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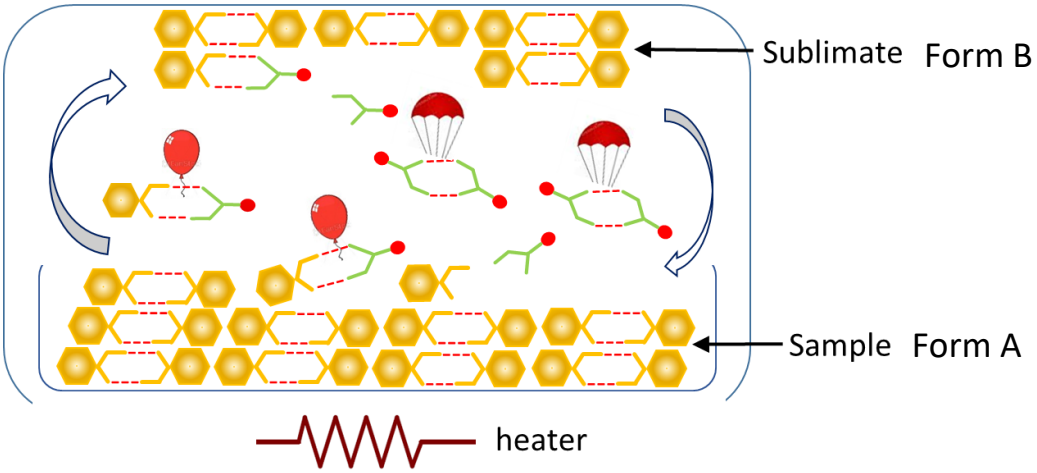
ABSTRACT

In pursuit of a solvent free green alternative to solution based processes, we have applied the combined use of catalytic additives and polycrystalline powder templates for polymorph control of gas phase crystallization to a range of pharmaceuticals and related compounds. Complementary volatile additives have been found which can catalyse the sublimation of a range of typical active pharmaceutical ingredients, APIs. Sublimation temperatures are typically reduced by up to 20 °C and the process is accelerated. The use of polycrystalline powder templates for polymorph control has also been successfully applied in several cases. Temperature control at the sites of both sublimation and desublimation is often required. The absence of even traces of solvent in the polymorphs produced appears to give the samples higher stability than samples obtained by crystallization from solution.

Complete polymorph control was achieved with the following APIs, carbamazepine (5 polymorphs), metaxalone (2 polymorphs), mefenamic acid (2 polymorphs), paracetamol (2 polymorphs) and *ortho*-, *meta*- and *para*-amino benzoic acids (1, 4 and 2 polymorphs respectively).



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In pursuit of a solvent free green alternative to solution based processes, we have applied the combined use of catalytic additives and polycrystalline powder templates for polymorph control of gas phase crystallization to a range of pharmaceuticals and related compounds. Complementary volatile additives have been found which can catalyse the sublimation of a range of typical active pharmaceutical ingredients, APIs. Sublimation temperatures are typically reduced by up to 20 °C and the process is accelerated. The use of polycrystalline powder templates for polymorph control has also been successfully applied in several cases. Temperature control at the sites of both sublimation and desublimation is often required. The absence of even traces of solvent in the polymorphs produced appears to give the samples higher stability than samples obtained by crystallization from solution.

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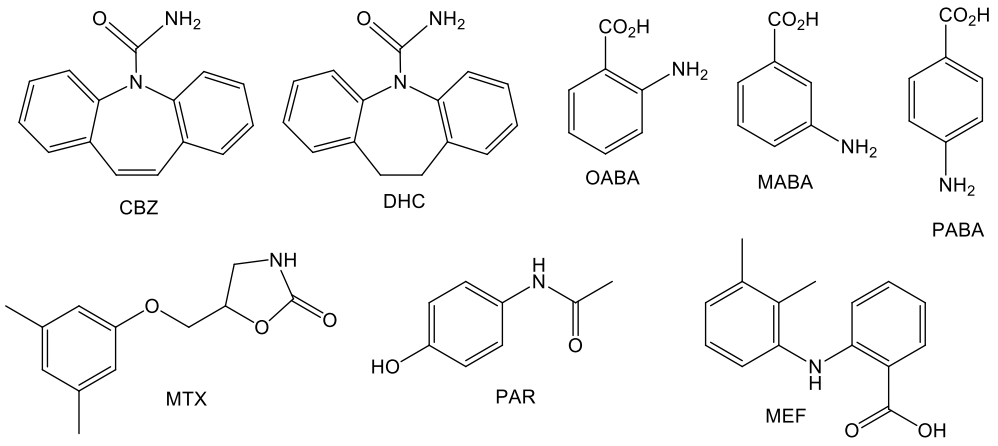
1. Introduction

Polymorphism is of considerable importance in the pharmaceutical industry as different polymorphs of an API can have different physical and chemical properties which can lead to differences in bioavailability.[1,2] Polymorph problems can include the appearance of an unwanted form, the disappearance of the required

form and concomitant polymorphism.[3-6] Solution crystallization is the dominant method used in industry for the production of crystalline solids and careful control of cooling rate, choice of solvent, the use of additives and seeding are all in use for polymorph control.[7,8] Examples of the use of sublimation for polymorph control are rare. However, form IV of *m*-aminobenzoic acid has been produced by sublimation and condensation onto a cold finger and sublimation is used for the industrial production of fine chemicals.[8-10]

Attempts to develop the theoretical prediction of the crystal structures of organic molecules and the calculation of the relative stability of possible polymorphic forms have been underway for some time.[8] And while the results of the sixth blind test of crystal structure prediction, which included a compound that had five polymorphic forms, have been impressive it will clearly be some time before crystallization from solution is included in these calculations.[11] It is possible that sublimation based solvent free polymorph control may provide examples which are more amenable to theoretical simulation than solution based polymorph transformations. The presence of small amounts of solvent within crystals grown from solution may itself be a problem. The much studied case of paracetamol, PAR, where there are difficulties in the reliable production of the more desirable form II [12] is a good example of these problems.

In an effort to develop sublimation as a green solvent free method of crystal processing, we recently reported that the sublimation process can be catalysed by complementary additives and that desublimation templates can provide excellent polymorph control.[13] Desublimation templates are a solvent free equivalent of crystal seeding in solution. In this paper we show that this is not confined to a few specific examples, but can be applied to a range of sublimable compounds.



Scheme 1. Structure of APIs.

2. Sublimation

2.1 The sublimation process. Many pharmaceutical compounds are known to sublime. For example the thermal conversion of carbamazepine, CBZ, form III to metastable form I at temperatures below the melting point has been shown to involve sublimation.[14] However, attempts to measure the vapour pressure of CBZ to provide more detail on its gas phase properties were not successful as its thermal stability was not high enough at the temperatures required.[15] The sublimation process is described here in two parts, sublimation catalysis and sublimation onto polycrystalline powder templates.

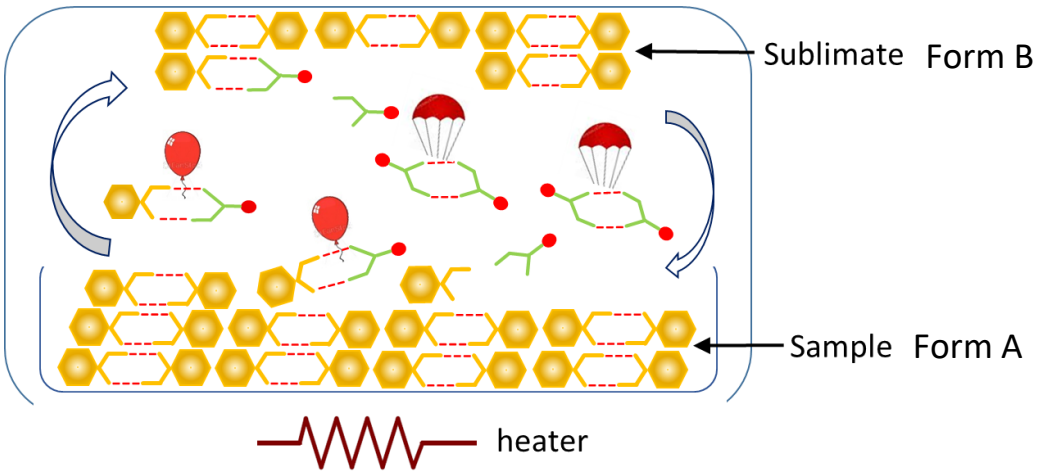


Figure 1. The lower molecular weight H-bonder (red) catalyses the sublimation of the higher molecular weight API (yellow).

2.1.1 Sublimation catalysis. We have shown that the sublimation process can be catalysed if the molecular weight of the gas phase species can be reduced.[13] This is possible if a compound which forms a hydrogen bonded dimer in the gas phase can be brought into equilibrium with a catalytic amount of a complementary hydrogen bonding molecule of lower molecular weight. In the CBZ case 5% acetamide functioned as a lower molecular weight sublimation catalyst. The acetamide would be coloured red in the diagram in Figure 1 and the CBZ yellow. The catalyst reduced the CBZ sublimation temperature by 20 °C, the sublimation time was also reduced and there was no trace of acetamide in the sublimate.[13] The sublimation is carried out inside a Petri dish which is placed above a small heater inside a vacuum oven. The local concentration of the lower molecular weight catalyst is maintained for the duration of the

sublimation process by the almost closed nature of the apparatus. Further details of the apparatus are given in the supporting information. The presence of dimers in the gas phase of CBZ is inferred from the presence of hydrogen bonded dimers in the crystal structures of the four CBZ forms that can be crystallized from solution and by analogy with carboxylic acids which have been long known to associate in solution[16,17] and for which there is direct evidence of dimer dominance in the gas phase.[18] There is also clear evidence that *p*-aminobenzoic acid, PABA, is present as dimers in the gas phase.[19]

2.1.2 Sublimation onto polycrystalline powder templates. Following the successful application of sublimation to the production of the first solvent free single crystals of stanozolol and ethinylestradiol[20, 21] and the interesting report of the use of a single crystal template for polymorph control during sublimation [22] we decided to modify our sublimation apparatus to allow the use of polycrystalline powder templates for polymorph control.[13] Almost simultaneously and in an attempt to improve the polymorph control produced by single crystals the use of liquid drop cast polycrystalline film templates for sublimation at atmospheric pressure was reported.[23] The apparatus we have used for sublimation is described in detail in the supporting information where a movie of template production is included, Figure S1.

3. Results and discussion

3.1 Preparation of PAR forms II and III. PAR is known to exist in three polymorphic forms, stable monoclinic form I, metastable orthorhombic form II and highly unstable form III.[24-27] PAR form II when crystallized from solution is found to be more soluble and has better tableting properties than form I and would be preferred in production.[12] Pure crystalline form III has been prepared in a sealed glass capillary from which water was rigorously excluded.[27] It is also possible to stabilize low concentrations of PAR form III in a suitable excipient matrix.[28]

It has been reported that solution crystallization of PAR form II is not as reliable as melt quenching. Thus melting small quantities of PAR on a microscope slide gives an amorphous glass which crystallized in air to pure form II.[29] This small amount of form II was then used as seed for solution crystallization from ethanol.[30] The yield of those crystals was reported to be not more than 30% and residual solvent left over in the crystals led to the transformation of form II to form I upon storage. Further work on PAR form II crystallization reported higher yields of up to 60%.[31] There is also a study of crystallization of PAR from water which under carefully controlled conditions claimed the production of form II crystals with a 95% success rate.[32] Interestingly PAR II crystals grown from water contain trapped water that can be observed by DSC to melt at 0 °C.[33] The thermal conversion of form II to form I has been reported to take place at a

range of temperatures. It appears that the form II→ form I transition below the melting point and even at ambient temperature can be accelerated by solvent inclusions.[33, 34] A recent study has suggested that crystallization of PAR in the presence of high concentrations of potential co-crystal formers gave form II crystals.[35]

In an effort to provide a reliable solvent free method for the conversion of PAR form I to form II the use of melt quench sublimation templates was examined. Small quantities of PAR were melted on a microscope slide using a spirit lamp and its crystallization was observed by placing the microscope slide directly in a powder diffractometer. After 5 mins only an amorphous halo was observed, after 15 mins the 002 and 004 reflections of form II were observed and after 60 mins the sample had fully crystallized to form II, Figure 2. The crystallized sample on the microscope slide was used as a template in a sublimation experiment and pure PAR form II was recovered. This was repeated four times with the same template yielding 1 g PAR form II in total. It is noticable that the relative intensities in the crystallized melt, Figure 2(c), are different from those of the recovered sample, Figure 2(d). This is reasonable as the crystallized melt clearly has unique preferred orientation while the recovered sample, which was mounted in the normal way, has relative intensities which closely match the calculated form II pattern. This sample of form II was stable at 40 % relative humidity for two years. Samples of form II produced by sublimation show a small DSC peak at 108 °C attributed to the transformation to form I before melting at 170 °C, S11.[33]

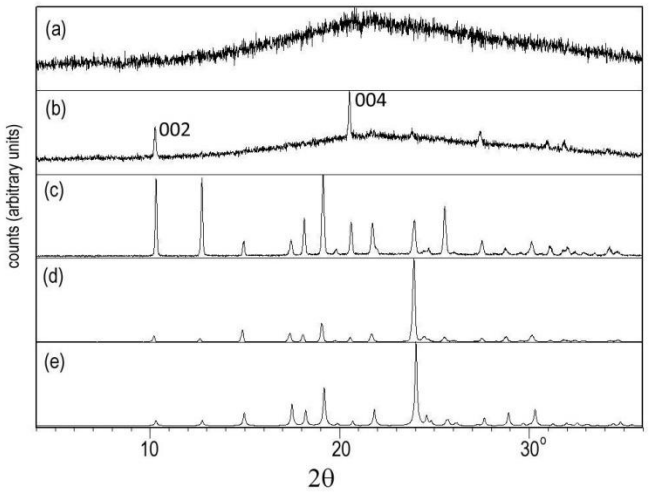


Figure 2. XRPD patterns (Cu radiation) showing the PAR glass to form II transition after (a) 5 min, (b) 15 min, (c) 60 min and (d) PAR form II recovered from template sublimation and (e) PAR form II pattern generated from single-crystal data (refcode: HXACAN23).

3.2 Sublimation of carbamazepine, CBZ. CBZ has five known polymorphs. The crystal structures of forms I to IV contain hydrogen-bonded dimers and form V in contrast contains a hydrogen-bonded catemer. Forms I to III can be obtained by simple solution crystallization.[22, 36-39] Solution crystallization of form IV has been reported when polymer heteronuclei are present and form V has been crystallized by sublimation onto a template of a related catemeric derivative.[23,36,39] We have previousely reported the succesful use of sublimation polycrystalline powder templates for CBZ forms I to III.[13]

3.2.1 Carbamazapine, CBZ, form IV. Crystallization of carbamazepine from saturated solutions which contained some hydroxypropylcellulose has been reported to give plate like crystals of CBZ form IV which are occasionally contaminated with CBZ form I needles.[39] Using a sublimation template of CBZ form IV it is possible to generate pure CBZ form IV by sublimation. The XRPD pattern indicates that no other form is present, Figure 3.

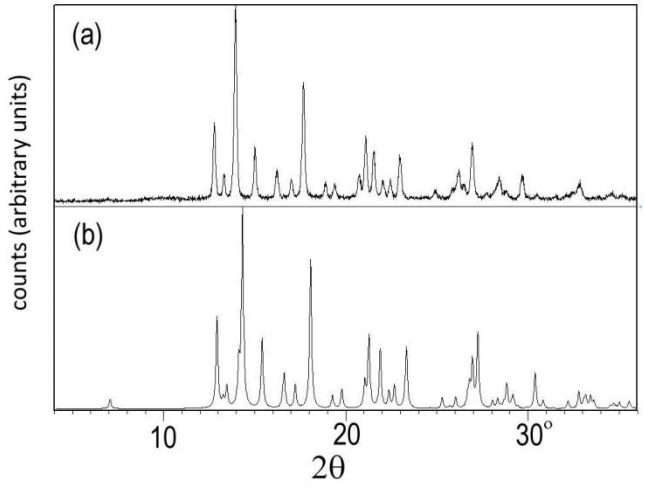


Figure 3. XRPD pattern (Cu radiation, ambient temperature) of (a) CBZ form IV obtained by template sublimation and (b) pattern of CBZ form IV generated from single-crystal data (refcode: CBMZPM1202, structure determined at 158 K).

3.2.2 Carbamazepine form V. Following the report of the use of dihydrocarbamazepine, DHC, form II for the template sublimation at ambient pressure of CBZ form V we have examined CBZ form V production in our apparatus.[23] We obtained DHC in essentially quantitative yields by catalytic hydrogenation of CBZ.[40] DHC form II was obtained by crystallization from ethyl acetate. The DHC

template and CBZ form V crystals growing on it are shown in Figure 4. The XRPD of form V (Figure S2) shows no contamination with DHC, when the sublimate is gently scraped off, as the template adheres strongly to the sticky tape.

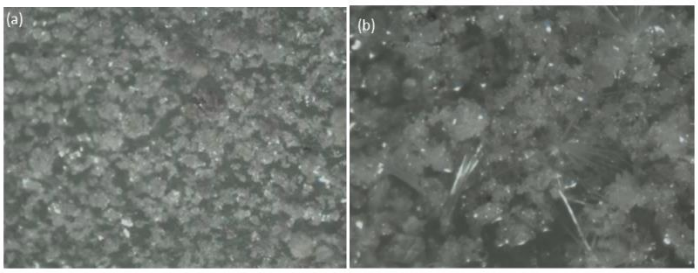


Figure 4. (a) DHC form II as the template on double sided sticky tape and (b) CBZ FV needles sublimed onto DHC form II.

3.3 Sublimation of DHC. Under a vacuum of 300 mm Hg DHC sublimed to give a mixture of forms I and II. The XRPD pattern is shown in Figure S3. At a vacuum of 0.2 mm Hg DHC sublimed to give form I with a tiny amount of form II impurity, Figure S4. In the presence of a template of CBZ form III and at a pressure of 0.2 mm Hg only DHC form II grew on the CBZ form III template, Figures 5 and S4. As CBZ form III has hydrogen bonded dimers in its structure the growth of crystals with a catemeric motif was not expected. The known dimeric DHC form IV might have seemed a more likely result. However, the catemeric DHC forms I to III have all been calculated to be more stable than dimeric form IV and this could be the reason for the latter's failure to form.[41]

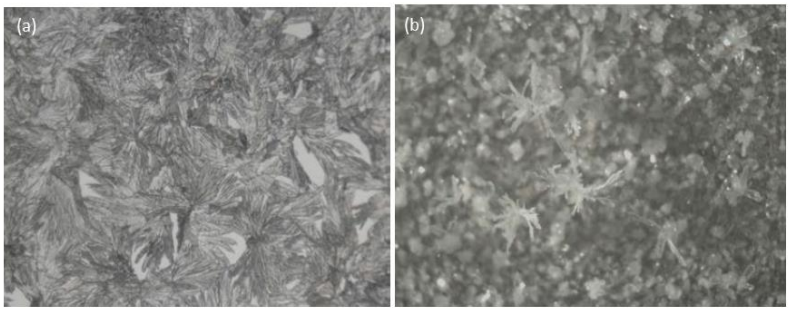


Figure 5. (a) CBZ form III as the template on double sided sticky tape and (b) DHC form II sublimed onto CBZ form III.

3.4 Sublimation of mefenamic acid. Mefenamic acid, MEF, has three known polymorphs. Forms I and II can be prepared by solution crystallization and form III crystallized during attempted co-crystallization experiments with adenine. All three forms contain hydrogen bonded carboxylic acid dimers.[42] Sublimation of mefenamic acid gave a mixture of forms I and II in the sublimate. XRPD patterns clearly show that the use of templates of forms I and II gave effective polymorph control of the sublimation process, Figure 6.

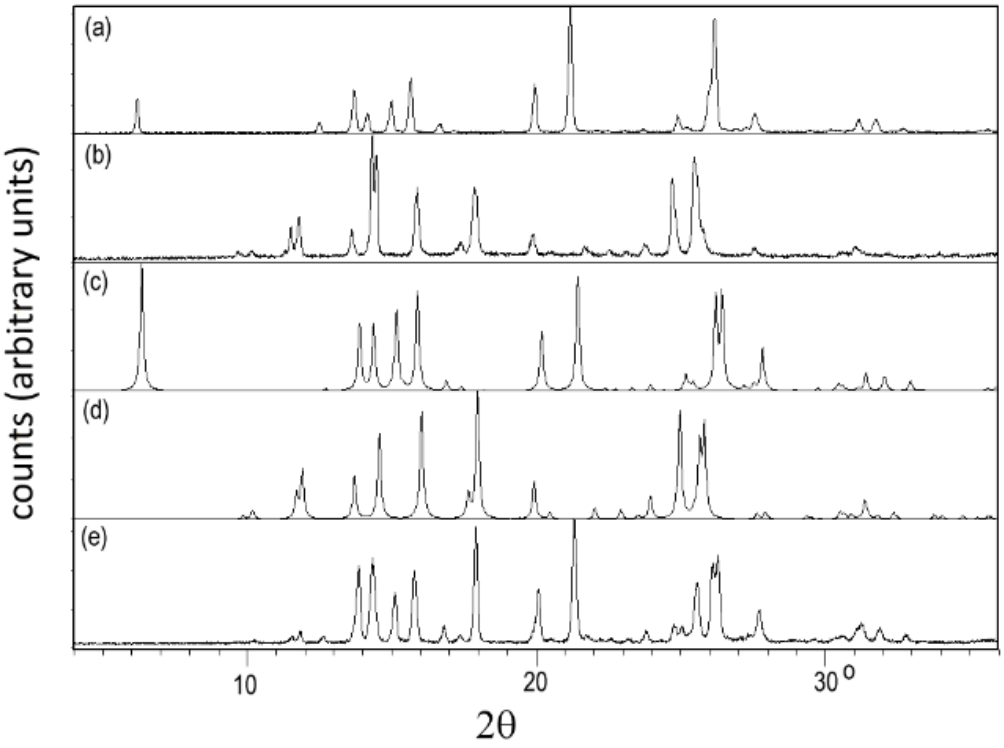


Figure 6. XRPD patterns: (a) MEF sublimed onto MEF form I template, (b) MEF sublimed onto MEF form II template, (c) calculated pattern of MEF form I, (d) Calc. pattern MEF form II and (e) MEF sublimed without a template.

3.5 Sublimation of metaxalone. There are two known polymorphs of metaxalone, MTX. Form I contains hydrogen bonded imide imide catemer chains and form II contains imide imide dimers.[43] This suggested that a suitable amide could function as a sublimation catalyst. Gas phase calculations of the energy differences between MTX dimers, MTX butyramide adducts and their components gave values of 74.4 and 71.9 kJ/mol for the energies of dimer and adduct formation respectively. Since there is little

difference between the energies of the dimer and the butyramide adduct these calculations suggest that butyramide could be an effective sublimation catalyst. Sublimation of MTX alone gives form I in the sublimate. However the sublimation process is slow and the addition of butyramide reduced the sublimation temperature by 20 °C and the sublimation time from 24 hrs to 6 hrs. Sublimation onto a form II template gave only form II on the template, Figure 7 and Figure S5.

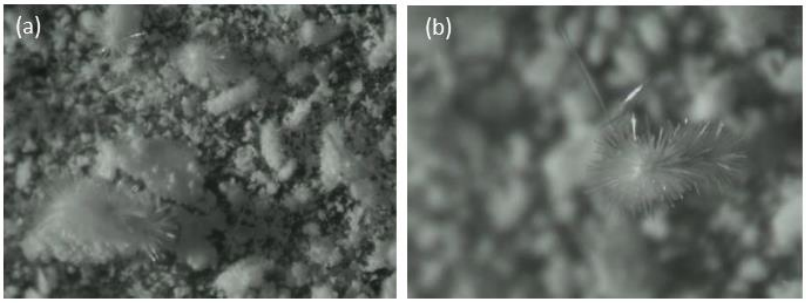


Figure 7. MTX sublimation onto MTX form II: (a) focus on the template and (b) focus on crystals of form II grown on the template.

3.6 Sublimation of amino benzoic acids

3.6.1 *p*-Aminobenzoic acid (PABA). p-Aminobenzoic acid (PABA) has three well characterized polymorphs. Crystallization of PABA from solution yields form I (α form) above 13.8 °C and form IV (β form) can crystallize below this temperature.[44, 45] The other form for which a crystal structure is available is numbered form V.[46] This was crystallized from selenous acid solution and it appears to have been a fortuitous crystallization. Attempts to reproduce the crystallization of PABA form V from selenous acid at concentrations up to 10% gave only the hydrated salt $(H_3NC_6H_4CO_2H)^+(HOSeO_2)^-.H_2O$. Crystallization was also attempted from solutions of the related phosphinic acid but again only a salt, $(H_3NC_6H_4CO_2H)^+(H_2PO_2)^-$, and a hydrated salt, $(H_3NC_6H_4CO_2H)^+(H_2PO_2)^-.H_2O$ were obtained. Details of these structures are in the supporting information, Figures S6-S8. It was therefore surprising to find that on sublimation most of the crystals were form V crystals with about 10% of them being form I. Since the crystals were growing on the glass Petri dish lid the use of glass wool as a template was examined. An example of the crystals obtained are shown in Figure 8. All of the crystals grown on the glass wool that were examined were form V. When PABA form I was used as a template and with the vacuum oven set to 300 mm Hg the template controlled crystal nucleation and growth and only pure form I was found in the sublimate.

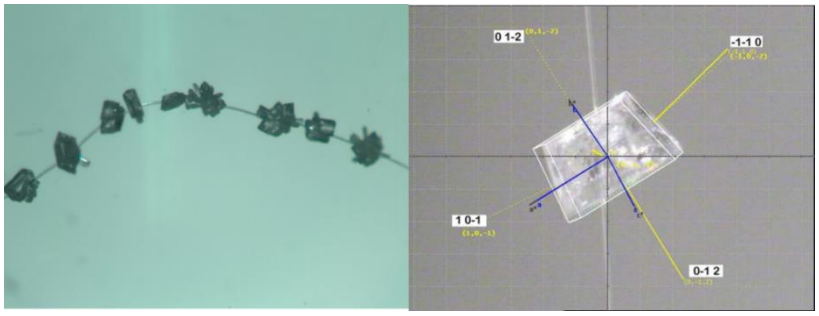


Figure 8. Crystals of PABA form V grown on glass wool and a crystal on the glass fiber indexed on the diffractometer (R_{int} = 2.3%).

3.6.2 *m*-Aminobenzoic acid, MABA. MABA has five well characterized polymorphic forms. The commercial form is form III. Forms I and III can be obtained by solution crystallization, form IV by sublimation and forms II and V by complex heat treatment of the other forms.[47] We were unable to obtain samples of form V. Sublimation without a template gave form IV at a vacuum of 0.2 mm Hg (as reported) and at pressures of 300 and 760 mm Hg forms IV and II, respectively, were obtained. However, sublimation onto templates of forms I to IV gives pure samples of forms I to IV. The XRPD patterns are in Figure 9. There is no crystal structure available for form I. The reported crystal structure of form IV was calculated from a powder pattern.[47] However, crystals grown by sublimation were of suitable quality for single crystal study which confirmed the reported structure solution from powder data. The crystal data are in the supporting information.

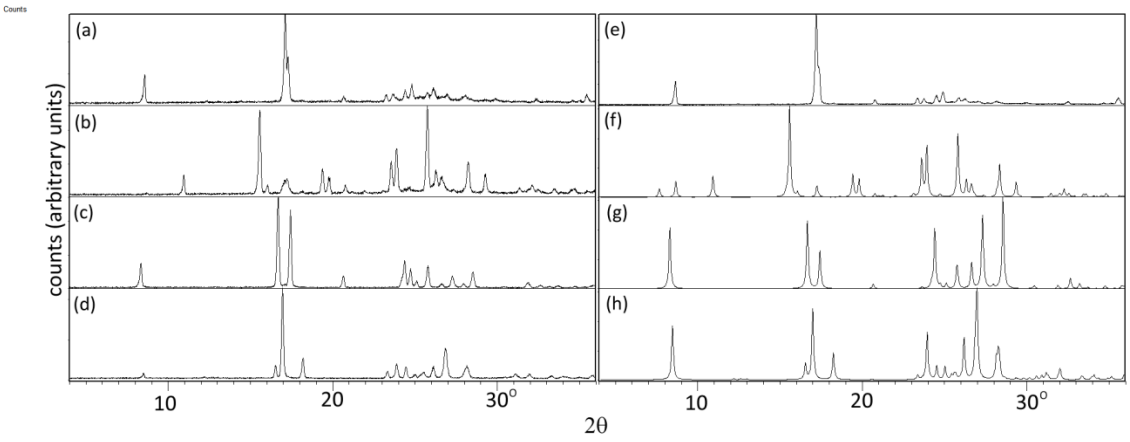


Figure 9. XRPD patterns of MABA forms I – IV, (a) to (d) grown on templates of forms I to IV and (e) pattern of a form I sample and (f) to (h) patterns generated from single-crystal data using refcodes: AMBNZA, AMBNZA01 and AMBNZA02 respectively.

3.6.3 *o*-Aminobenzoic acid, OABA. OABA has three known polymorphic forms.[48-51] The commercial forms obtained from two suppliers were mixtures of forms II and III. It was more difficult to control the sublimation of OABA than the other systems examined. The lower temperature limit of the apparatus of approximately 50 °C was probably too high for more complete control of OABA sublimation. Sublimation in the presence of valeric acid gave pure form II and the process was catalysed by this additive (Table 1). The use of lower desublimation temperatures gave mixtures of forms II and III which were similar to the commercial form.

3.6.4 Do zwitterions sublime? It is interesting to speculate on the nature of the species in the gas phase during aminobenzoic acid sublimation. In MABA aqueous solution crystallization zwitterions may play an important role as 50% of the species in solution are zwitterionic and perhaps less of a role in PABA crystallization where the zwitterion content is less than 20% .[52, 53] Gas phase calculations show that in the case of PABA and MABA the zwitterions are less stable than the unionized forms by 295.4 and 236.4 kJmol^{-1} respectively. It is therefore likely that the gas phase species are not zwitterionic and that the proton transfer probably takes place as part of the crystal growing process. Another point in favor of this idea is that gas phase calculations suggest that OABA zwitterions have no stability in the gas phase since any attempt at structure optimization leads to proton transfer to the unionized form. Yet despite this clear OABA zwitterion instability one of the two moieties in the asymmetric unit of OABA form I is zwitterionic.[50] It is likely that OABA form I uses some of its lattice energy for proton transfer and zwitterion formation during crystal growth.

4. Experimental

4.1 Materials and methods. Carbamazepine, CBZ; mefenamic acid, MEF; paracetamol, PAR and metaxalone, MEX were purchased from TCI and XRPD confirmed that they were forms III, I, I and I respectively. *p*-Aminobenzoic acid, PABA; *m*-aminobenzoic acid, MABA and *o*-aminobenzoic acid, OABA were purchased from Sigma-Aldrich and XRPD patterns showed that they were forms I, III and a mixture of forms II and III respectively. Solvents were purchased from Merck and used without further

purification. Dihydrocarbamazepine, DHC was obtained by reduction of CBZ and further details are given in the supporting information.

4.2 Low-temperature gradient sublimation

Details of the sublimation apparatus and a movie of template preparation are shown in the supporting information, S1.

4.3 Single crystal X-ray diffraction

An Oxford Diffraction Xcalibur system was used to collect X-ray difraction data at ambient temperature for MABA FIV and the PABA salts. The crystal structures were solved using ShelxT [54] and refined by full matrix least-squares using ShelxL [55] both of which were driven by the Oscail package.[56]

4.5 X-ray powder diffraction

X-ray powder patterns were recorded on an Inel Equinox 3000 powder diffractometer between 5 and 90 ° (2θ) using Cu K_α radiation (λ = 1.54178 Å, 35 kV, 25 mA). Theoretical powder patterns of the different polymorphs were calculated using the Oscail software package.[56]

4.6 Molecular orbital gas phase calculations

Molecular orbital DFT calculations were carried out using Gaussian 09 [57] using the B3LYP functional and 6-31G* basis sets. Molecules were constructed using Moilin within the Oscail package.[56]

5. Conclusions

The use of additives which accelerate the sublimation process and polycrystalline desublimation templates increase the polymorph selectivity of the sublimation process. Using these methods it is possible to selectively produce pure samples of all five forms of carbamazepine and the form II of paracetamol. Solvent free samples of paracetamol form II obtained by sublimation have long term stability to polymorph transformation. In particular for the sublimation of CBZ onto the DHC template and vice versa, an interesting question would be if the templating effect is due to expitaxial growth or whether a more general heterogenous mechanism is operative. CBZ form V and DHC form II are isomorphous. However, because of the small particle size of the powder template the directed formation of CBZ form V / DHC form II was not investigated further in this work, but will be addressed in a separate study.

In summary, for sublimable compounds sublimation can provide a selective and 'green' method for the production of pure polymorphic forms. The focus of future work will be the scale-up of the additive- and template-enhanced sublimation process.

6. Assocciated content

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Sublimation apparatus and video; additional XRPD patterns; crystal data and refinement data of $HPABA^{+}H_2PO_2^{-}$, $HPABA^{+}H_2PO_2^{-}\cdot H_2O$, $HPABA^{+}HSeO_3^{-}\cdot H_2O$ and MABA FIV and figures of the X-ray structures; experimental details of the preparation of DHC, DSC plot of PAR FII.

CCDC 1824340–1824343 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

7. Acknowledgment

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Table 1. Sublimation experiments and conditions.

Initial form	Sublimate	Vacuum	Sublimation template
CBZ FIII	CBZ FI	0.2 mmHg	CBZ FI
CBZ FIII	CBZ FII	0.2 mmHg	CBZ FII
CBZ FIII	CBZ FIII	0.2 mmHg	CBZ FIII
CBZ FIII	CBZ FIV	0.2 mmHg	CBZ FIV
CBZ FIII	CBZ FV	0.2 mmHg	DHC FII
PAR FI	PAR FI	0.2 mmHg	
PAR FI	PAR FII	0.2 mmHg	PAR FII
PABA FI	PABA FI+ V	0.2 mmHg	-
PABA FI	PABA FV	0.2 mmHg	Glass wool
PABA FI	PABA FI	300 mmHg	PABA FI
MABA FIII (Z)	MABA FIV (Z)	0.2 mmHg	-
MABA FIII (Z)	MABA FIV (Z)	300 mmHg	-
MABA FIII (Z)	MABA FII	760 mmHg	-
MABA FIII (Z)	MABA FI (Z)	0.2 mmHg	MABA FI Z
MABA FIII (Z)	MABA FII	0.2 mmHg	MABA FII
MABA FIII (Z)	MABA FIII Z	0.2 mmHg	MABA FIII Z
MABA FIII (Z)	MABA FIV (Z)	0.2 mmHg	MABA FIV Z
OABA*	OABA FII +FIII	0.2 mmHg	-
OABA*	OABA FII	0.2 mmHg**	-
MTX FI	MTX FI	0.2 mmHg	-
MTX FI	MTX FII	0.2 mmHg***	MTX FII
MEF FI	MEF FI	0.2 mmHg	MEF FI
MEF FI	MEF FII	0.2 mmHg	MEF FII

* commmercial form (FII + FIII). ** Valeric acid used as an additive. *** Butyramide used as an additive. Z indicates the presence of zwitterionic species in the solid state. FI, FII, FIII, FIV denotes form I, form II, form III, form IV.

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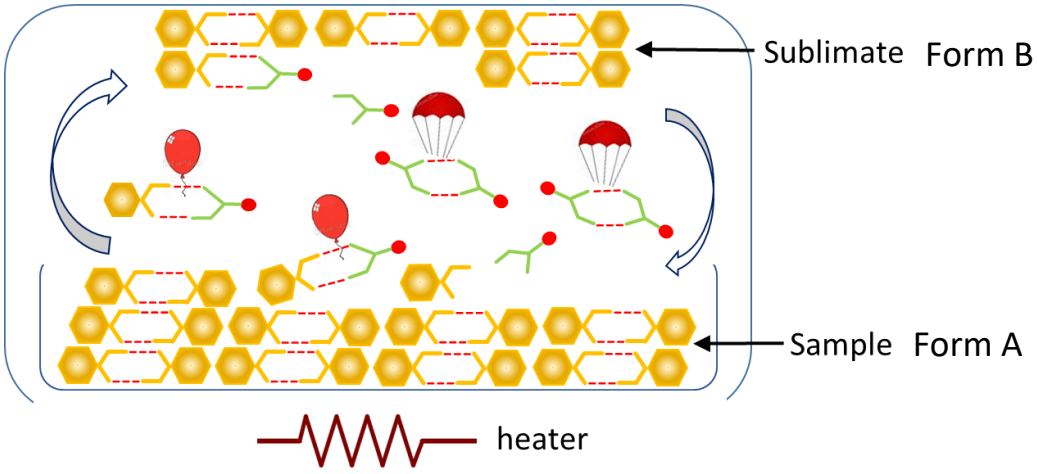
The use of sublimation catalysis and polycrystalline powder templates for polymorph control of gas phase crystallization

Naghmeh Kamali, Ciaran O'Malley, Mary F. Mahon, Andrea Erxleben* and Patrick McArdle*



Complete polymorph control of gas phase crystallization was achieved for carbamazepine, metaxalone, mefenamic acid, paracetamol, and *ortho*-, *meta*- and *para*-amino benzoic acids through the combined use of catalytic additives and polycrystalline powder templates.