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Concerning Elusive Crystal Forms: the case of paracetamol

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Abstract

Increasing commercial application of state of the art crystal structure prediction to aid solid form discovery of new molecular entities allows the experimentalist to target the polymorphs with desired properties. Here we remind ourselves that in this field the gap between such prediction and experimentation can be vast, the latter depending strongly on kinetic processes not accounted for in the computations. Nowhere is this gap more evident than in examples of so-called ‘elusive’ polymorphs, forms that have been found difficult to crystallise, sometimes taking years to appear or sometimes disappearing altogether. In attempting to probe the origins of such phenomena this work targets a well-known, relatively simple molecule, paracetamol (PCM), and explores the structural and kinetic origins of its elusive nature. It is noted that in general comparisons of the kinetic factors (nucleation and crystal growth) between polymorphs have been rarely reported and of course in cases where one or more forms is ‘elusive’ this will, by definition, be essentially impossible. PCM however offers a unique opportunity and we show how the recent discovery of the impact of metacetamol (MCM) in stabilising PCM form II can be used to advantage, enabling otherwise impossible comparative kinetic experiments to be made. Resulting from this study we now appreciate that MCM has a selective impact in blocking the growth of the thickness and width of PCM form I whilst it has no impact on form II. This is interpreted in terms of strong adsorption of MCM on the {011} faces (width and thickness) of form I in orientations that inhibit crystal growth (“wrong” orientations). Of more significance here is the use of the additive in allowing an otherwise impossible comparison of linear growth rates of forms I and II. This leads to the appreciation that only through calculation of growth volumes can we finally appreciate how the relative growth kinetics lead inevitably to the elusive nature of Form II.

1. Introduction

The drugs we take to manage, cure and prevent numerous conditions and diseases almost always come in the form of tablets. The active pharmaceutical ingredient (API) is contained in these pills as finely ground molecular crystals designed to dissolve in our digestive tracts

yielding species which perform their therapeutic task. One of the abiding and intractable issues of materials chemistry surrounding the formulation of such tablets concerns the crystal structure of the API. Three major, inter-related, factors are of importance. Firstly, most pharmaceutical molecules are able and likely to adopt more than one crystal structure, a phenomenon known as polymorphism.¹ Secondly, the physical properties of some of these polymorphs will differ significantly in terms of both their physical stability and their biological efficacy. Thirdly, regulatory controls require that robust, safe and consistent processes are defined for making the chosen crystal form.² This means that from both patent and processing perspectives the issue of polymorphism has largely dominated the solid-state chemistry of pharmaceuticals over the last several decades. There has, for example, been a significant activity in developing computational tools for the prediction of all possible crystal structures³ of newly invented drug molecules and this technology is now becoming a standard tool in the formulators' armoury helping to answer questions such as – 'have I found all the polymorphs of this molecule?' and 'which form is likely to be the most stable?'.^{4,5} Since essentially all active molecules come from liquid phase synthetic chemical reactions, this latter issue equates to an ability to design a solution based crystallisation process that yields crystals with the designated form day in, day out. History is littered with examples where such product consistency has proved difficult to achieve. Polymorphic structures have simply disappeared^{6,7} and could not be made again. Some forms are described as 'difficult to crystallise' so that having made one form for years a second, previously uncrystallised, form unexpectedly appears yielding a product which no longer meets specifications.^{8,9} Such occurrences can be costly. While much has been written concerning disappearing polymorphs little seems to be understood about polymorphs which are 'elusive'¹⁰⁻¹² or 'difficult to crystallise'.^{5,13} Often this has been attributed to issues surrounding nucleation, typically associated with molecular flexibility (large numbers of torsions)^{8,14}. However, little direct evidence is available. Certainly this issue is recognised in the field of protein crystallisation and is being increasingly encountered in the pharma sector as drug molecules become more complex and of high molecular weights. Interestingly, even for some relatively simple molecules it is, apparently, difficult to crystallise certain polymorphs even when they have desirable product qualities. We believe that much may be learned from consideration of such cases of which paracetamol (PCM, Figure 1) is an excellent example.

Figure 1. Molecular structure of paracetamol (PCM, left) and metacetamol (MCM, right).

Paracetamol is undoubtedly one of the most widely used drugs in the world, being routinely administered to children and adults for the treatment of moderate pain and fever. Production and sales data indicate that, at least in the UK, each person buys an average of 70 tablets of PCM per year.^{15,16} It exists in three known anhydrous forms: Form I (monoclinic, $Z'=1$)¹⁷ which is the most stable form and the one currently used in tablets, Form II (orthorhombic, $Z'=1$)¹⁸ which has mechanical properties best suited to tablet production¹⁹ and Form III (orthorhombic, $Z'=2$)^{20,21} which is highly metastable. Although Form II offers a highly desirable product, having both solubility and tableting advantages over Form I, the latter remains the commercial form because its crystallisation is facile and it is the most stable. Indeed, since its discovery in 1974,¹⁸ form II PCM has been found to be ‘elusive’¹⁰ and hence not readily amenable to commercialisation. In the original report by Haisa et al.,¹⁸ form II was reportedly obtained from ethanol by cooling crystallisation. Subsequent attempts to produce it in this way, however, failed unless the solutions were seeded. While seeds of form II can be reliably crystallised from the melt such seeded crystallisations are still problematic due to the rapid appearance of form I. Nichols and Frampton showed that to obtain pure form II in this way the crystals needed to be removed quickly from the mother liquors and dried to avoid the appearance of form I.²² The reliable preparation of pure batches of form II via robust crystallisation processes thus remained challenging under these conditions. Recently research using both batch and continuous crystallisation has described cooling crystallisations in various solvents in the presence of 25 wt% of metacetamol (MCM, Fig1) in which 100% phase pure form II can be reliably obtained.^{23,24} Actually, although it has been known for over 20 years that MCM (at levels of 0.5 – 5 wt%) has an impact on the morphology and the nucleation rates of PCM form I,^{25,26} it was not until the 2016 work by Agnew et al.²³ that its selective impact enabling the reproducible crystallisation of form II was noted. Such selectivity induced by additives is, of course, well known and usually attributable to selective adsorption onto surfaces of one polymorph, leaving the other free to crystallise.²⁷ It is unknown how such a mechanism translates to PCM but Agnew et al have speculated that a ‘templating’ process may be at work.^{23,24} Certainly, in the absence of additives the elusive, difficult to crystallise, nature of form II is linked to the rapid competitive crystallisation of form I.²² Thus in a batch crystalliser, an initial population of form II crystals are rapidly joined and overtaken by new form I crystals that then, being the more stable phase, drive the system to equilibrium. The crucial question here is how, in this competition for solute, does form I win? What kinetic advantage does form I have over form II? Obviously in this, as in many other cases, the relative metastability of form II over form I makes experiments extremely difficult, however, as we show here, the action of MCM in enabling the isolation of form II offers a unique opportunity to study the relative growth kinetics of the forms and to

understand the origin of form II's elusive nature. The results also allow us to examine whether or not a templating mechanism offers a realistic explanation of the data.

2. Results and Discussion

2.1 Solubilities of Forms I & II.

The solubility of PCM form I in IPA increased slightly (~4% in wt% terms, ~0.001 in mole fraction) in the presence of MCM (ESI). All calculated supersaturation values for form I were corrected accordingly, although even at the highest concentration of MCM, the impact on the supersaturation ($S = C/C_{eq}$ with C in g/kg solvent) is only of the order of 5%. The solubility of PCM form II in IPA could not be measured due to rapid transformation to form I; instead, it was estimated from the known solubility ratio of the forms in water, 1.39¹³. Some minor additional corrections were applied to ensure consistency with the growth rate data (ESI). Accordingly, the solubilities in IPA at 20 °C have been taken to be 108.78 and 137.33 g PCM/kg IPA for forms I and II respectively. These values mean that under conditions in which the solution is supersaturated with respect to form II, the same solution will be supersaturated by an additional 26% with respect to form I.

2.2 Morphologies and Growth directions.

Form I crystals are rather equant whilst form II crystals are needle like and Figure 2 provides details of these experimental morphologies related to the crystal packing. Face indexing of the seeds of both forms revealed that the length dimension of both corresponds to the [100] direction. In form I, crystals are terminated by {10-1}, {101} and {110} planes whilst in form II by only {111}. In both forms, the crystals are bound by only one family of planes along the width and thickness dimensions: {011} in form I and {012} in form II. This makes the system ideal for growth rate measurements since although only measurement of the length and width are possible with a normal microscope, growth in the thickness dimension in both forms can be taken as equal to the width.

Figure 2. Packing views (form I along a-axis, form II along b-axis) and crystal morphologies (experimental from water) of forms I and II PCM.

2.3 Growth rates of Forms I & II

Growth rate measurements for forms I and II PCM in IPA and IPA at 0, 5, 12.5, 25 and 35 wt% of MCM are shown in Figure 3[§]. For form I in pure solutions the growth rates along the length (Fig 3a, [100]) and the width (Fig 3b, [011]) are similar at equivalent values of S . This is consistent with the observed equant shaped crystal morphologies of form I in pure IPA. The addition of MCM to the solution has a tremendous impact on the width, [011]. As little as 5 wt% of MCM stopped form I width growth completely across the entire range of S . By contrast, there is only a small effect on the length growth rates of form I. This effect can also be appreciated in the aspect ratio of form I crystals growth under the presence of MCM (see ESI).

For form II, it was not possible to measure its growth in pure IPA without the appearance of form I crystals: a minimum of 25 wt% MCM was required to completely stabilise solutions against form I appearance. Figures 3c and d show the form II length and width growth rates in the presence of 25 and 35wt% MCM from which it is clear that further addition of MCM beyond 25% has no further inhibitory effect. Thus, although we cannot be totally certain, it seems reasonable to assume that our measured data provide a good approximation to the growth rates of form II in pure solution. The relative growth rates of length to width are then consistent with the needle like habit of form II in which the aromatic stacking direction is aligned with the crystal length.

Figure 3. Growth rates (R) as a function of supersaturations (S_I and S_{II}) for forms I (a =length, b =width) and II (c =length, d =width) PCM in IPA at 20 °C and various contents of MCM.

Comparing these linear kinetic data, with the exception of the form II width growth, both forms have essentially equivalent growth rates. It is not obvious, therefore, how these results explain the overwhelming kinetic advantage of form I over form II in pure solution. However, if these data are converted, using equation 1 (see methods), into overall growth volumes then, as seen in the next the section, the situation becomes clearer.

2.4 Overall Growth kinetics: form I vs. form II.

The growth volumes of forms I and II PCM were calculated according to equation 1 and are plotted in Figure 4 which compares the linear rates with the growth volumes. For these calculations, initial seed sizes were taken to be $200\mu\text{m} \times 100\mu\text{m} \times 100\mu\text{m}$ in both forms (in accordance with the experiments) and a growth time of 60 minutes was chosen (further data in the ESI shows that the observed behavioral trend in volumes is independent of seed size and growth times). Concentration rather than supersaturation is used since, as discussed above, at a given PCM concentration the system has different supersaturations with respect to

forms I and II. Here we see very clearly that in pure solutions for concentrations in excess of the solubility of form II, where competitive growth is possible, the linear rates offer conflicting views of the kinetic differences between the forms: form II outstrips form I in length growth but form I is faster than form II in the width. Only the growth volume data enables us to see that in volume, and hence mass and yield terms, form I always wins out over form II in pure solutions and by up to an order of magnitude.

Figure 4. Experimental growth rates along the crystal length (a) and width (b) and overall growth volumes (c) as a function of PCM concentration in IPA for seeds of form I in pure IPA (orange), form I in IPA with 5 wt% MCM (yellow), form I in IPA with 25 wt% MCM (green) and form II in IPA with 25 wt% MCM (blue). Initial seed sizes of 200 x 100 μm were assumed and a growth time of 60 mins.

Vertical dashed lines in the plots indicate the solubility values for forms I and II and form I in the presence of 25 wt% of MCM.

Upon the addition of MCM, its selective impact on form I means that at levels above 5 wt% form II begins to grow faster than form I. With increasing additions up to 25 wt% MCM, form II is the only outcome. Thus the selective nature of the kinetic effect is evident – form II is elusive because in pure solutions form I is significantly faster growing. In contrast, increasing amounts of added MCM selectively inhibit form I allowing form II growth to dominate. The mechanism by which this takes place is considered below.

2.5 The mechanism – surface docking or templating?

While there are many literature examples in which additives have been successfully designed for selective inhibition of crystal growth^{27–30} this is the first time, to our knowledge, that an additive effect has been used to enable comparison of polymorph growth rates under conditions not accessible in pure solutions. Insight into the mechanism of action of such additives can often be inferred from observed morphological changes. Thus, in this case the major impact of MCM is to inhibit growth along [011] in form I with no other directions in either polymorph being significantly affected. These observations are accompanied by incorporation of MCM into the growing crystals with both forms having similar segregation coefficients (ratio between the concentration of impurity in the crystal and in solution) – 0.05

for form I and 0.04 for form II. We note that Hendriksen et al²⁶ found a much higher segregation coefficient of 0.28 for form I. We offer no explanation for this difference except to say that they used a chromatographic technique, much lower additive levels and do not describe the origin of their crystals. Thus overall, we wish to understand not only how MCM is able to incorporate equally into the lattices of both forms but also why it is an *ineffective* growth inhibitor for form II whilst inhibiting the growth of form I.

In seeking a structural basis for these effects the potential impact of MCM incorporation on the hydrogen bonding networks of forms I and II is considered. In both structures PCM molecules are hydrogen bonded to four nearest neighbours, in each case utilising two NH...O- and two OH...O= interactions (Figure 5). In form I these create a corrugated 2-D hydrogen bonded layer lying roughly in the (010) plane while in form II the equivalent network is planar lying in the (100) plane. To illustrate the potential impact of MCM on these networks, the change in hydrogen bonding resulting from a substitution of a molecule of PCM by MCM is illustrated in Figure 5. In inserting an MCM molecule, although there is a loss of one hydrogen bond of the type NH...O, the hydroxyl group in the *meta* position is still able to take part in an OH...O= interaction. This suggests that the additive, MCM, will be able to insert itself in the hydrogen bonded layers of both forms with only minor disruption, a conclusion consistent both with the observed incorporation of MCM in the crystals and with the computed lattice energies. These are -133.2 and -132.9 kJ/mol for composition pure forms I and II respectively, dropping to -129.1 and -128.5 kJ/mol upon insertion of 12.5 % of MCM into the lattices indicating that although there is an energy penalty upon insertion of MCM, it is small and it has a similar impact in both forms I and II.

Figure 5. Impact of MCM insertion (right) in the hydrogen bonding layers of PCM polymorphs as in the (010) plane of form I (upper) and the (100) plane of form II (lower).

The corollary to this potential for incorporation of MCM into lattice sites is that its presence in any surface should offer no barrier to growth; indeed this is exactly as found with the exception of the [011] direction of form I. To gain further insight into MCM's selective kinetic effect, the stable configurations of an isolated PCM or MCM molecule adsorbed on the various faces of forms I and II PCM were explored computationally (see methods). The first step in these simulations was performed by treating both the surface and the adsorbent as rigid bodies in vacuum and allowing single PCM and MCM molecules to independently sample multiple surface sites (see methods) on all relevant surfaces. The 14 most stable of the resulting configurations per surface and adsorbent system were then fully relaxed (nb for the (011) in form I, the 28 most stable were relaxed since many of the low energy configurations had very similar energies). The relaxed adsorption energies per adsorbent molecule (E_{ad}) for these were then calculated. Table 1 provides numerical values for the lowest energy (LE) adsorption configuration per crystal face, whether this corresponds to adsorbed PCM or MCM and whether the LE geometrical configuration corresponds to that of the lattice site required for crystal growth ("crystal configuration"). The number of "non-crystal configurations" with lower energy than that of the most stable PCM-crystal configuration is also given together with difference in adsorption energies between the lowest energy configuration and the PCM-crystal configuration.

In form II, the LE configurations always correspond to a PCM-crystal configuration for all crystal faces along both the length and width of form II. This is consistent with the fact that MCM has no impact on the growth kinetics.

In form I, the situation is more complex. Of the three faces expressed in the length dimension, the lowest energy configuration matches the PCM-crystal configuration only on the (110) face. For the width and thickness, the LE configuration corresponds to a non-crystal MCM adsorption ($E_{ad} = -61$ kJ/mol). Most strikingly, the model predicts 31 non-crystal configurations to be more stable than the PCM-crystal configuration required for crystal growth ($E_{ad} = -52$ kJ/mol). One such stable configuration is shown in Figure 6a which illustrates how MCM attaches to the (011) face of form I in this "wrong" LE orientation. We notice that PCM is also able to attach to the (011) in other "wrong" orientations but these are just 8 configurations in PCM compared to 23 in MCM. These specific, yet non-crystallographic, multiple stable adsorption configurations halt growth of PCM on the {011} faces (crystal width).

One major conclusion from these insights is that the action of MCM does not derive from behaviour as a 'tailor-made additive' nor does it have a 'templating' effect, rather it inhibits growth through various strong non-crystallographic adsorption geometries.

Clearly, these simulation results should be viewed with caution because of the limitations of the model. For example, no account was taken of the impact of solvent. What

seems clear however, is that PCM in the crystal configuration is the most stable adsorbent in all faces of form II whilst the situation is more complex in form I. The fact that many stable non-crystallographic sites are possible to block the growth seems to be a logical explanation.

We note that, while MCM is an isomer of PCM, other studies have reported similar effects on the crystallisation of PCM using stoichiometric amounts of benzoic acid derivatives.¹⁰ Study of these additives was beyond the scope of this current work.

Table 1. Experimental crystal dimensions and corresponding crystal faces, their multiplicity (M) and adsorption energy (E_{ad}) for the lowest energy (LE) configuration. The compound (MCM or PCM) affording the LE configuration is indicated and whether or not that configuration correspond to a crystallographic orientation.

PCM Form	Crystal Dimensions [§]	Face	M	E_{ad} [LE] (kJ/mol) [¶]	LE Compound	LE Configuration	Number of stable Non-Crystal Configurations, ΔE_{ad} [*]
I	L	(101)	2	-54	PCM	Non-Crystal	18, +7
		(-101)	2	-63	MCM	Non-Crystal	7, +5
		(110)	2	-76	PCM	Crystal	0, 0
	W, T	(011)	4	-61	MCM	Non-Crystal	31, +9
II	L	(111)	8	-67	PCM	Crystal	0, 0
	W, T	(012)	4	-85	PCM	Crystal	0, 0

[§]L=length, W=width, T=thickness ; [¶] E_{ad} [LE]=adsorption energy for the lowest energy configuration;

^{*} $\Delta E_{ad}=E_{ad}[\text{PCM-crystal}]-E_{ad}[\text{LE}]$

Figure 6. Example of a non-crystal adsorption configuration of an MCM molecule on the (011) face of form I PCM. (Left) Orthogonal view looking down on a MCM molecule interacting with surface PCM which are in sticks; the rest of surface molecules are in lines only. (Right) View along (011) contrasting the required lattice orientation (blue arrow) with the MCM orientation in yellow.

Discussion

This work clarifies the role and molecular mechanism by which MCM allows crystallisation of the elusive form II of PCM. First, measurements of growth rates and the calculation of experimental growth volumes of forms I and II in the presence of different amounts of MCM clearly indicate that form I always grows faster than form II unless some MCM, even at low concentrations, is present in solution. Upon addition of just 5wt% of MCM, form II grows faster than form I at PCM solution concentrations above the solubility of form II. At this point we then question, why significant amounts of MCM (25wt% and above) are required to produce phase pure PCM form II. The answer to this question lies in Hendriksen's 1995

induction time experiments²⁶ which clearly show that MCM inhibits, but does not prevent, the nucleation of form I. Thus for example at a value of $S_{II}=1.01$ there is a significantly higher driving force for nucleating form I ($S_I=1.27$) so that at low concentrations of MCM, where form II grows faster than form I, there is *still* the possibility for form I to nucleate. To be able to obtain phase pure form II, we require not only to slow down the growth of form I but to stop it completely. Actually, in the presence of form II seeds, heterogeneous nucleation of form I seems facile. In fact, we observed formation of form I crystals on the surfaces of form II seeds at low concentrations of MCM. As the concentration of MCM is increased, the crystallisation of form I is slowed until it is completely prevented at 25wt%. This value is consistent with the Agnew paper²³ in that we required at least 25wt% to fully avoid the nucleation of form I, allowing form II to grow. Actually, given the correlation we have observed previously³¹ between growth and nucleation it seems reasonable to conclude that MCM also prevents the nucleation of form I.

The measurement of the growth rates along the different crystal dimensions showed that the main mechanism by which the growth of form I is inhibited is the blocking of the {011} faces. Adsorption simulations revealed that MCM adsorbs preferentially over PCM on the (011) form I face and that it can do so in a number of wrong orientations. This “wrong” attachment of MCM results in a complete blocking of the growth along the [011] direction (the width and thickness) of the crystal. This has a huge impact on the overall growth volume which results in form I growing much slower than form II at MCM levels in excess of 5wt%. This result enables some more realistic comments to be made concerning the use of the term ‘templating’ offered as an explanation for form II crystallisation in a number of publications.^{10,23,24} Thomas et al¹⁰ suggest that a templating mechanism takes place ‘within the solution phase’ using ‘a co-molecule to perturb the solution environment’. Actually, in the ternary system used here (PCM/MCM/IPA), any form of solution phase complexing between PCM and MCM can be ruled out since it would be accompanied by a solubility relationship between PCM and MCM with a slope of approximately 1 or greater (depending on the stoichiometry of the complex).³² Here the slope is ~ 0.2 and so we can infer that such complexation simply does not take place and that the slight solubility increase is due to the enhanced aromatic nature of the solvent which is now an IPA-MCM mixture. As we show here, the impact of MCM is simply a further example of an additive molecule that, far from ‘templating’ and catalysing the appearance of the metastable phase actually inhibits the crystallisation of the stable phase.

In this light, it now appears clear that the reason why form II PCM is an elusive polymorph is three fold: thermodynamics, kinetics of nucleation and kinetics of growth, *all* favour form I. There is thus, no possible way in the race of crystallisation that form II will beat form I unless

the kinetics of both nucleation and growth of form I are totally prevented by an impurity. In this case, MCM significantly impacts both the kinetics of growth (at low concentrations) and nucleation (at higher concentrations). MCM achieves such effects by strongly adsorbing on faces of form I in the *wrong* orientation. Such blocking of form I allows for form II to thrive.

Conclusions

Despite paracetamol being one of the world's most used and studied drugs, our understanding of the crystallisation of its metastable form, form II, has been very limited. Form II is an elusive form, hard to crystallise unless selective impurities are present in solution. This work has demonstrated three new outcomes which have important implications not only for this system but also in our more generic attempts to understand polymorphic systems in pharmaceutical drugs. First, we have successfully used an additive to enable the measurement of relative growth rates of the two polymorphs of PCM. Comparison of the growth rates of those two forms in pure solutions was not possible due to the highly elusive nature of form II PCM. Second, we have shown how it is the magnitude of the relative growth volumes of the forms that illustrates the kinetic advantage of the stable form I. Comparison of these volumes rather than the individual rates proved essential. Third we have discovered that, in this case, the selectivity of the additive (MCM) arises from its strong adsorption on the width and thickness faces of form I in “wrong”, non-crystallographic, orientations which prevent crystal growth. This study has created a much clearer picture of why form II PCM is elusive. In a nutshell, form II is less stable and both grows and nucleates slower than form I. Thus, form I always beats form II unless a selective additive inhibits its growth and nucleation while not impacting form II. Whilst the use of selective additives can help achieve “phase purity” of elusive forms, such additives may also incorporate in their lattices lowering the “compositional purity”. The extent of this incorporation and the toxicology of the additive will of course determine the commercial application of such a process. With this new data it has been possible to rule out any form of solution phase templating mechanism. This rationale should be transferable to other systems of interest and shed light on how to control and realise the growth of metastable elusive polymorphs.

Methods

Materials. Acetaminophen (Paracetamol, PCM; Sigma-Adrich, $\geq 99.0\%$), 3-Acetamidophenol (Metacetamol, MCM; Alfa Aesar, 99%), and isopropanol (IPA; Sigma-Aldrich, $\geq 99.5\%$) were purchased and used as received without any further purifications. De-ionised water (ASTM D1193–91 Type I) was prepared in the laboratory and used shortly after it was produced.

Solubility Measurements. The solubility of PCM form I in IPA at 20 °C was measured in the presence of various MCM concentrations (4.95wt%, 12.18wt% and 23.90wt% with respect to the total mass of dissolved PCM) using a gravimetric method (ESI). Each measurement was repeated five times and an average solubility value and uncertainty was calculated.

Seeds of forms I and II PCM. Briefly, good quality single crystals of PCM forms I and II suitable as seeds were grown at room temperature from aqueous solution by slow and rapid evaporation respectively. In the case of form II 10 wt% of MCM was added to the solution. Full details are given in the ESI.

Powders of form II PCM. Form II powder was prepared by cooling an ethanolic solution from 70 °C to 5 °C at a rate of 1°C/min. The solution was filtered as soon as crystals appeared to avoid transformation to form I. Full details are given in the ESI.

Face Indexing. Seeds of forms I and II PCM were face indexed using a Rigaku Oxford Diffraction FR-X DW diffractometer equipped with MoK α X-rays ($\lambda = 0.71073$ Å) rotating anode system VarimaxTM microfocus optics. Data was collected in a series of ω -scans at ambient temperature. Crystal face indices were assigned relative to the following cell-settings: form I- $P2_1/n$ (HXACAN04)³³ and form II- $Pcab$ (HXACAN21)³⁴ with the aid of CrysAlis Pro version 171.40.14d.³⁵ We note that other space group settings may have been used for face indexing in previous studies which naturally results in different indexes for the various dominant faces.

Growth rate measurement. Growth rates of the seeds were measured at 20 °C *in situ* using a growth cell coupled with an inverted microscope (Olympus CKX41) as described previously by Black et al.²⁸ Both length and width growth rates were measured. A wide range of PCM concentrations were covered in pure solutions and with added MCM up to 35 wt% (based on the mass of PCM). Seed crystals of form I were typically partially dissolved before growth while form II seeds were grown without dissolution. This avoided both subsequent irregular growth as well as phase transformation to form I. In these measurements precise definition of supersaturation requires that seed crystals grow with no additional nucleation of other forms over the three hour experimental time period. While this was always the case for form I measurements in pure IPA and in the presence of various amounts of MCM (5, 12.5 and 25 wt%) for form II, concentrations the MCM or 25 wt% or higher were needed to prevent spurious nucleation of form I.

In order to convert the measured linear rates into volumes equation 1 was used. This relates the seed volume at any time t to the size of the initial seed and the measured linear growth rates.

$$V[t,C]=(L_0+R_L[C]t)(W_0+R_W[C]t)(T_0+R_T[C]t) \quad (1)$$

where L_0 , W_0 and T_0 are length, width and thickness of the original crystals at $t=0$ and $R_L[C]$, $R_W[C]$ and $R_T[C]$ are the growth rates of the length, width and thickness at given concentrations of paracetamol in IPA (C). It is noted that from symmetry considerations (see 3.2) that in both forms $R_W[C] = R_T[C]$. The growth volume is thus a function of the growth time, original seed dimensions, the growth rates and the solution concentration of PCM. Using the measured linear growth rates we calculated the growth volumes of PCM forms I and II as a function of concentration for a number of seed size values and growth times (see ESI).

Levels of incorporation of MCM. Single crystals of PCM forms I and II were prepared by slow and fast evaporation from aqueous solutions (with and without seeding respectively) containing 25wt% of MCM at room temperature. Individual crystals were harvested, washed and approximately 10mg samples dissolved in acetone- D_6 . The MCM content in such samples was detected by 1H -NMR measurements (128 scans per sample) carried out using a 400MHz NMR spectrometer (Bruker). The proton NMR scans were recorded and analysed using MestReNova version 14.1.0-24037.³⁶ The accuracy of the method was validated using a solution containing 5wt% MCM relative to PCM which was correctly quantified to contain 5.05wt% of MCM relative to PCM.

Computations. All calculations utilised the COMPASS II forcefield³⁷ (with its own forcefield charges) as implemented in the Forcite module of Materials Studio (2019)³⁸ together with the crystal structures of forms I and II PCM as given by the Cambridge Structural Database refcodes HXACAN04³³ and HXACAN21³⁴.

Lattice Energy Calculations. Lattice energies of PCM forms I and II were calculated by performing full geometry optimisation of their respective crystal structures (allowing for relaxation of both unit cell parameters and atomic positions) and subtracting the energy of a PCM molecule in the gas phase from the energy of a PCM molecule in forms I and II. After optimisation, P1 supercells of eight molecules were generated and one of those molecules was replaced by a MCM molecule. The lattice energy was recalculated relative to the gas-phase energy of the PCM and MCM molecules and normalised per molecule.

Adsorption Calculations. For calculations of surface adsorption energies, crystal structures were geometry optimised relaxing all atomic positions and unit cell parameters. Crystal faces of interest (see section 3.2 - (-101), (101) and (011) for form I and -(100) and (012) for form II) were then generated by cleavage to a thickness of approximately 30 Å. Each face was cleaved several times at different shifting positions and only the surface with the highest molecular density was retained. A supercell of each cleaved surface was generated so that the two periodic vectors were of at least 30 Å each, requiring 2 to 3 times the original cleaved surface in each of the two boundary directions. After this, a 3D supercell was generated by adding 20 Å of vacuum on top of the cleaved surface. This results in 3D supercells of a

minimum of 30 Å x 30 Å x 50 Å (surface direction) and in between 200-300 molecules of PCM. Once the supercells were generated for each of the surfaces, the same energy model (COMPASS II) was used for the Adsorption Locator module. The most stabilising adsorption geometries for one individual molecule of PCM/MCM on the various form I and II surfaces were sampled using a Simulated Annealing algorithm. Each adsorption sampling was run five independent times in which 100000 configurations were sampled each time. These simulations are performed in vacuum treating both the surface and the adsorbent as rigid. The fourteen most stable of such configurations (within 10 kcal/mol) were retained and subsequently fully optimised using the same model - the 28 most stable for the (011) face of form I. The adsorption energy (E_{ad}) of each of such adsorption configurations was calculated by subtracting the energy of the relaxed isolated surface and the relaxed isolated adsorbent (MCM or PCM) from the energy of the relaxed surface-adsorbent configuration (given per molecule of adsorbent). Solvent was not modelled.

Supporting Information. Detailed description of experimental methods. Face Indexing. Additive effect on the solubilities and morphologies. Details and images of growth rate measurements. Growth volume calculations.

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References

[§]After an initial less-linear behaviour at low S values (<1.15), growth rates fit well ($R^2 > 0.9$) to linear equations of the type $R = (kS + a)$ with derived rate constants, k, of 4.17 and 3.78 $\mu\text{m}/\text{min}$ for the length and width respectively. Derived rate constants values for growth in IPA with no additive, 5, 12.5 and 25 wt% of MCM are 4.17, 3.69, 3.40 and 3.17 $\mu\text{m}/\text{min}$ respectively. The length of form II grows much faster than the width with fitted k values of 16.88 and 1.13 $\mu\text{m}/\text{min}$ respectively.

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