<td>-13.1</td>
</tr>
<tr>
<td>1-Propanol</td>
<td>-34.6/34.4</td>
<td>-25.2</td>
<td>-18.1</td>
</tr>
<tr>
<td>Toluene</td>
<td>-22.8</td>
<td>-10.1</td>
<td>-7.1</td>
</tr>
</tbody>
</table>

*Data determined in this work. Rest of data is extracted from J. Zeglisnki et al. (2018)*.

While the interaction of four of the solvents with the different sites has been discussed previously, the data for ethanol are new for the present work. The molecular modelling
results for ethanol are consistent with those previously reported for the rest of solvents. The interaction of ethanol with polar site 1 is weaker than those of acetonitrile, ethyl acetate and n-propanol. At polar site 2, the interaction is stronger than those of ACN and EA but comparable to that of n-propanol. Ethanol interaction with site 3 refers to the interaction of OH hydrogen with the π cloud of electrons of the aromatic ring of tolbutamide. It is well known that H-π interactions are weaker than hydrogen bonds. Considering that in a bulk solution the overall interaction strength refers to the sum of all interactions, the lower overall strength of the interaction at polar site 1 with ethanol may explain why Fl crystals grow significantly faster in ethanol in comparison to n-propanol and to ethyl acetate. For acetonitrile, the fact that interaction at site 2 is significantly weaker than in the rest of the solvents except in toluene, may suggest that this site is important for the overall growth rate in this solvent, in which the growth is the fastest.

Because of the broad range of properties of the solvents and of the tolbutamide sites, there is no particular site interaction that can fully explain the order of the solvents with respect to the tolbutamide growth rate. However, as an example the sum of the binding energies of sites 1 and 2, for four of the solvents provides a nice correlation with the growth rates, as is illustrated in Figure 12. In toluene, the growth rate is remarkably slow in spite of the weakest binding to all three sites compared to the other solvents. In the previous nucleation work, it was found that the nucleation was much more difficult in toluene compared to in the other solvents. A conformational analysis was performed, and the results suggested that specifically in toluene the tolbutamide molecule, because of an intramolecular hydrogen bonding, may obtain a conformation that is very different from that found in the crystal structure. The conformational transformation required along the pathway from being solvated by toluene in the solution to being integrated into the crystal structure would significantly slow down the process. If the hypothesis is correct for the slow nucleation in toluene, it is to be expected that also the crystal growth in toluene would be particularly slow, and that is exactly what has been shown in the present work.
As previously reported, it has been found for solute-solvent system of salicylic acid,\textsuperscript{5} risperidone,\textsuperscript{4} fenoxycarb\textsuperscript{42} and tolbutamide,\textsuperscript{6} that the rate of nucleation can be related to the strength by which the solvent binds the solute molecule in solution. The stronger the solvent–solute binding, the more difficult the nucleation becomes, suggesting that desolvation is an important step in formation of the nucleus. In recent work, it has further been found for salicylic\textsuperscript{19} acid and for salicylamide\textsuperscript{37} that there may be a similarity in the nucleation and growth properties of a crystalline phase. The results of the present work give further support to this.

As shown above, the interfacial energies determined from nucleation of tolbutamide FI\textsuperscript{1} in the same solvents\textsuperscript{6} and from the crystal growth data presented in this work, are well correlated. Furthermore, as is shown in figure 13, the driving force required to reach a certain nucleation induction time increased in the order ACN< EA< 1-PrOH < TOL, and this is exactly the same order found in the present work for decreasing crystal growth rate. In the figure is plotted the crystal growth rate in four of the solvents (since ethanol was not included in the nucleation study) at four different conditions in terms of temperature and supersaturation, versus the driving force required to reach a 2 h crystal nucleation induction time depending on the solvent. The figure clearly shows that in a solvent where the nucleation is easy the crystal growth is fast and vice versa. To be noted is that the nucleation data are systematic with

\textbf{Figure 12.} Growth rates at 277 K and (S-1)=0.07 vs. sum of binding energies of sites 1 and 2 for the polar protic and polar aprotic solvents evaluated.
respect to the influence of the solvent such the order does not depend on the selected induction time.

Except for toluene the crystal growth rate decreases as the solute-solvent binding energy increases. The fact that toluene having the weakest binding energy to tolbutamide, is having the slowest nucleation and crystal growth is very strongly evidencing the relation between nucleation and crystal growth, however also revealing that other factors besides desolvation can have a strong influence on the crystallization kinetics. As a final remark, perhaps the link established between nucleation and crystal growth can contribute to the question of the importance of crystal growth in the investigation of crystal nucleation rates.

![Graph](Figure 13. Growth rates at different supersaturations and temperatures vs. nucleation driving forces for an induction time of 2h. Nucleation data is extracted from Zeglinski et al. (2018). Dashed lines are guide to the eye.)

5. Conclusions

The crystal growth rates of the tolbutamide FI polymorph have been studied in a range of organic solvents, and power law empirical equations and the mechanistic BCF and B+S models can be well fitted to the experimental desupersaturation data. Activation energies and growth exponents suggest surface integration controlled growth as confirmed by a separate mass transfer analysis. From the fitting of the B+S model, the solid-liquid interfacial energies
have been found to vary from 1.23 to 1.90 mJ/m², depending on the solvent. The estimated
mean diffusion distances on the surface range from 1 to 15 nm and are also consistent with
how the growth rate depend on the solvent.

The crystal growth of the tolbutamide FI polymorph decreases in the order acetonitrile >
ethanol > ethyl acetate > 1-propanol > toluene. This order is in good agreement with how the
nucleation difficulty differs depending on the solvent as established in previous work. There
is also a good correlation between the interfacial energy determined from the present crystal
growth work, and the interfacial energies determined in the previous nucleation investigation,
the latter being higher than the former as expected. The DFT calculated solute-solvent
binding energies of the solvent to different sites on the tolbutamide molecule surface, reveal
that the growth rate decreases with increasing binding energy. Toluene is a clear exception
from this having the lowest binding energy to all the sites but is also the solvent where the
growth rate is the slowest. However, this low growth rate is in agreement with the low
nucleation rate in toluene. The proposed explanation for the latter is based on the formation of
a particular intra-molecular hydrogen bonded conformation in solution, and that should be
equally valid for the low growth rate. The results suggest that desolvation is not only a
governing step in crystal nucleation but also in crystal growth, and that also other features of
the solvent-solute interaction may have a similar influence on both nucleation as well as on
crystal growth.

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Associated content. Supporting Information.

Characterization of commercial tolbutamide and properties of solvents used. Solubility of
TBM-FIL. Optical microscope images of tolbutamide polymorphs prepared and further
characterization details. Estimation of volume and area shape factors. Examples of IR and
FBRM signals obtained during a typical growth experiment. Reproducibility of the isothermal
seeded desupersaturation experiments. Characterization by PXRD of harvested crystals after

References


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Crystal growth kinetics of a metastable polymorph of Tolbutamide in organic solvents

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The crystal growth of tolbutamide (Form II) in different solvents has been investigated by isothermal seeded desupersaturation experiments at different temperatures (268-283 K) and initial supersaturations. The estimated growth rates decrease in the order: acetonitrile > ethanol > ethyl acetate > n-propanol > toluene. The crystal growth becomes slower as the overall strength of the solute-solvent binding increases.