Angewandte Chemie International Edition

Mechanochemistry

International Edition: DOI: 10.1002/anie.201501638
German Edition: DOI: 10.1002/ange.201501638

# Cocrystal Formation through Mechanochemistry: from Neat and Liquid-Assisted Grinding to Polymer-Assisted Grinding**

*Dritan Hasa, Gabriela Schneider Rauber, Dario Voinovich, and William Jones**

**Abstract:** *Mechanochemistry is an effective method for the preparation of multicomponent crystal systems. In the present work, we propose an alternative to the established liquid-assisted grinding (LAG) approach. Polymer-assisted grinding (POLAG) is demonstrated to provide a new class of catalysts for improving reaction rate and increasing product diversity during mechanochemical cocrystallization reactions. We demonstrate that POLAG provides advantages comparable to the conventional liquid-assisted process, whilst eliminating the risk of unwanted solvate formation as well as enabling control of resulting particle size. It represents a new approach for the development of functional materials through mechanochemistry, and possibly opens new routes toward the understanding of the mechanisms and pathways of mechanochemical cocrystal formation.*

Cocrystals may be defined as stoichiometric multicomponent systems in which each component is solid under ambient conditions.[1] Compared to synthetic chemistry, cocrystallization is a noncovalent method used to improve the properties of molecules by simply modifying their solid-state arrangement rather than their chemical structure. Cocrystallization is particularly important in the pharmaceutical field as a result of its impact on drug candidate performance, for example, biopharmaceutical properties, stability, and compressibility as well as potential patentability.[1]

There are many approaches and strategies for cocrystal formation, which include solution-based or solid–solid reactions. Classical solution-based methods, however, are not always successful—in part because of differences in solubility of the individual components. On the other hand, solid-state approaches, such as mechanochemistry and high-pressure techniques, have shown high efficiency for producing multiple-component materials.[2] Neat grinding of two or more components represents the simplest case of a cocrystallization reaction through mechanochemistry. However, several examples of incomplete reaction and nonaccessible cocrystals are reported in Ref. [2].

An alternative has been liquid-assisted grinding (LAG), in which the addition of small amounts of a liquid can dramatically increase mechanochemical productivity.[2,3] The role of the liquid phase during the cocrystal formation by grinding is likely to vary from one system to another and the mechanistic aspects involved are still not fully clarified.[3]

One negative outcome frequently observed using LAG is the (unintentional) formation of crystal solvates. For example, in a recent study five different cocrystal solvates of caffeine and anthranilic acid were formed by LAG during a screening study for different (nonsolvated) polymorphic forms.[4]

In this study, we explore the use of grinding in the presence of polymeric macromolecules for the synthesis of multicomponent crystals. We were motivated by the important observation of polymer-induced heteronucleation by Matzger and co-workers.[5] Their strategy used insoluble polymeric films, as heteronuclear sites, during solution crystallization for the discovery of new extended solids and for the selective nucleation of different polymorphic phases. We were also encouraged by the recent report of Boksa et al.,[6a] who used matrix-assisted cocrystallization as a novel method for the simultaneous production and formulation of pharmaceutical cocrystals by hot-melt extrusion, and of Hasa et al.,[6b] who discovered that the protonation rate of an amorphous salt obtained through mechanochemistry can be significantly increased by the addition of a polymer.

The employment of polymers as catalysts for the mechanochemical preparation of multicomponent crystalline forms can, additionally, bring a series of advantages. Firstly, by using this new class of catalyst it is possible to avoid the formation of solvates. Moreover, when incorporated in a suitable formulation, polymers may positively influence the properties of the cocrystals such as the dissolution rate and bioavailability.[7] Regarding the intrinsic characteristics of the polymers, they can be “ad hoc” catalysts for a specific system, by appropriately modifying their physical state (i.e., by increasing or reducing the polymer chain length) or chemical composition (changing the substituents/functional groups). Potentially, the physical state (liquid or solid) of the polymer could help understanding the mechanochemical cocrystallization mechanisms during the nucleation and growth phases. Also, the large chemical versatility among possible polymers could be used as different chemical templates for polymorph screening.

The experimental dataset was developed with three different cocrystal systems that have been reported in the

---

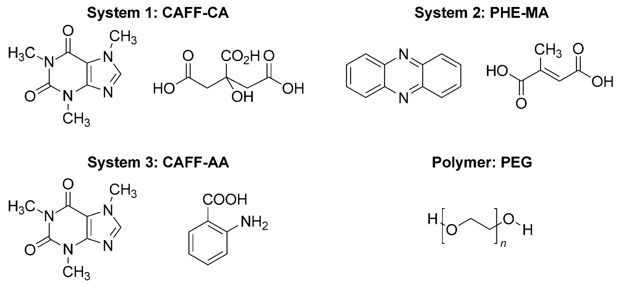
[*] Dr. D. Hasa, G. Schneider Rauber, Prof. W. Jones
Department of Chemistry, University of Cambridge
Lensfield Road, Cambridge, CB2 1EW (UK)
E-mail: wj10@cam.ac.uk

Dr. D. Hasa, Prof. D. Voinovich
Department of Chemical and Pharmaceutical Sciences
University of Trieste
P.le Europa 1, 34127, Trieste (Italy)

G. Schneider Rauber
CAPES Foundation, Ministry of Education of Brazil
Brasilia - DF 70040-020 (Brazil)

[**] D.H. and D.V. thank the University of Trieste for partially supporting this study (FRA 2013). G.S.R. acknowledges CAPES-Brazil and COT-UK for her scholarship (CsF BEX 9530/13-4).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201501638.



*Scheme 1.* Structures of PEG monomer unit and of the compounds forming the cocrystal systems used in this study.

literature (Scheme 1): system 1 is reported to be formed by caffeine and citric acid (CAFF-CA)[8] mechanochemically only by using LAG; system 2 is formed by phenazine and mesaconic acid (PHE-MA)[9] and LAG significantly increased the rate of mechanochemical cocrystallization;[10] system 3 is formed by caffeine and anthranilic acid (CAFF-AA) by neat grinding and LAG, with LAG also enabling product polymorphism.[4,11]

The polymer selected as a catalyst was polyethylene glycol (PEG). PEG is obtained by the polymerization of ethylene oxide under alkaline catalysis, and has a wide range of applications both in the chemical and pharmaceutical industries.[12] In this study, six different PEGs with molecular weight from 200 to 10 000 were used (three liquids having different viscosities and three crystalline solids with different melting points). The characteristics of the polymers used in this study are reported in Table 1.

*Table 1:* The properties of different PEGs used in this study.

| Polymer | Physical state | Viscosity[a] | Melting point |
|---|---|---|---|
| PEG 200 | liquid | 60 mPa s (20 °C) | −55 to −40 °C[a] |
| PEG 300 | liquid | 95 mPa s (20 °C) | −20 to −15 °C[a] |
| PEG 400 | liquid | 120 mPa s (20 °C) | 4 to 8 °C[a] |
| PEG 3000 | solid | N/A | 60.1 °C[b] |
| PEG 6000 | solid | N/A | 63.3 °C[b] |
| PEG 10 000 | solid | N/A | 63.7 °C[b] |

[a] Information reported on the technical data sheet. [b] Data obtained experimentally. N/A = not applicable.

Neat grinding (see Supporting Information (SI) for full details) of CAFF and CA did not result in the cocrystal formation in agreement with the results of Karki et al.[8] In that study, the authors reported that the cocrystal is formed in the presence of water, which can be present as added liquid and/or incorporated in the crystal structure of caffeine hydrate.

Grinding experiments using PEG with different chain lengths provided the CAFF-CA cocrystal. We firstly investigated the influence of the polymer amount on the reaction rate. As an illustrative example, in Figure 1 is reported the case of CAFF-CA cocrystal prepared using different amounts of PEG 10 000. In all the PXRD patterns, the presence of starting materials can be noticed particularly from the diffraction peak at 12° of $2\theta$ angle, which is typical of the pure CAFF (Figure 1). Although we did not perform quantitative analysis, it is worth noting that the intensity of the CAFF peak at 12° is high when low amounts of PEG (1 % and 5 %) are used. The presence of starting materials would appear to be lower in the PXRD pattern of a CAFF-CA cocrystal prepared using 10 % of PEG 10 000 (Figure 1 g). Interestingly, at higher percentages of PEG (especially in the case when 60 wt % of PEG 10 000 is used) the peak intensity typical of the pure CAFF increases again. A similar trend was also observed in other experiments in which PEGs with different chain lengths were used (SI). An explanation of why high amounts of polymer are not appropriate may be related to sample agglomeration, mixing problems, and to a general reduction of the total number of contacts between the reagents—a fundamental condition for the progress of the mechanochemical reaction.[13] Additional grinding experiments showed that the presence of residual starting material in the PXRD patterns of CAFF-CA cocrystals prepared in the presence of 10 wt % of different PEGs can be significantly reduced at a higher milling time (SI). The PXRD patterns of CAFF-CA cocrystals prepared in the presence of 10 wt % of different PEGs (Table 1) are reported in Figure 2 (PEG 200, 300, and 400 are liquids at room temperature). The PXRD patterns of the CAFF-CA cocrystal samples prepared in the

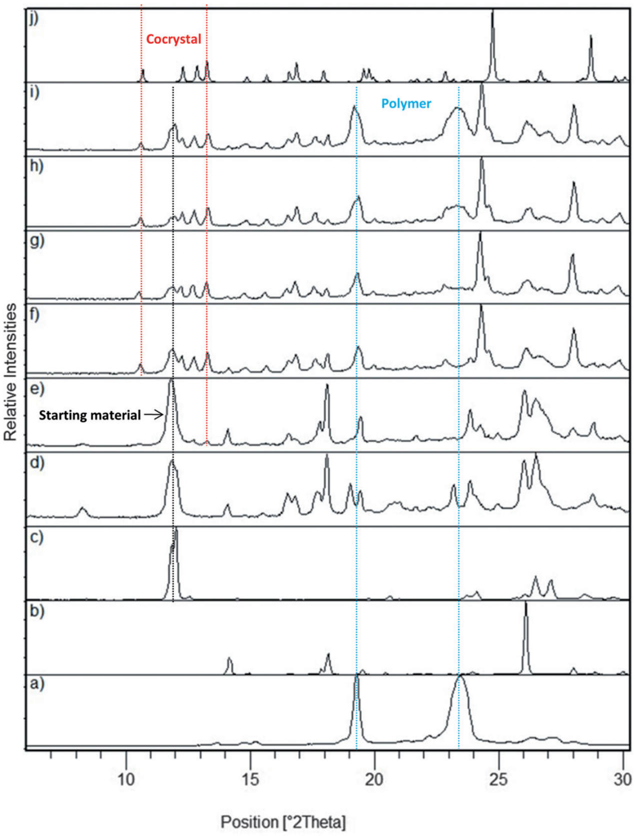


*Figure 1.* PXRD pattern of: a) pure PEG 10 000, b) pure CA, c) pure CAFF, d) CAFF and CA physical mixture neatly ground for 20 min. e), f), g), h), and i) CAFF-CA ground for 20 min with the addition of 1, 5, 10, 30, and 60 wt % of PEG 10 000, respectively. j) Calculated CAFF-CA.[8]

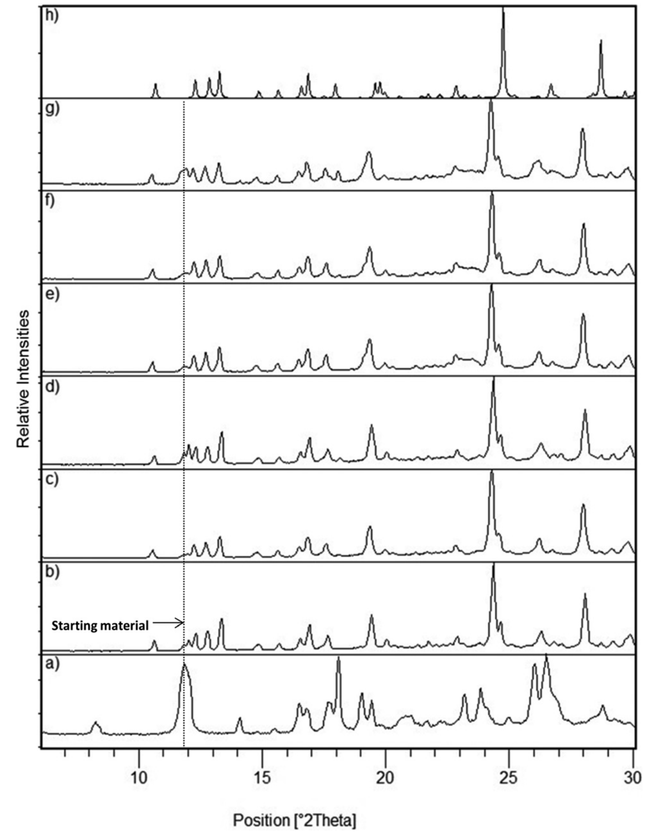


*Figure 2.* PXRD pattern of: a) CAFF-CA mixture neatly ground for 20 min, CAFF-CA cocrystal prepared using 10 wt% of b) PEG 200, c) PEG 300, d) PEG 400, e) PEG 3000, f) PEG 6000, and g) PEG 10000. h) Calculated CAFF-CA.[8]

presence of these polymers are very similar to those prepared using solid polymers such as PEG 3000, PEG 6000, and PEG 10000. In fact, the typical diffraction peak of the pure CAFF at 12° of $2\theta$ is present in all the samples and its intensity does not noticeably change when passing from the liquid to the solid polymers (Figure 2). We can therefore speculate that in the case of the CAFF-CA cocrystal system the physical state (liquid or solid) of the polymer and the polymer chain length does not play a major role on the progress of the reaction rate. This represents the first example in which the same catalyst is used both in the form of a liquid and as a solid. The physical state of the polymer does, however, influence the particle size of the resulting powders. SEM analysis showed that when 10 wt% of a liquid polymer is added, the particle size of the cocrystal powder is larger than the particle size of the powder prepared with the addition of 10 wt% of solid polymers (Figure 3). The particle shapes remain similar in all the samples.

The addition of a liquid or solid polymer during the mechanochemical cocrystallization process appears to have significant catalytic effects. In fact, on the basis of the experimental results reported above, there is strong evidence that the added polymer “assists” cocrystal nucleation and growth which, in the case of the CAFF-CA cocrystal system, does not occur under neat conditions. For this reason, we distinguish this process as “polymer-assisted grinding (POLAG)” regardless of whether the polymer is in the liquid or solid state.

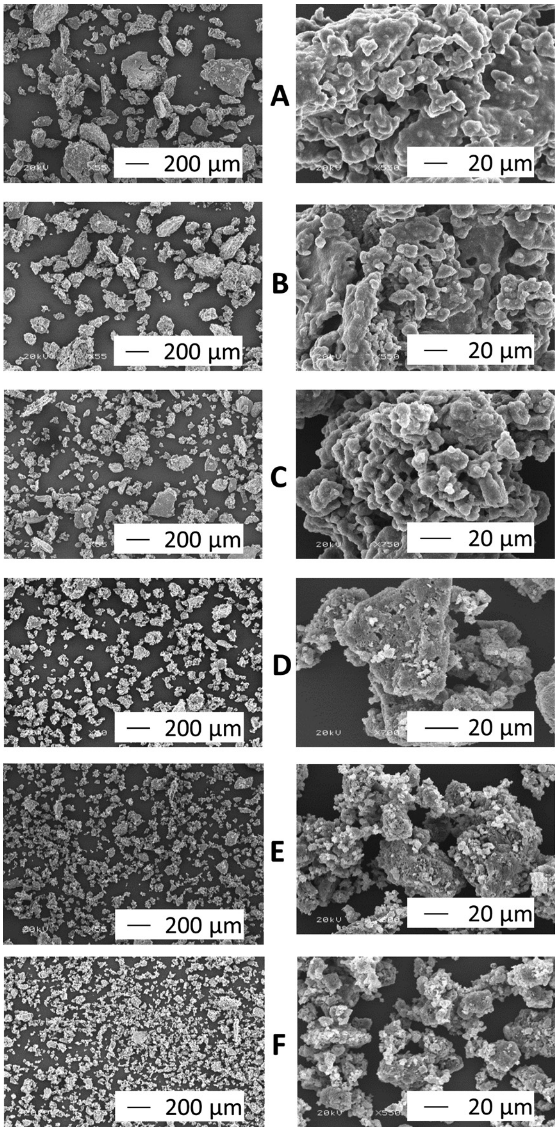


*Figure 3.* SEM image of CAFF-CA cocrystal prepared using 10 wt% of A) PEG 200, B) PEG 300, C) PEG 400, D) PEG 3000, E) PEG 6000, and F) PEG 10000.

The role of the polymer in the early stages of cocrystal formation through mechanochemistry may be similar or completely different from the already reported role of the liquid in the case of LAG.[14,15] Supplementary grinding experiments of pure CAFF and CA revealed that the starting materials neither convert into the amorphous form nor solubilize into the polymer (SI). More detailed studies are hence necessary to understand the mechanistic aspects of this process.

The second system analyzed was the cocrystal of PHE and MA in a 1:1 molar ratio.[9] The PHE-MA cocrystal has been used previously as a model system for polymorph screening[16] and to investigate the mechanisms of cocrystal formation.[10] Neat grinding of PHE and MA for 30 min resulted only in a partial conversion to the cocrystal form I, and the PXRD

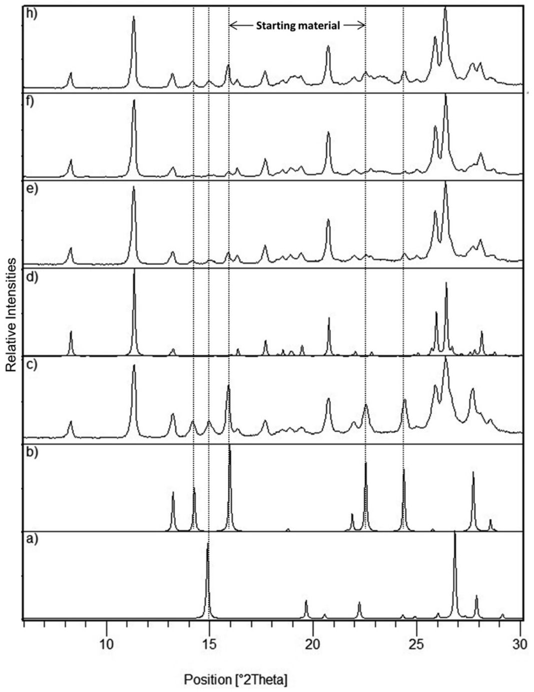


***Figure 4.*** PXRD pattern of: a) calculated MA,[17] b) calculated PHE,[18] c) PHE-MA cocrystal prepared in neat conditions, d) calculated PHE-MA,[9] e), f), and h) PHE-MA cocrystal prepared using 2.5, 5 and 10 wt% of PEG 10000 respectively.

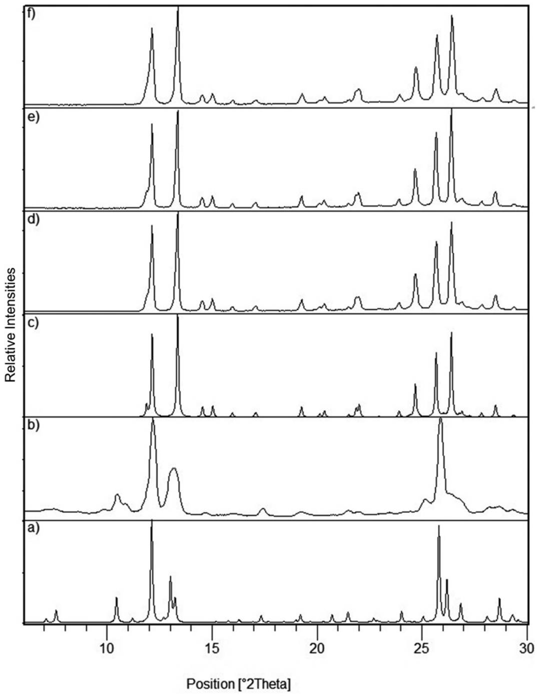


***Figure 5.*** PXRD pattern of: a) calculated CAFF-AA form I,[11] b) CAFF-AA form I prepared by neat grinding, c) calculated CAFF-AA form II,[11] d) CAFF-AA prepared by LAG with acetonitrile; CAFF-AA prepared by POLAG using 1 wt% of e) PEG 200 and f) PEG 10000.

pattern showed clear presence of starting materials (Figure 4).

We performed several POLAG experiments using different amounts of PEG 10000. The addition of 2.5 wt% of PEG 10000 reduced the intensities of the $2\theta$ diffraction peaks at 14.2° and 15.8° typical of pure PHE, and 15.0° typical of pure MA (Figure 4), whereas an almost total conversion of the starting material to the PHE-MA cocrystal could be observed when increasing the amount of the polymer to 5 wt%. As in the case of the CAFF-CA system a further increase of the polymer amount to up to 10 wt%, led to a decrease in POLAG efficiency. It is also worth noting that the physical state of the polymer, once again, did not influence the POLAG efficiency. In fact, the PXRD of the PHE-MA cocrystal prepared by POLAG using 5 wt% of a liquid polymer (PEG 200) resulted in a PXRD pattern perfectly superimposable on that obtained from a sample prepared with the addition of 5 wt% of PEG 10000 (SI).

Specifically for the CAFF-AA cocrystal system, an extensive polymorph screening study using LAG with different solvents resulted in the formation of two nonsolvated and five solvated cocrystals. However, the majority of solvents that did not form solvates led to CAFF-AA form I, whereas CAFF-AA form II, the metastable form, could be prepared in the presence of acetonitrile.[11]

Neat grinding of CAFF and AA produced the thermodynamic polymorphic form (form I)[11] of the cocrystal (Figure 5). Instead, POLAG experiments using 1 wt% of PEG 200 and PEG 10000 gave CAFF-AA form II (Figure 5). It was therefore possible to modify the polymorphic form obtained by mechanosynthesis using a polymer without any other additive. The polymer benefits are related not only to the increase of product diversity, but also on the possible stabilization of metastable phases.[19,20] In this context, it would be instructive to observe and compare the effect of other polymers, for example, different PEG derivatives, on the polymorphic outcome of this system and this is part our of proposed future work.

Additionally, SEM analysis showed that the powder particle size of the cocrystal prepared by POLAG using a liquid polymer (PEG 200) is similar to the cocrystal prepared by LAG, whereas in the case of POLAG with PEG 10000 the powder particle size is smaller and more homogeneous (SI).

In conclusion, we have demonstrated that the addition of a polymer during cocrystallization through mechanochemistry (POLAG) can have similar advantages to the LAG process. A practical consequence of POLAG consists of the enlargement of the catalysts choice during cocrystal screening and the prevention of solvate formation. Polymers are demonstrated to selectively drive the polymorphic outcome of the reaction. The next step will be to use different polymer libraries for the screening and control of cocrystal polymorphic forms through POLAG.

In addition to the effect of the physical state of the catalyst on cocrystal formation and on the reaction, POLAG has allowed a better control of powder particle size. Also, the results reported here suggest that there may be an optimal amount of polymer when used as an additive for cocrystallization. These are both important issues when the aims are the formulation, the co-processing of cocrystals in the presence of matrix, the scale up, and the other manufacturing phases of drugs the in pharmaceutical industry.

POLAG would seem to represent a new approach for the development of functional materials through mechanochemistry, and may open new routes toward the understanding of the mechanisms and pathways of mechanochemical cocrystal formation and polymorphism. We note that even if the presence of polymer is seen as disadvantageous in producing pure cocrystal product, its ability to add to the methods for screening cocrystal formation (e.g., when solvate formation is an issue) remains noteworthy. Indeed, when the polymer itself is biocompatible the process may be a single-step strategy for obtaining cocrystals within a polymer matrix.

## Experimental Section

All chemicals were obtained from Sigma–Aldrich Company, Ltd. (Gillingham, UK) and were used without further purification.

The mechanochemical experiments were performed according to the experimental conditions already reported in Ref. [4, 8, 10], and are described in detail in the SI.

Solid-state characterization. PXRD analyses were performed using a Panalytical X′Pert Pro Diffractometer with Ni-filtered Cu-Kα radiation at a wavelength of 1.5418 Angstrom equipped with an RTMS X′celerator detector. A small amount of powder from each sample (15–25 mg) was gently pressed on a glass slide to give a flat surface. The data were collected in the $2\theta$ range 3–50° at room temperature.

SEM analyses were performed using a JEOL JSM-5510LV scanning electron microscope. The samples were mounted with carbon adhesive on an aluminum holder and sputtered with gold.

**Keywords:** cocrystals · mechanochemistry · polymers · polymorphism · solid-state reactions

**How to cite:** *Angew. Chem. Int. Ed.* **2015**, *54*, 7371–7375
*Angew. Chem.* **2015**, *127*, 7479–7483

---

[1] a) R. Thakuria, A. Delori, W. Jones, M. P. Lipert, L. Roy, N. Rodríguez-Hornedo, *Int. J. Pharm.* **2013**, *453*, 101–125; b) A. V. Trask, *Mol. Pharmaceutics* **2007**, *4*, 301–309.
[2] a) S. L. James, *Chem. Soc. Rev.* **2012**, *41*, 413–447; b) E. Boldyreva, *Chem. Soc. Rev.* **2013**, *42*, 7719–7738; c) V. V. Boldyrev, *Russ. Chem. Rev.* **2006**, *75*, 177–189; d) D. Braga, F. Grepioni, *Angew. Chem. Int. Ed.* **2004**, *43*, 4002–4011; *Angew. Chem.* **2004**, *116*, 4092–4102.
[3] a) T. Friscic, W. Jones, *Faraday Discuss.* **2007**, *136*, 167–178; b) N. Shan, F. Toda, W. Jones, *Chem. Commun.* **2002**, 2372–2373; c) T. Friscic, S. L. Childs, S. A. A. Rizvi, W. Jones, *CrystEngComm* **2009**, *11*, 418–426.
[4] N. Madusanka, M. D. Eddleston, M. Arhangelskis, W. Jones, *Acta Crystallogr. Sect. B* **2014**, *70*, 72–80.
[5] a) A. D. Grzesiak, F. J. Uribe, N. W. Ockwig, O. M. Yaghi, A. J. Matzger, *Angew. Chem. Int. Ed.* **2006**, *45*, 2553–2556; *Angew. Chem.* **2006**, *118*, 2615–2618; b) C. P. Price, A. L. Grzesiak, A. J. Matzger, *J. Am. Chem. Soc.* **2005**, *127*, 5512–5517.
[6] a) K. Boksa, A. Otte, R. Pinal, *J. Pharm. Sci.* **2014**, *103*, 2904–2910; b) D. Hasa, B. Perissutti, C. Cepek, S. Bhardwaj, E. Carlino, M. Grassi, S. Invernizzi, D. Voinovich, *Mol. Pharmaceutics* **2013**, *10*, 211–224.
[7] S. L. Childs, P. Kandi, S. R. Lingireddy, *Mol. Pharmaceutics* **2013**, *10*, 3112–3127.
[8] S. Karki, T. Friscic, W. Jones, W. D. S. Motherwel, *Mol. Pharmaceutics* **2007**, *4*, 347–357.
[9] E. Batchelor, J. Klinowski, W. Jones, *J. Mater. Chem.* **2000**, *10*, 839–848.
[10] K. L. Ngyen, T. Friscic, G. M. Day, L. F. Gladden, W. Jones, *Nat. Mater.* **2007**, *6*, 206–209.
[11] F. Fischer, G. Scholz, S. Benemann, K. Rademann, F. Emmerling, *CrystEngComm* **2014**, *16*, 8272–8278.
[12] T. Henning, *PharmaChem* **2002**, *2*, 57–59.
[13] V. V. Boldyrev, *Annu. Rev. Mater. Sci.* **1979**, *9*, 455–469.
[14] T. Friscic, W. Jones, *Cryst. Growth Des.* **2009**, *9*, 1621–1637.
[15] W. Jones, M. D. Eddleston, *Faraday Discuss.* **2014**, *170*, 9–34.
[16] M. D. Eddleston, S. Sivachelvam, W. Jones, *CrystEngComm* **2013**, *15*, 175–181.
[17] M. P. Gupta, S. R. P. Yadav, *Acta Crystallogr. Sect. B* **1972**, *28*, 2682–2686.
[18] T. Lee, H. R. Chen, H. Y. Lin, H. L. Lee, *Cryst. Growth Des.* **2012**, *12*, 5897–5907.
[19] T. P. Shakhtshneider, *Solid State Ionics* **1997**, *101*, 851–856.
[20] G. Baaklini, V. Dupray, G. Coquerel, *Int. J. Pharm.* **2015**, *479*, 163–170.

Received: February 19, 2015