Characterization and Crystal Nucleation Kinetics of a New Metastable Polymorph of Piracetam in Alcoholic Solvents

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ABSTRACT: A new polymorph of the drug active pharmaceutical ingredient piracetam (Form VI) has been discovered and characterized by X-ray powder diffraction (PXRD), solid-state Raman, attenuated total reflectance infrared spectroscopy, and differential scanning calorimetry. The PXRD diffractogram of Form VI shows a distinct peak at 24.2° (2θ) that distinguishes it from the previously known polymorphs and solvates. Form VI is metastable with respect to the previously known polymorphs Form II and Form III; in ethanol solution at 288 K, Form VI transforms into Form II within 15 min, while in isopropanol solution Form VI is kinetically stable for at least 6 h. A total of 1200 crystal nucleation induction time experiments of piracetam in ethanol and isopropanol solutions have been conducted, in sets of 40−80 repeat experiments carried out at different temperatures and solute concentrations. Each solution nucleated as a single polymorph, and each set of repeat experiments resulted in different proportions of Form II, Form III, and Form VI, with Form VI dominating at low nucleation temperatures and Form II at higher nucleation temperatures. The induction time data for Form VI at 288 K have been evaluated within the framework of the classical nucleation theory. At equal driving force, nucleation of Form VI is less obstructed in ethanol than in isopropanol, as captured by a lower interfacial energy and higher pre-exponential factor in ethanol. The proportion of Form VI obtained at a comparable driving force increases in the order ethanol < isopropanol.

1. INTRODUCTION

Crystallization from solution is a common unit operation in the pharmaceutical industry. In crystallization processes, primary nucleation is of crucial importance for the resulting product properties. The fundamental mechanisms underlying nucleation are not well understood; thus, nucleation tends to be unpredictable. Controlling nucleation is necessary to control particle size, size distribution, and polymorphic form, which is further affected by many factors, such as temperature and supersaturation.1,2 Different solid forms can lead to variations in product performance, such as solubility, dissolution rate, or tablet hardness. Polymorphism can lead to dramatic effects in biological activity between two forms of the same drug. In 1999, Griessler and Burger reported that out of 953 drug molecules tested, more than 59% are known to exist in more than one crystal form.3 During the late 20th and early 21st centuries, many drugs were recalled4,5 in the United States and Europe because of the unexpected appearance of a new polymorph, e.g., Ritonavir (Norvir) and Rotigotine (Neupro).

In polymorphic systems, the overall effect of the solvent on nucleation can be very important for the outcome.6−12 Davey et al. explored the link between supramolecular structuring in solution and the polymorph nucleating from different solvents, for the compound 2,6-dihydroxybenzoic acid.7 Gracin et al.13 in a study of p-amino benzoic acid, an enantiotropic polymorphic system, showed that the influence of the solvent on nucleation could be explained by analyzing the crystal structure and the possible solute−solvent interactions in the solution. Chiarella et al.14 in another nucleation study of inosine with a combination of computational and experimental tools explored the relationship between the solution-phase inosine species and the structural synthons present in its crystal structures. Overall, the mechanisms behind the influence of the solvent are insufficiently understood, and the polymorphic outcome cannot be predicted. Thus, more studies are required to understand these mechanisms, which can differ greatly between different systems.

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Piracetam (PCM, 2-(2-oxopyrrolidin-1-yl)-acetamide), shown in Figure 1, is a nootropic agent used for memory enhancement in humans. Piracetam is approved in many European countries for myoclonus and aging-related conditions like Alzheimer’s disease. It is an effective drug for memory dysfunction, alcoholism, Raynaud’s phenomenon, deep vein thrombosis (DVT), stroke, tardive dyskinesia, dyslexia, brain injury, and vertigo. Previously five polymorphic forms of piracetam have been reported, but two of these (Form IV (8.954) and Form V (6.390)) have only been obtained at high-pressure (>0.5 GPa) conditions. The remaining three polymorphs (Form I (6.747), Form II (6.403), and Form III (6.525)) have been identified and structurally characterized under ambient conditions. For clarity, the numbers within parentheses refer to the unit cell dimension along the A-axis in Å. The trimorphic thermodynamic stability relationship is rather complex, which despite being well-studied is not completely elucidated. Out of the three polymorphs, Form I is unstable below 383.15 K and can be isolated only by heating Form II or Form III to 400 K and then quenching to room temperature, which however typically leads to transformation back to Form II within a few hours. Form I is thus not of much practical relevance. At ambient temperature, Form II is metastable, and Form III is the stable polymorph. Form I and Form III are enantiotropically related, with a reported transition temperature at 393 K. The solubilities of Form II and Form III have been determined in a range of organic solvents together with an investigation into the polymorphic transformation behavior. These studies have shown that there is no transition in stability between these two polymorphs over the temperature range 278–323 K. Kuhnert-Brandstatter et al. have proposed that all three polymorphs are enantiotropically interrelated, with Form II and Form III having a transition temperature greater than 348.15 K, but because both forms tend to transform to FI at high temperatures, there is only indirect experimental evidence for the existence of such a transition temperature. In addition to the anisotropic forms, crystallization experiments in water have revealed the existence of a monohydrate form of piracetam, as well as a dihydrate form that has however only been obtained at high pressure.

Various analytical techniques like powder X-ray diffraction (PXRD), in situ energy dispersive X-ray diffraction, in situ Raman spectroscopy, infrared spectroscopy (IR), and near-infrared spectroscopy have been used to investigate the solid-state, solution-mediated, and wet granulation-induced polymorphic transformations of piracetam. Recently, our group published a detailed study on the crystal growth kinetics of the metastable Form II and the stable Form III in two organic solvents. However, to the best of our knowledge, no crystal nucleation induction time study of piracetam has been reported so far.

During preliminary nucleation experiments in ethanol and isopropanol, a new crystal polymorph (Form VI) was encountered. The new Form VI has been characterized using X-ray powder diffraction (PXRD), Raman spectroscopy, attenuated total reflectance infrared spectroscopy (ATR-IR), and differential scanning calorimetry (DSC). A total of 1200 isothermal nucleation induction time experiments have been performed under different conditions of temperature and concentration, resulting in Form VI nucleating in the majority of cases. The solubility of Form VI has been determined by a gravimetric method, and the nucleation parameters of the new polymorph were determined in ethanol and isopropanol.

2. EXPERIMENTAL SECTION

2.1. Materials. Piracetam (PCM Form III, 2-(2-oxopyrrolidin-1-yl)-acetamide, 99.9% wt., CAS number 7491-74-9) was supplied by Baoji Guokang Bio-Technology Co., Ltd., Baoji, China, complying with European Pharmacopeia standards EP 6.0. The solvents used were ethanol (EtOH, 99.8% GC, CAS number: 64-17-5), and isopropanol (IPrOH, 99.98%GC, CAS number: 67-63-0), both supplied by Fisher Scientific Ltd. All chemicals were used as received without further purification.

2.2. Polymorph Characterization. PXRD, solid-state Raman spectroscopy, differential scanning calorimetry (DSC), and ATR-IR have been used to characterize Form III (as received), Form II, and Form VI (obtained in nucleation experiments). Crystals of the three polymorphs have also been characterized using optical microscopy (Olympus X53) and scanning electron microscopy (JEOL JCM-5700). Transmission powder X-ray diffractograms were recorded using an Empyrean diffractometer (Malvern PANalytical Ltd.) with Cu Kα, radiation (λ = 1.5406/1.5444 Å) operating at 40 kV and 40 mA at room temperature. Samples were scanned from 13° to 35° (2θ) with 0.006°/min step size and 48.19 s per step, on a flat stage that was spinning at 4 rpm on transmission mode. Reflection X-ray powder diffractograms were recorded using an Empyrean diffractometer (Malvern PANalytical Ltd.) with Cu Kα, radiation (λ = 1.5406 Å) operating at 40 kV and 40 mA at room temperature. Samples were scanned from 13° to 35° (2θ) with 0.026°/min step size and 112.97 s per step, on a flat stage that was spinning at 4 rpm on reflection mode. Ex situ Raman spectroscopy was performed using a probe Mettler Toledo spectrometer. For each spectrum, five scans were collected for 30 s each from 4000 to 100 cm⁻¹ at 1 cm⁻¹ resolution using iCRaman software v4.3. Ex situ infrared spectroscopy was performed using a PerkinElmer Spectrum One spectrophotometer with an ATR accessory equipped with a ZnSe sample plate. For each spectrum, four scans were collected from 4000 to 650 cm⁻¹ at a resolution of 4 cm⁻¹. DSC was performed using a Netzsch Polyma DSC 214 instrument, with Concovus Al pans with pierced lids. All runs were performed at a heating rate of 10 K min⁻¹ heating rate, from 293 K to 443 K.

2.3. Induction Time Experiments. Initially, 240 induction time experiments (Set I) were carried out at different solute concentrations and temperatures in the range 283.15–298.15 K in ethanol only, with 40 repeat experiments at each condition. The concentration and temperature combinations were selected somewhat arbitrarily, with the primary goal to find a suitable basis for an investigation into the kinetics of nucleation of piracetam. A further 960 induction time experiments (Set II) were then carried out at 288.15 K in ethanol and isopropanol, with 80 repeat experiments at each condition, to estimate the interfacial energy, pre-exponential factor, and solubility of the new polymorph.

An agitation rate of 200 rpm was used in all the experiments. Temperature control and agitation were achieved using thermostatic water baths (Grant, GR150-S26 stirred with pump and a C2G cooling unit) equipped with submersible multipole magnetic stirrer plates. The experiments were carried out in batches of 40 simultaneous
induction time experiments, in glass vials (VWR, 70.5 × 27.5 mm). Two water baths, each with a submersible 20-plate magnetic stirrer plate, were set at the nucleation temperature, and one water bath with a submersible 40-plate magnetic stirrer plate was used for dissolution. For the nucleation experiments, all the 40 vials were moved from the high-temperature water bath to the low-temperature water baths (20 vials in each bath). The vials were recorded using a high-definition camera (Sony HDRXS20VE). The visible onset of nucleation was characterized by a sharp transition from a clear to a completely opaque solution within 5–10 s. The induction time was taken as the time interval between the insertion of a vial into the bath at the nucleation temperature and the first change noticed in the sample, as observed by the naked eye from the camera. As soon as each specific vial had visibly nucleated, the suspension was filtered using a ~2 min using a filter paper (Whatman), and the solids were dried on the filter paper at room temperature for 24–72 h in a laboratory fume hood to complete dryness. The samples were then analyzed for the polymorphic form using PXRD and Raman spectroscopy, with the dried powder samples used directly with only light or no grinding to avoid polymorphic transformation. From each sample, at least 3 days or until all solvent had evaporated, as verified by regular recording of the initial weights. Once dry, the final mass of each vial was recorded, and the solution concentration in mole fraction was calculated from the initial and final masses. Solubility values were also converted to mol L⁻¹ using eq 1, assuming that the density of the solution can be approximated by the density of the pure solvent, 0.789 g L⁻¹ for ethanol and 0.785 g L⁻¹ for isopropanol. The final solubility estimates were taken as the average of three samples and are reported in Table 3.

\[
\text{concentration (mol L}^{-1}) = \frac{\text{mass of solute (g mL}^{-1}) \times \text{density of solvent (g mL}^{-1}) \times 1000}{\text{molecular weight of solute (g mol}^{-1})}
\]  

### 3. RESULTS

#### 3.1. Polymorph Characterization

Figure 2 shows the transmission PXRD diffractograms of Form VI of piracetam obtained in the present work by nucleation from ethanol and isopropanol solutions at 298.15 K, together with the theoretical PXRD patterns of Forms I, II, III, IV, and V, and the reported monohydrate and dihydrate forms, obtained from structures deposited in the Cambridge Structural Database (CSD). As shown in Figure 2, a unique, characteristic peak at a 2θ-value of 24.2° was observed for the new polymorph. More reflection PXRD graphs obtained from nucleation experiments for this polymorphic form are shown in Figure S1 (Supporting Information).

Figure 3 shows PXRD diffractograms of solids nucleating as Form VI sampled immediately after nucleation and following additional time in an agitated suspension, compared with diffractograms of Form II and Form III obtained using crystal structures available in the CSD. In ethanol, Form VI is verified to have completely transformed into Form II after 15 min, but in isopropanol Form VI remains unchanged for at least 6 h of observation.

Figure 4 compares Raman spectra of different piracetam polymorphs. The spectra obtained for Form I, Form II and Form III match perfectly with spectra already reported for these forms. Characteristic Raman shifts of Form III are observed at 1433 cm⁻¹, 1416 cm⁻¹, and 1438 cm⁻¹, and of Form II at 1438 cm⁻¹, 1424 cm⁻¹, 1408 cm⁻¹, and 1434 cm⁻¹. Raman shifts of Form VI are observed at 851 cm⁻¹, 865 cm⁻¹, 1418 cm⁻¹, and 1433 cm⁻¹, differing from the other polymorphs mainly with respect to the peak at 1418 cm⁻¹ (representing C−H symmetric bending) which is found at 1408 cm⁻¹ for Form II and at 1438 cm⁻¹ for Form III. The Raman spectrum of Form VI is more similar to that of Form II than that of Form III. The results obtained with Raman spectroscopy agree with PXRD in that there is no change in the solid form obtained from isopropanol solution immediately after nucleation and after 15 min in suspension, as shown in Figure 4d. In ethanol suspension, the Raman spectrum obtained after 15 min indicates a complete transformation into Form II, as shown in Figure 4e. Additional solid-state Raman spectra of Form VI obtained from nucleation are shown in Figure S2 (Supporting Information). The full Raman spectra of all the forms presented here are shown in Figure S3 (Supporting Information).

Figure 5 shows the ATR infrared spectra of crystals of Form II, Form III, and Form VI. As for Raman spectroscopy, the
three spectra exhibit very small differences. The main region of distinguishing features between these three polymorphs is located in the range 1400−1500 cm$^{-1}$.

DSC thermograms obtained for the three solid phases (Form II, Form III, and Form VI; shown in Figure S4 of the Supporting Information) exhibit qualitatively similar behavior; a weak endothermic transformation peak with an onset between 390 and 400 K, followed by a melting peak with an onset at around 426 K, corresponding to the reported melting point of Form I.20,27

The estimated solubility of Form VI in ethanol and isopropanol at 288.15 K is summarized in Table 3. In mole fraction terms, the estimated solubility is higher in ethanol than in isopropanol, in agreement with data reported for Form II19 and Form III.18 At 288.15 K, the solubility ratios in terms of mole fraction solubility of Form VI: Form II: Form III is 1.195:1.080:1.000 ± 0.004 in ethanol and 1.196:1.090:1.000 ± 0.006 in isopropanol. It should be stressed here that the relative uncertainty in the Form VI solubility values is higher compared to the Form II and Form III data because of the difference in method (approaching equilibrium by nucleation and growth) as well as the short equilibration time (necessary to avoid transformation).

Four samples of the different polymorphs of piracetam were analyzed further using optical microscopy and scanning electron microscopy, shown in Figure 6 and Figure 7. The figures show that the habit of Form III and Form VI (more clearly seen in samples from isopropanol) is relatively blocky, while the habit of Form II is more plate-like, for crystals from both solvents.

**3.2. Nucleation.** Figure 8 shows the fractions of Set I experiments resulting in each polymorphic form for ethanol solutions nucleating at different temperatures and concentrations. In all the Set I experiments, all 40 vials nucleated within 2.5 h. Moreover, each vial resulted in a single polymorphic form, i.e., the material in each vial was polymorphically pure, but different vials were observed to yield different polymorphs. Samples from each vial were collected by filtering within 5 min of the cloud point being attained in the vial to ensure no further transformation. The results clearly show changes in experimental conditions affecting the polymorphic outcome in statistical terms. As the sample size was relatively small, and as concentrations and temperature combinations were selected somewhat arbitrarily primarily to find a suitable basis for the Set II experiments, it is not straightforward to draw clear conclusions about the...
influence of individual process conditions. In the figure, the driving force is given with respect to Form VI, for 288 K as obtained using the experimentally determined Form VI solubility, and for other temperatures as calculated from the solubility of Form III and using the solubility ratio Form VI/Form III at 288.15 K. The driving force is expressed as a chemical potential difference, $\Delta \mu$, estimated using eq 2 by approximating activities with concentrations:

$$
\Delta \mu = \mu_{\text{VI}} - \mu_{\text{III}}
$$

Figure 4. Solid-state Raman spectra of (a) Form III as received, (b) Form II obtained in this work, and Form VI obtained immediately after nucleation in (c) isopropanol and (e) ethanol and following a further 6 h and 15 min in stirred suspension in (d) isopropanol and (f) ethanol, respectively. Arrows indicate the location of the characteristic Raman peak value distinguishing Form VI from Form II.

Figure 5. ATR FTIR spectra of (a) Form II obtained in this work, (b) Form III as received, and (c) Form VI obtained in this work. The region where differences could be expected to be found between the three polymorphs is highlighted.

Figure 6. Optical micrographs of Form III (as received), Form II, and Form VI obtained from isopropanol and ethanol.

Figure 7. SEM images of Form III (as received), Form II, and Form VI obtained from isopropanol and ethanol.

Figure 8. Polymorphic outcome of Set I experiments in ethanol at different nucleation temperatures and solute concentrations, along with the nucleation temperature ($T_N$) and nucleation driving force with respect to Form VI. The fraction of vials (%) nucleated as each respective polymorph are given as numerical values, and error bars show 95% confidence limits calculated using the Wilson method with no correction for continuity.
where $T_N$ is the nucleation temperature, and $S$ is the supersaturation ratio approximated as the ratio of mole fraction concentrations in the supersaturated solution ($x$) and at saturation ($x^*$). The corresponding driving forces with respect to Form II and Form III for each experiment can be calculated from the solubility ratios given above.

The Set I experiments at different nucleation temperature show that Form VI is predominantly obtained at low nucleation temperatures, with the fraction of experiments resulting in Form II increasing with nucleation temperature. This observation is true both for the entire set of experiments, as well as when comparing experiments carried out at equal driving force. The experiment at the highest nucleation temperature yielded a small proportion of vials nucleating as the stable Form III. No clear indication of the influence of driving force at constant temperature on the nucleating polymorph is obtained from the Set I experiments, with discrepancies between the results obtained at 288 and 293 K.

In order to evaluate the nucleation kinetics of Form VI, a low nucleation temperature (288.15 K) was chosen for a second set (Set II) of induction time experiments in ethanol and isopropanol solutions. In Set II, all 80 vials nucleated within the experimental time frame, and each set of repeat experiments resulted in proportions of vials each nucleating as a single polymorph. The polymorphic outcome is given in Table 1. All conditions resulted in the majority of vials nucleating as Form VI: > 83% of the vials in ethanol and >88% in isopropanol.

$$
\Delta \mu \approx RT_N \ln S = RT_N \ln \frac{x}{x^*}
$$

(2)

Figure 9. Polymorphic outcomes at different solute concentrations and nucleation driving forces, at 288.15 K in (left) ethanol and (right) isopropanol (Set II). The fraction of vials (%) nucleated as each respective polymorph are given as numerical values, and error bars show 95% confidence limits calculated using the Wilson method with no correction for continuity.
ethanol < isopropanol. This indicates that nucleation of Form II and Form III is even more obstructed in isopropanol compared to ethanol. In other words, the influence of the solvent on nucleation appears to be more pronounced for Form II and Form III than for Form VI.

According to the classical nucleation theory (CNT),\(^3\) the rate of nucleation (\(J\)) as a function of \(S\) can be expressed as

\[
J(S) = A S \exp \left[ -\frac{B}{T_N^3 \ln^2 S} \right]
\]

where \(T_N\) (K) is the nucleation temperature, \(A\) (m\(^3\)s\(^{-1}\)) is the pre-exponential factor, and \(S\) is the supersaturation ratio. Assuming the induction time to be equal to \(1/JV\):

\[
\ln(\tau_{50}S) = -\ln\left(\frac{JV}{S}\right) = -\ln(AV) + \frac{B}{T_N^3 \ln^2 S}
\]

where \(\tau_{50}\) denotes the median induction time, extracted directly from the experimental induction time distributions, and \(V\) is the solution volume (20 mL). Figure 12 shows classical nucleation plots of \(\ln(\tau_{50}S)\) against \(\ln^{-2} S T_N^{-3}\) for nucleation in both solvents. The pre-exponential factor (A) value is calculated from the intercept, and the interfacial energy (\(\gamma\)) is further calculated from the slope B through the equation:

\[
\gamma = \left( \frac{3kB}{16\theta^2} \right)^{1/3}
\]

where \(k\) (J·K\(^{-1}\)) is the Boltzmann constant, and \(\theta\) (m\(^3\)) is the molecular volume. For all the calculations, the molecular volume of piracetam was taken as that in the crystal structure of Form II (CSD refcode BISMEV) equal to 1.74 \times 10^{-28} m\(^3\). The values of the pre-exponential factor and the interfacial energy are given in Table 12. The easier nucleation in ethanol is reflected in both a lower interfacial energy and a higher pre-exponential factor.

### 4. DISCUSSION

As the comparison of PXRD patterns shows (Figure 2), Form VI is a new polymorphic form of piracetam. The structural changes that occur over time clarify that this polymorphic form is less stable than both Form II and Form III under ambient conditions. The stability relationship is also evident from a comparison of the solubility of the three forms in the same solvents. At 288 K, the estimated solubility of Form VI (0.0311 g g\(^{-1}\) in EtOH and 0.0143 g g\(^{-1}\) in IPrOH) as shown in Table 3 (C\(^6\)) is higher than that of Form II\(^16\) (0.0287 g g\(^{-1}\) in EtOH and 0.131 g g\(^{-1}\) in IPrOH) and of Form III\(^18\) (0.026 g g\(^{-1}\) in ethanol and 0.012 g g\(^{-1}\) in isopropanol). The transformation of Form VI is slower in isopropanol than in ethanol, in line with the fact that the solubility in isopropanol is lower.

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**Table 2. Median Induction Times of Form VI Obtained at Different Driving Forces, at a Nucleation Temperature of 288.15 K (Set II)**

| Solvent       | \(\Delta \mu\) (kJ mol\(^{-1}\)) | Induction time (s) |
|---------------|----------------------------------|--------------------|
| ethanol       | 1.40 1.46 1.51 1.61 1.67 1.73    | 2013 1711 1506 1269 1071 986 |
| isopropanol   | 1.50 1.67 1.73 1.84 1.96 2.07    | 4698 3246 2645 2337 1794 1555 |

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**Table 3. Molecular Volume Calculations**

| Form       | Molecular Volume (m\(^3\)) |
|------------|---------------------------|
| Form II    | 2970 Å\(^3\)              |
| Form III   | 3215 Å\(^3\)              |
| Form VI    | 3000 Å\(^3\)              |

---

**Figure 10.** Induction time distributions of Form VI in (a) ethanol and (b) isopropanol at a nucleation temperature of 288.15 K at different driving forces with fitted log-normal cumulative distribution functions (black solid lines). Each data point represents the induction time obtained in one single experiment.

**Figure 11.** Influence of the nucleation driving force on the median induction time for Form VI in ethanol (blue, ●) and isopropanol (orange, ■), from Set II experiments, together with exponential trend lines.
All these three polymorphic forms of piracetam (Form VI, Form II, and Form III) have been obtained in induction time experiments at different nucleation temperatures and solute concentrations. It can be concluded that Form VI is the overall most common result in the range of conditions evaluated herein. With increased nucleation temperature and associated higher concentrations, the proportion of experiments resulting in the more stable polymorphs (Form II and Form III) increases. This is in general agreement with observations reported for other systems that with higher concentrations the greater the tendency to nucleate more stable forms, as a result of an interplay of thermodynamic and kinetic factors.

The driving force required to reach the same induction time increases in the order of solvents as ethanol < isopropanol. The estimated interfacial energy is lower, and the pre-exponential factor is higher for Form VI in ethanol compared to isopropanol, as summarized in Table 3, with both parameters capturing that nucleation is easier in ethanol. Thus, from both the above statements, the ease of nucleation of this polymorphic form of piracetam increases in the order of solvents as isopropanol < ethanol. Moreover, given the fact that the proportion of Form VI obtained at equal driving force is higher in isopropanol than in ethanol, nucleation of Form II and Form III appears even more difficult in isopropanol.

A similar order between these two particular solvents has also been observed for nucleation of n-butyl paraben and fenoxycarb, where the interfacial energy was found to be lower in ethanol compared to a propanol isomer (n-butyl paraben: 1-propanol and fenoxycarb: isopropanol). The difficulty of nucleation in isopropanol can be attributed to the fact that there is a stronger interaction between the solute and solvent molecules compared to ethanol, as shown in previous work by Maher et al.17 using molecular simulation. In previous works on nucleation of inorganic compounds in water, an inverse relationship between the interfacial energy and the natural logarithm of the solubility was identified. This relationship is also found in the present work for the two evaluated solvents. However, in several other studies of a solute nucleating in different solvents, this relationship is not found.18–30 As shown in Table 3, the normal boiling point is higher for isopropanol compared to ethanol, similar to the order of interfacial energies of Form VI in the same solvents. A similar relationship has been observed in other studies while there are also examples of the opposite.31–36

In previous work by our group28 for piracetam Form II and Form III in the same solvents, the interfacial energy calculated from growth experiments was found to be lower in ethanol (1.12 mJ m⁻² Form II; 1.75 mJ m⁻² Form III) and higher in isopropanol (1.18 mJ m⁻² Form II; 2.08 mJ m⁻² Form III), the same order between the solvents as obtained in the present nucleation work for Form VI (4.15 mJ m⁻² in ethanol, 4.45 mJ m⁻² in isopropanol). Interfacial energies are expected to increase with increasing thermodynamic stability of the polymorphic form. Accordingly, please note that the values for Form II and Form III are obtained from growth experiments, while the values for Form VI are from nucleation experiments. Values obtained from growth experiments are expected to be lower than those determined in nucleation experiments since in the former type the determination is related to a 2D nucleation on a crystal face, while the latter is related to a 3D nucleation in a solution.28,43

The pre-exponential factor is dependent on the attachment factor, the Zeldovich factor, and the concentration of nucleation sites.40 The attachment factor and the Zeldovich factor both depend on the interfacial energy. The attachment factor describes the rate by which molecules attach to the nucleus surface and depends on the rate of transport to the nucleus and the surface area of the nucleus. The surface area of the nucleus is governed by the interfacial energy and the supersaturation. The Zeldovich factor is related to the interfacial energy (γ−3/2). Thus, the pre-exponential factor is dependent on interfacial energy as per eq 6:

\[
A = A_1 \left( \frac{\phi M}{\eta} \right)^{0.5} \exp \left( - \frac{C^*}{\eta} \right)
\]  

where \(M\) (g mol⁻¹) is the solvent molecular weight, \(C^*\) (mol L⁻¹) is the solubility obtained in this work as described in section 2.3.2, and \(A_1\) is a proportionality constant assumed to be independent of the solvent. \(\eta\) (mPa s⁻¹) is the solution viscosity at the nucleation temperature (288.15 K), here approximated by the solvent viscosity, and \(\phi\) is the empirical parameter used for calculating diffusion coefficient using the Wilke–Chang equation, whose value is 1 for most solvents but 1.5 for ethanol.44 The obtained values of \(A/A_1\) are summarized in Table 3. Both this ratio as well as the experimentally determined pre-exponential factor values (\(A\)) exhibit a higher value in ethanol compared to isopropanol and thus with respect to the influence of the solvent show a correlation.

| solvent | \(\gamma\) (mJ m⁻²) | \(A\) (m⁻³ s⁻¹) | \(C^*\) (g mol⁻¹ mol L⁻¹) at 288.15 K | \(x^*\) at 288.15 K | solvent normal boiling point (K) | \(A/A_1\) ((g mol⁻¹)⁰.⁵ (mol L⁻¹)⁻¹ (mPa s)⁻¹) |
|---------|-------------------|----------------|---------------------------------|-----------------|-------------------------------|--------------------------------|
| ethanol | 4.15              | 75             | 0.0311                          | 0.00998 ± 0.00006 | 351.52                        | 0.623                          |
| isopropanol | 4.45            | 35             | 0.0143                          | 0.00601 ± 0.00003 | 355.65                        | 0.148                          |

Figure 12. Classical nucleation plot of Form VI in ethanol (blue, □) and isopropanol (orange, ■), together with respective linear correlations.

Table 3. Solid–Liquid Interfacial Energy (\(\gamma\)), Pre-exponential Factor (\(A\)), Solubility at 288.15 K (g mol⁻¹, mol L⁻¹ (C^*) and Mole Fraction (\(x^*\))) of Form VI, Solvent Normal Boiling Points, and Pre-Exponential Factor (\(A/A_1\)) Calculated Using eq 6 from Physical Properties in Ethanol and Isopropanol.
Equation 6 indicates that with increasing interfacial energy the pre-exponential factor would of course be lower, and everything else unchanged. In the present work, a lower interfacial energy and a higher pre-exponential factor are found for ethanol solutions of Form VI compared to isopropanol solutions. Considering the fact that also the viscosity of isopropanol is higher, it is not surprising that the pre-exponential factor is lower in this solvent.

5. CONCLUSIONS
A new metastable polymorph (Form VI) of piracetam has been identified and characterized using PXRD, solid-state Raman, and IR spectroscopy. A characteristic peak in PXRD was identified at 24.2° distinguishing it from other known polymorphs. The new form nucleates preferentially over other polymorphs in both ethanol and isopropanol under the conditions investigated, but in ethanol Form VI crystals transform to Form II within approximately 15 min at 288 K, while in isopropanol the nucleated Form VI crystals remain unchanged for at least 6 h. At constant supersaturation, the proportion of experiments nucleating as Form VI is higher and the pre-exponential factor is higher in ethanol. However, the proportion of experiments nucleating as Form VI is higher in isopropanol than in ethanol.

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NOTATIONS
$A$ pre-exponential factor
$A_0$ arbitrary constant of pre-exponential factor
$B$ thermodynamic factor of nucleation
$C$ solute concentration
$C^*$ solubility
$J$ nucleation rate
$M$ molecular mass
$R$ gas constant
$S$ supersaturation
$T_N$ nucleation temperature
$V$ volume
$x$ solute concentration (in mole fraction)
$\tau_0$ induction time
$\gamma$ interfacial energy
$\eta$ solution viscosity
$\theta$ molecular/molar volume

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