

Unexpected Effects of Catalytic Amounts of Additives on Crystallization from the Gas Phase: Depression of the Sublimation Temperature and Polymorph Control

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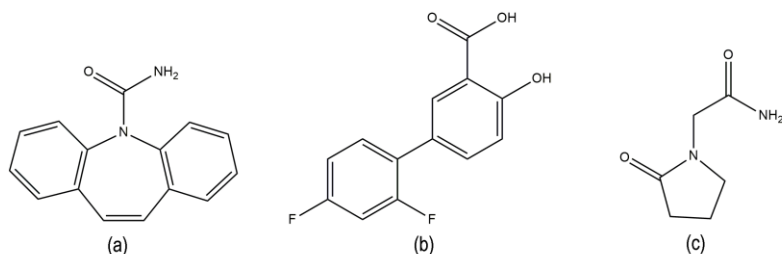
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Abstract

Sublimation of carbamazepine, piracetam, diflunisal and p-aminobenzoic acid is enhanced by the presence of additives. Temperature reductions and polymorph control have been observed. Sublimation of carbamazepine containing less than 5% by weight of acetamide reduces the sublimation temperature by 20 °C and yields pure form 1. In the absence of acetamide carbamazepine sublimation yields forms I and III. The enhancement mechanism appears to involve more volatile adduct formation. Sublimation of carbamazepine onto polycrystalline powder templates of carbamazepine forms I, II and III yields pure samples of these forms. Valeric acid is an effective additive in sublimations of diflunisal, piracetam and p-aminobenzoic acid.

The use of additives to provide polymorph control of solution crystallization is well established. ¹ Some examples include the stabilization of the metastable polymorphs of L-glutamic acid, sulfamerazine, flufenamic acid and paracetamol using structurally related additives. ²⁻⁵ In the case of sulfathiazole the presence of 1 mol.% of ethamidosulphathiazole gave crystals of metastable form I. At concentrations lower than 1 % polymorph control was lost. ⁶ Polymorph control of sublimation crystallization has relied

on temperature control and in the case of carbamazepine (CBZ) on the use of a template crystal of a structurally related compound.^{7,8} Polymorph control of CBZ solution crystallization using nucleation onto polymers has also been reported.⁹ In contrast, the use of additives for polymorph control of sublimation crystallization or enhancement of the sublimation process has not been reported.



Scheme 1. Structures of (a) carbamazepine, (b) diflunisal and (c) piracetam

In the present study vacuum sublimation of commercial CBZ form III was found to lead to crystallization of a mixture of CBZ forms I and III at 120 °C and 0.2mm Hg pressure. However, the addition of less than 5% by weight of acetamide to CBZ sublimation reduces the sublimation temperature to just below 100° C and leads to the selective crystallization of only form I. PXRD patterns are shown in Figure 1.

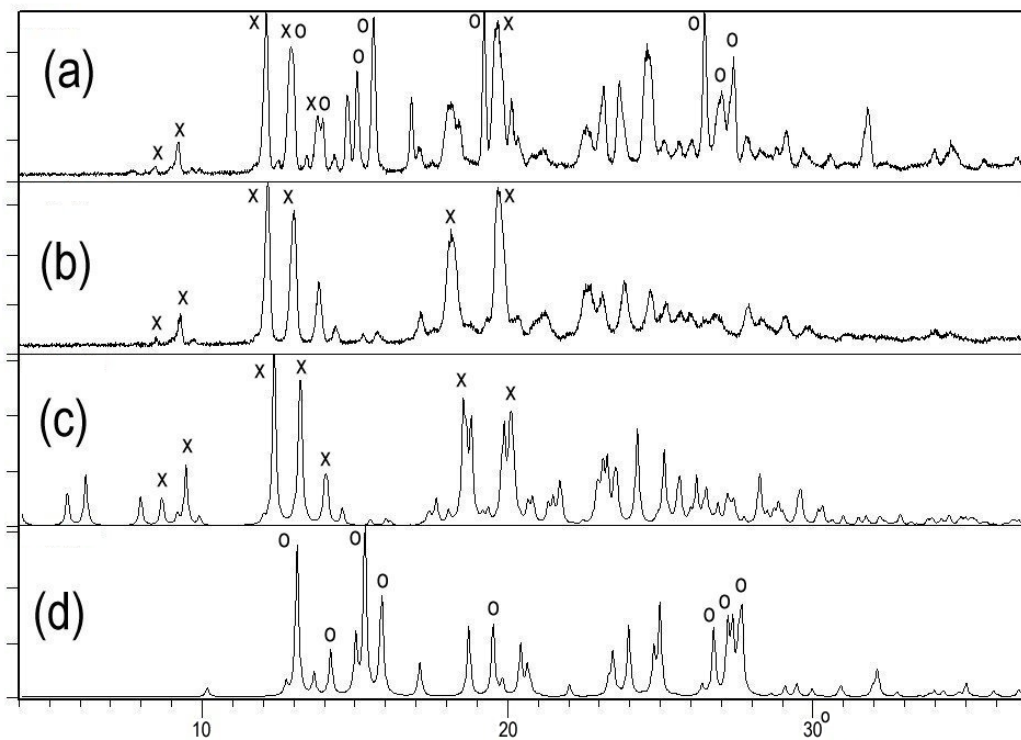


Figure 1. PXRD patterns, (a) CBZ sublimed in the absence of additives; formation of forms I (x) and III (o), (b) CBZ sublimed with acetamide; formation of form I, (c) calculated pattern for CBZ form I, (d) calculated pattern for CBZ form III

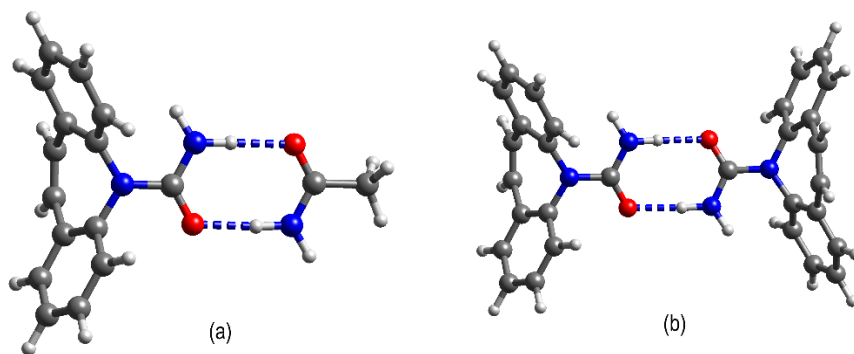


Figure 2. Optimized hydrogen bonded adduct structures for (a) CBZ-acetamide and (b) the CBZ dimer.

The depression of the sublimation temperature by a catalytic amount of an additive is an effect that has not been previously described. We propose that the mechanism for this sublimation enhancement is the formation of the more volatile CBZ-acetamide hydrogen bonded adduct on the surface of evaporating CBZ crystals which transports CBZ at lower temperatures to the crystal growing sites than would be possible for CBZ dimers. The energy differences between the optimized structures of the CBZ-acetamide adduct and the CBZ dimer (Figure 2) and their components have been calculated to be 74 and 72 kJ/mol respectively (see SI for details). We attribute polymorph selection in the presence of this additive to a temperature effect. CBZ form I has a stacked lattice in which the molecules are in vdW contact (see SI). This enhances rapid growth of this polymorph at lower temperature.¹⁰ We have found that accurate control of the sample temperature makes the sublimation experiments described here highly reproducible. The sublimation apparatus consists of a Petri dish sitting on top of a small heater in a vacuum oven and it is described in detail in the Supporting Information (SI). The life time of acetamide in the Petri dish at the sublimation temperature used for CBZ sublimation is approximately the same as the sublimation process itself. Indeed, it is only the almost closed nature of the Petri dish, which slows the loss of acetamide, that makes the process possible. The possibility of contamination of the CBZ sublimate with acetamide has been tested by comparing the powder patterns of CBZ form I (prepared without the use of acetamide),¹¹ CBZ form I to which 1% of acetamide had been added, CBZ sublimed in the presence of acetamide and acetamide, Figure 3.

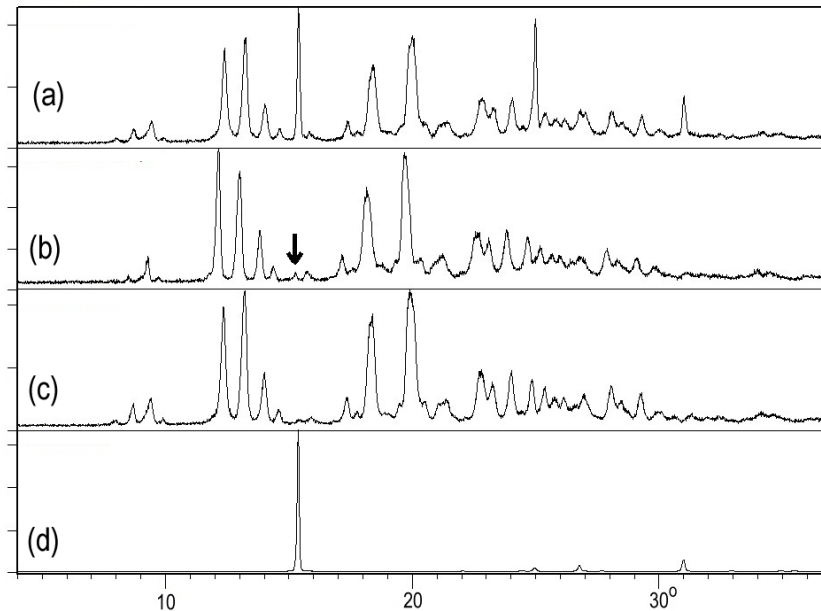


Figure 3. XRD patterns, (a) CBZ form I with 1% acetamide, (b) CBZ sublimed with acetamide (as in Figure 1(b)), (c) CBZ form I and (d) acetamide.

The XRD patterns in Figure 3 indicate no detectable acetamide in the sublimed CBZ sample. There is a tiny peak in the pattern of CBZ sublimed with acetamide (which is marked in Figure 3(b) and also observed in pure CBZ form I) at 15.26° which is close to the strongest peak in the acetamide pattern at 15.38°. Even if this peak were assigned to acetamide it is estimated that it would represent less than 0.03% of the sample. No evidence for either the crystallization of acetamide on the glass condensing surface or the formation of a cocrystal between CBZ and acetamide was found. These results can be contrasted with reports of co-crystals grown by sublimation. For example, cocrystals of 4-hydroxybenzamide and salicylic acid derivatives have been obtained by sublimation.¹² In those examples the volatilities of the cocrystal and its components are similar and do not have the quite large volatility differences which exist between the relatively low molecular weight additives and the compounds sublimed in this work.

In addition to additive control of polymorph selectivity we have also observed even more effective polymorph control using templating with polycrystalline powders of CBZ polymorphs. Thus using double sided sticky tape to hold powders of CBZ forms I, II and III onto the condensing plate, yields pure CBZ forms I, II or III (Figure 4). The strong preferred orientation and the small number of observed peaks in the PXRD pattern of form II, Figure 4 (b), is due to the needle shape of the sublimed crystals. This templating effect can be compared to that reported for the sublimation of CBZ in the presence of a template single crystal of 10,11-dihydrocarbamazepine, DHC, which led to the growth of catameric CBZ form V crystals on the lateral faces of the template crystal and a mixture of forms I and III elsewhere in the apparatus.⁸

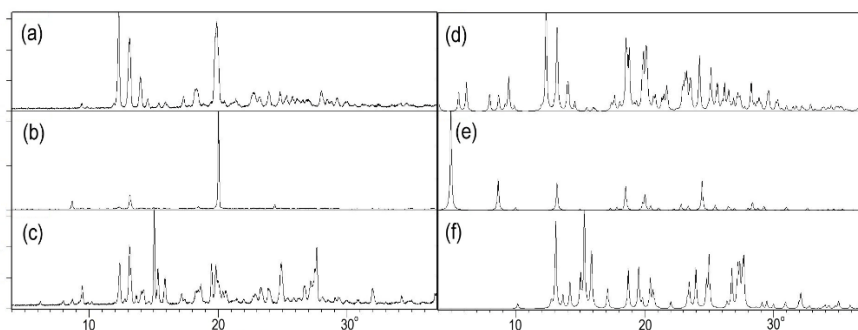


Figure 4. PXRD patterns, (a) CBZ sublimed onto CBZ form I powder, (b) CBZ sublimed onto CBZ form II powder, (c) CBZ sublimed onto CBZ form III powder. (d), (e) and (f) are the calculated patterns.

CBZ form II is a channel solvate that can be grown from several solvents.¹³ There is clear crystallographic evidence for solvent in the channels in the case of tetrahydrofuran, (THF).¹⁴ Indeed on the Cambridge database THF containing form II is not classified as a CBZ polymorph. The solvent channels occupy 9% of the structure¹⁵ and it has been estimated that the solvent in the channels stabilizes the structure by up to 9 kJ/mol.¹³ Lattice energy calculations for CBZ forms suggest that CBZ form II without solvent is 6.8 kJ/mol less stable than the more stable form III.⁸ Interestingly CBZ dihydrate collapses to form II when freeze dried and to a mixture of amorphous CBZ and forms I and III

at atmospheric pressure when the relative humidity is below 40%.^{16,17} The question of whether truly solvent free form II can be prepared has been raised.¹⁴ The solvent-free sublimation experiments described here show clearly that solvent free crystals of CBZ form II can indeed be grown and that these solvent free crystals may be the first pure sample of solvent-free form II. It appears that crystals grown by sublimation for molecules similar in size to CBZ can be stable with void volumes of up to 10%. This is consistent with our observation that CBZ form II crystals grown from toluene (that contain some toluene in the channels) do not decompose or change their PXRD pattern after several hours under vacuum. Stanazolol is another example where solvent free void containing crystals of its forms I and II, with estimated void volumes of 4 and 10%, can be grown by sublimation.⁷ The much higher estimated void volume of 20% of a solvent free CBZ dihydrate structure may be the reason why it cannot be dehydrated without structure collapse when CBZ dihydrate crystals are placed under vacuum.¹⁶

Valeric acid, VA, is a low melting and relatively high boiling carboxylic acid which can form complementary hydrogen bonds to other carboxylic acids and amides. Using 5% VA accelerated sublimation has been observed for piracetam, diflunisal and p-aminobenzoic acid, PABA. The sublimation temperature reductions observed are 10, 15 and 20 °C respectively. In the case of PABA a templating effect was also observed. PABA sublimes at 80 °C under a vacuum of 0.2 mm Hg to give block like crystals of form V which has been described as a rare form and has only been obtained from an aqueous solution containing a mixture of PABA and selenous acid (H₂SeO₃).^{18,19} It was also found that at 140 °C under a vacuum of 400 mm Hg PABA sublimes to again give form V but with a needle like habit, Figure 5. Sublimation of PABA onto a PABA form I template at 80 °C did not yield form I but again gave form V. However, the tendency of sublimation to give form V was successfully overcome when templating using form I was repeated at 140 °C. PXRD patterns of PABA forms I and V are quite similar and the forms were identified by indexing single crystals on a diffractometer. The FT-IR spectra of form I

and V differ in the 900 – 920 cm^{-1} region and this difference was used to further confirm the polymorphic form (SI).

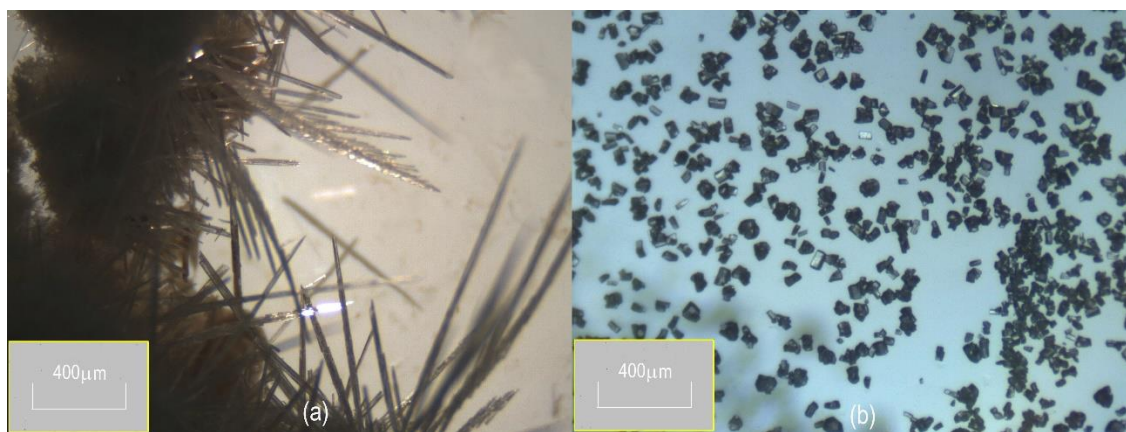


Figure 5. PABA sublimed (a) at 140 °C and (b) at 80 °C

Usually, polymorph control is achieved through time-consuming, trial-and-error based screening of solution crystallization conditions. Since many pharmaceutical APIs can be sublimed and have carboxylic acid, amide groups and related functional groups sublimation enhanced by suitable additives can potentially provide a green, solvent free, more targeted method for polymorph control. The use of polycrystalline powder templates seems to offer an alternative to the not always successful polymorph seeding in solution crystallization. Furthermore the economic advantages of any sublimation temperature depression for industrial scale sublimation has been noted and has been achieved in the past not by the presence of additives but by the use materials with high numbers of lattice defects.^{20, 21} Since many pharmaceutical APIs can be sublimed and have carboxylic acid, amide groups and related functional groups sublimation enhanced by suitable additives can potentially provide a green, solvent free method for polymorph control.

Supporting Information

Description of the sublimation apparatus, molecular orbital calculations, description of hydrogen-bonding and dispersion forces in the structure of PABA forms I and V and FT-IR spectra of PABA forms I and V.

Acknowledgement

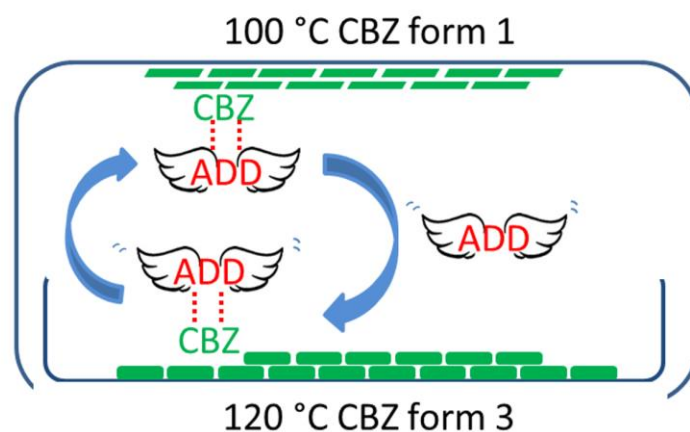
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- (1) Llinàs, A.; Goodman, J. M., *Drug Discovery Today* **2008**, 13, 198-210.
- (2) Davey, R. J.; Blagden, N.; Potts, G. D.; Docherty, R., *J. Am. Chem. Soc.* **1997**, 119, 1767-1772.
- (3) Gu, C.-H.; Chatterjee, K.; Young Jr, V.; Grant, D. J. W., *J. Cryst. Growth* **2002**, 235, 471-481.
- (4) Lee, E. H.; Byrn, S. R., *J. Pharm. Sci.* **2010**, 99, 4013-4022.
- (5) Thomas, L. H.; Wales, C.; Zhao, L.; Wilson, C. C., *Cryst. Growth Des.* **2011**, 11, 1450-1452.
- (6) Blagden, N.; Davey, R. J.; Rowe, R.; Roberts, R., *Int. J. Pharm.* **1998**, 172, 169-177.
- (7) Karpinska, J.; Erxleben, A.; McArdle, P., *Cryst. Growth Des.* **2011**, 11, 2829-2838.
- (8) Arlin, J.-B.; Price, L. S.; Price, S. L.; Florence, A. J., *Chem. Commun.* **2011**, 47, 7074-7076.
- (9) Lang, M.; Grzesiak, A. L.; Matzger, A. J., *J. Am. Chem. Soc.* **2002**, 124, 14834-14835.
- (10) Walshe, N.; Crushell, M.; Karpinska, J.; Erxleben, A.; McArdle, P., *Cryst. Growth Des.* **2015**, 15, 3235-3248.
- (11) O'Mahony, M.; Seaton, C. C.; Croker, D. M.; Veessler, S.; Rasmuson, A. C.; Hodnett, B. K., *CrystEngComm* **2014**, 16, 4133-4141.
- (12) Manin, A. N.; Voronin, A. P.; Shishkina, A. V.; Vener, M. V.; Churakov, A. V.; Perlovich, G. L., *The Journal of Physical Chemistry B* **2015**, 119, 10466-10477.
- (13) Cruz Cabeza, A. J.; Day, G. M.; Motherwell, W. D. S.; Jones, W., *Chem. Commun.* **2007**, 1600-1602.
- (14) Fabbiani, F. P. A.; Byrne, L. T.; McKinnon, J. J.; Spackman, M. A., *CrystEngComm* **2007**, 9, 728-731.
- (15) McArdle, P.; Hu, Y.; Lyons, A.; Dark, R., *CrystEngComm* **2010**, 12, 3119-3125.
- (16) Tian, F.; Zeitler, J. A.; Strachan, C. J.; Saville, D. J.; Gordon, K. C.; Rades, T., *J. Pharm. Biomed. Anal.* **2006**, 40, 271-280.
- (17) Kachrimanis, K.; Griesser, U. J., *Pharm. Res.* **2012**, 29, 1143-1157.
- (18) Sullivan, R. A.; Davey, R. J., *CrystEngComm* **2015**, 1015-1023.
- (19) Benali-Cherif, R.; Takouachet, R.; Bendeif, E.-E.; Benali-Cherif, N., *Acta Cryst. C* **2014**, 70, 323-325.
- (20) Lee, T.; Lin, M. S., *Cryst. Growth Des.* **2007**, 7, 1803-1810.
- (21) Lee, T.; Chang, S. C., *Cryst. Growth Des.* **2009**, 9, 2674-2684.

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Traces of acetamide (5 % by weight) reduce the sublimation temperature, increase the sublimation rate and lead to the selective crystallization of carbamazepine form I from the gas phase. Valeric acid reduces the sublimation temperatures of diflunisal, piracetam and p-aminobenzoic acid by 10 - 20 °C.