

Cocrystal Formation via Mechanochemistry: from Neat and Liquid-Assisted Grinding to Polymer-Assisted Grinding

Dritan Hasa,^{[a],[b]} Gabriela Schneider Rauber,^{[a],[c]} Dario Voinovich,^[b] and William Jones^{*[a]}

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 via mechanochemistry, and possibly opens new routes towards the understanding of the mechanisms and pathways of mechanochemical cocrystal formation and polymorphism.

Cocrystals may be defined as stoichiometric multicomponent systems where each component is solid under ambient conditions.^[1] Compared to synthetic chemistry, cocrystallization is a non-covalent 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, e.g. biopharmaceutical properties, stability and compressibility as well as potential patentability.^[1]

There are many approaches and strategies for cocrystal formation, which may be solution-based or via 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 via mechanochemistry. However, several examples of incomplete reaction and non-accessible cocrystals are reported in literature.^[2]

An alternative has been liquid assisted grinding (LAG), in which the addition of small amounts of a liquid can dramatically

increase the 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 were formed via LAG during a screening study for different (non-solvated) 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 via 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 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 increases dramatically 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

[a] Dr. D. Hasa, G. Schneider Rauber, Prof. W. Jones
Department of Chemistry, University of Cambridge, Lensfield Road,
Cambridge, CB2 1EW, UK

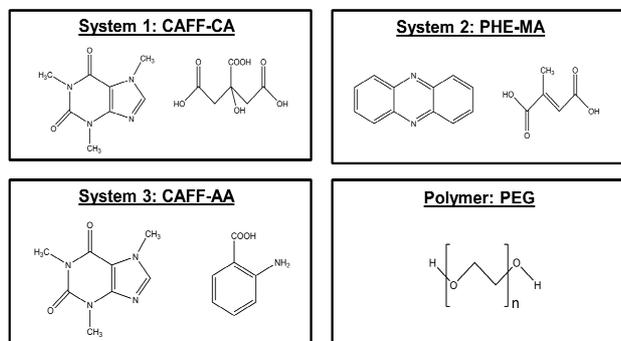
E-mail: wj10@cam.ac.uk Title(s), Initial(s), Surname(s) of Author(s)

[b] Prof. D. Voinovich
Department of Chemical and Pharmaceutical Sciences, University of
Trieste, P.le Europa 1, 34127, Trieste, Italy

[c] G. Schneider Rauber
CAPES Foundation, Ministry of Education of Brazil, Brasilia – DF
70040-020, Brazil

Supporting information for this article is given via a link at the end of the document.

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.



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

Neat grinding (see experimental for full details) of CAFF and CA did not result in the cocrystal formation in agreement with the results of Karki et al.^[9] 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 degrees of 2θ 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 degrees 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 CAFF-CA cocrystal prepared using 10% of PEG 10,000 (Figure 1g). Interestingly, at higher percentages of PEG (especially in the case when 60 weight percent 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 where PEGs with different chain lengths were used (supplementary information). 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 presence of 10 weight percent of different PEGs can be significantly reduced at a higher milling time (see supplementary file). The PXRD patterns of CAFF-CA cocrystals prepared in presence of 10 weight percent 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 presence of these polymers are very similar to those

prepared using solid polymers such as PEG 3,000, PEG 6,000 and PEG 10,000. In fact, the typical diffraction peak of the pure CAFF at 12 degrees of 2θ is present in all the samples and its intensity does not significantly change when passing from the liquid to the solid polymers (Figure 2). We can therefore speculate that in the case of CAFF-CA cocrystal system the physical state (liquid or solid) of the polymer and the polymer chain length does not play a significant role on the progress of the reaction rate. This represents the first example where 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 weight percent 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 weight percent of solid polymers (Figure 3). The particle shape and particle surface remain similar in all the samples.

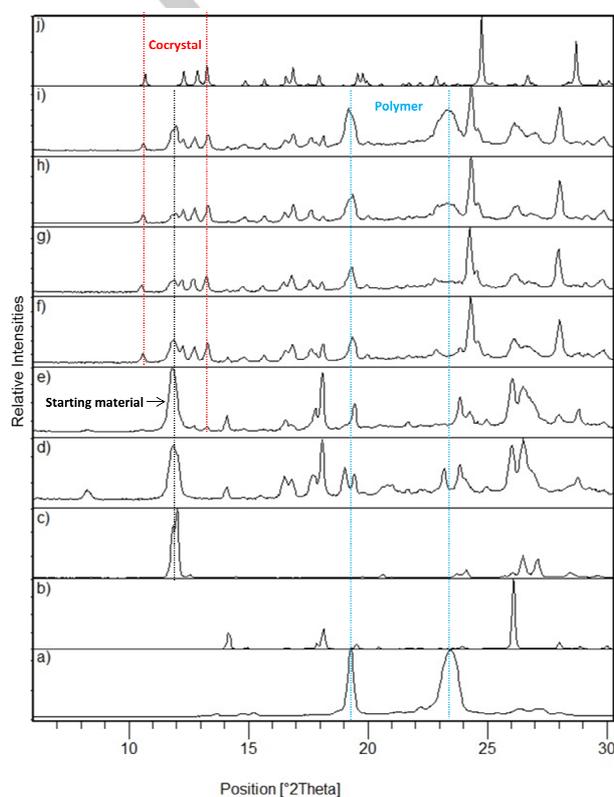


Figure 1. PXRD pattern of: (a) pure PEG 10,000, (b) pure CA, (c) pure CAFF, (d) CAFF and CA physical mixture neat ground for 20 min, (e), (f), (g), (h) and (i) CAFF-CA ground for 20 min with the addition of 1, 5, 10, 30 and 60 weight percent of PEG 10,000 respectively, (j) calculated CAFF-CA.^[9]

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 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. The role of the polymer in the early stages of cocrystal formation via 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 (supplementary information). More detailed studies are hence necessary to understand the mechanistic aspects of this process.

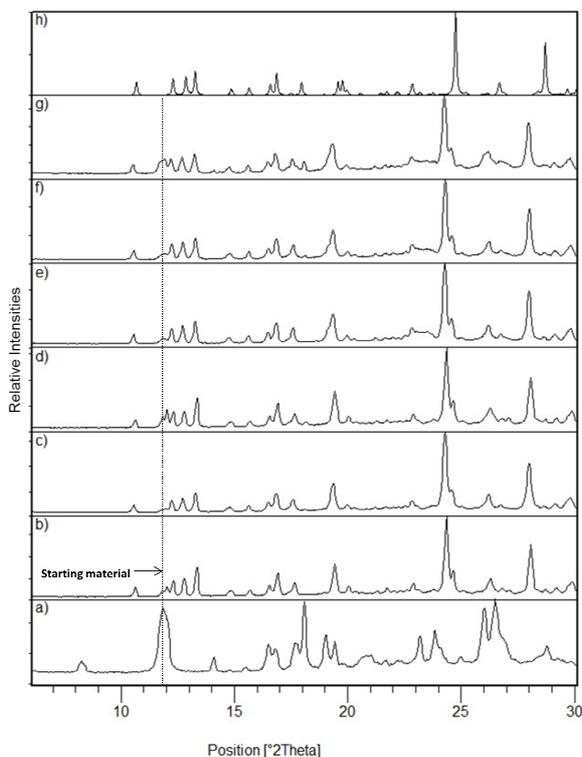


Figure 2. PXRD pattern of: (a) CAFF-CA mixture neat ground for 20 min, CAFF-CA cocrytal prepared using 10 weight percent of (b) PEG 200, (c) PEG 300, (d) PEG 400, (e) PEG 3,000, (f) PEG 6,000 and (g) PEG 10,000, (h) calculated CAFF-CA.^[8]

The second system analysed was the cocrytal of PHE and MA in a 1:1 molar ratio.^[9] PHE-MA cocrytal has been already used as a model system for polymorph screening^[16] and to investigate the mechanisms of cocrytal formation.^[10] Neat grinding of PHE and MA for 30 min resulted only in a partial conversion to the cocrytal form I, and the PXRD pattern showed clear presence of starting materials (Figure 4).

We performed several POLAG experiments using different amounts of PEG 10,000. The addition of 2.5 weight percent of PEG 10,000 reduced the intensities of the 2 θ diffraction peaks at 14.2° and 15.8° typical of pure PHE, and 15.0° typical of pure MA (Figure 4), while an almost total conversion of the starting material into PHE-MA cocrytal could be observed when increasing the amount of the polymer to 5 weight percent. Interestingly, also in the case of PHE-MA cocrytal system, a further increase of the polymer amount up to 10 weight percent, 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 PHE-MA cocrytal prepared via POLAG using 5 weight percent 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 weight percent of PEG 10,000 (supplementary file).

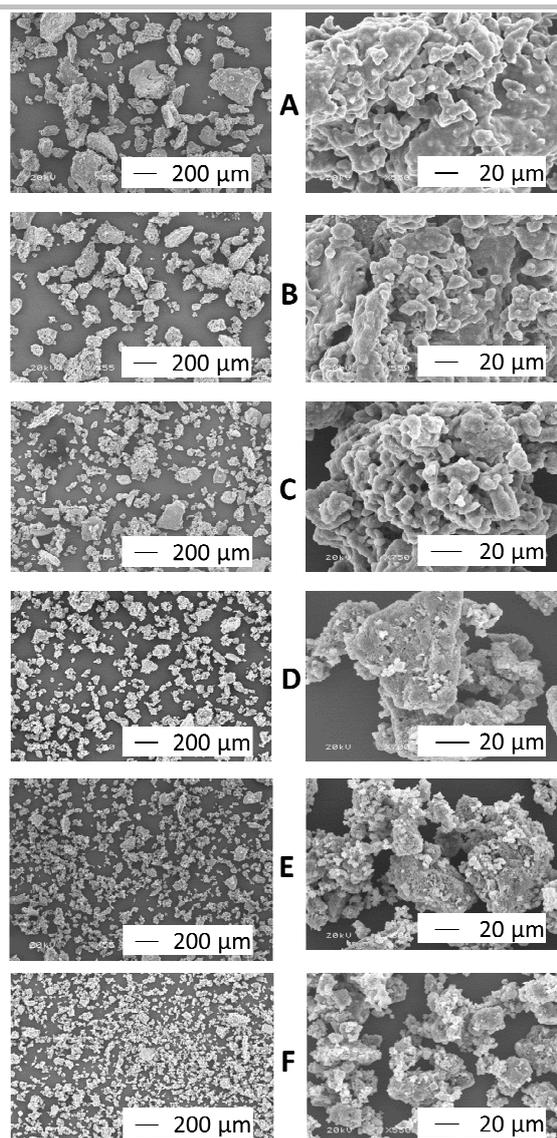


Figure 3. SEM image of CAFF-CA cocrytal prepared using 10 weight percent of (A) PEG 200, (B) PEG 300, (C) PEG 400, (D) PEG 3,000, (E) PEG 6,000 and (F) PEG 10,000.

Specifically for the CAFF-AA cocrytal system, an extensive polymorph screening study via LAG using different solvents led to the formation of two non-solvated forms and five different solvated cocrytals. However, the majority of solvents that did not form solvates led to CAFF-AA form I, while 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 cocrytal (Figure 5). Instead, POLAG experiments using 1 weight percent of PEG 200 and PEG 10,000 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, e.g. different PEG derivatives, on the polymorphic outcome of this system and it makes part of proposed future work.

Additionally, SEM analysis showed that the powder particle size of the cocrystal prepared via POLAG using a liquid polymer (PEG 200) is similar to the cocrystal prepared via LAG, while in the case of POLAG with PEG 10,000 the powder particle size is smaller and more homogeneous (supplementary file).

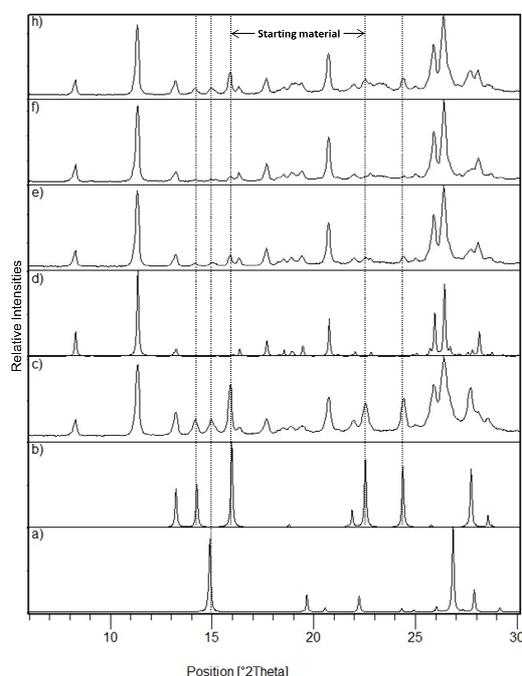


Figure 4. PXRD pattern of: (a) calculated MA,^[17] (b) calculated PHE,^[18] (c) PHE-MA cocrystal prepared in neat conditions, (d) calculated PHE-MA,^[9] (e), (f) and (h) PHE-MA cocrystal prepared using 2.5, 5 and 10 weight percent of PEG 10,000 respectively.

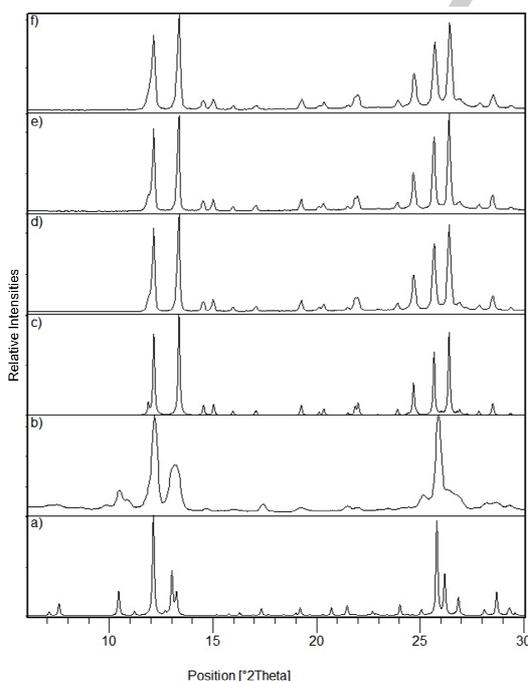


Figure 5. PXRD pattern of: (a) calculated CAFF-AA form I,^[11] (b) CAFF-AA form I prepared via neat grinding, (c) calculated CAFF-AA form II,^[11] (d) CAFF-AA prepared via LAG with acetonitrile, CAFF-AA prepared via POLAG using 1 weight percent of (e) PEG 200 and (f) PEG 10,000.

In conclusion, we have demonstrated that the addition of a polymer during cocrystallization via mechanochemistry (POLAG) can have similar advantages to the LAG process. A practical consequence of POLAG consists on 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 via 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 in the pharmaceutical industry.

POLAG would seem to represent a new approach for the development of functional materials via mechanochemistry, and might open new routes towards 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.

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 3,000	Solid	N/A	60.1 °C ^[b]
PEG 6,000	Solid	N/A	63.3 °C ^[b]
PEG 10,000	Solid	N/A	63.7 °C ^[b]

[a] Information reported from the technical data sheet [b] data obtained experimentally

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 references,^[4,8,10] and are described in detail in the supplementary information.

Solid-state characterization. PXRD analyses were performed using a Philips PW3710 X'Pert Diffractometer with Ni-filtered Cu-K α radiation at a wavelength of 1.5406 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 2θ range $3-50^\circ$ at room temperature.

SEM analyses were performed using a JEOL JSM-5510LV Scanning Electron Microscope. The samples were mounted with carbon adhesive on an aluminium holder and sputtered with gold.

Acknowledgements

D. Hasa and D. Voinovich thank University of Trieste for partially supporting this study (FRA 2013). G. Schneider Rauber acknowledges CAPES-Brazil and COT-UK for her scholarship (CsF BEX 9530/13-4).

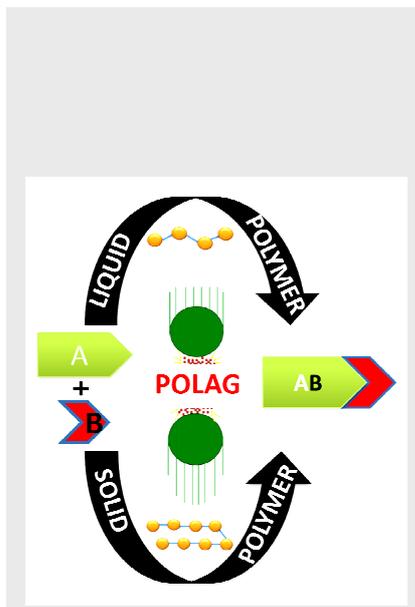
Keywords: Cocrystal • Mechanochemistry • Polymers •

Polymorphism • Solid-state reaction

- [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. Pharm.* **2007**, 4, 301-309.
- [2] a) S.L. James et al. *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.
- [3] a) T. Friscic, W. Jones. *Faraday Discuss.* **2007**, 136, 167-178. b) N. Shan, F. Toda, W. Jones. **2002**, 20, 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. Arhangel'skis, W. Jones. *Acta Cryst. 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. 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. Pharm.* **2013**, 10, 211-224.
- [7] S.L. Childs, P. Kandi, S.R. Lingireddy. *Mol. Pharm.* **2013**, 10, 3121-3127.
- [8] S. Karki, T. Friscic, W. Jones, W.D.S. Motherwel. *Mol. Pharm.* **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. Mat.* **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. *Ann. Rev. Mater. Sci.* **1979**, 9, 455-469.
- [14] T. Friscic, W. Jones, *Cryst. Growth Des.* **2009**, 9, 1621-1637.
- [15] W. Jones and M.D. Eddleston. *Faraday Discuss.* **2014**, 14, 9-34.
- [16] M.D. Eddleston, S. Sivachelvam, W. Jones. *CrystEngComm*. **2013**, 15, 175-181.
- [17] M.P. Gupta and S.R.P. Yadav. *Acta Cryst.* **1972**, B28, 2682-2686.
- [18] T. Lee, H.R. Chen, H.Y. Lin, H.L. Lee. *Cryst. Growth Des.* **2012**, 12, 5897-5907.
- [19] T.P. Shakhshneider. *Solid State Ionics*. 1997, 101-103, 851-856.
- [20] G. Baaklini, V. Dupray, G. Coquerel. *Int. J. Pharm.* 2015, 479, 163-170.

COMMUNICATION

In the present work, we propose polymer-assisted grinding (POLAG) as an original alternative to the liquid-assisted grinding technique for the synthesis of multicomponent crystals. POLAG would seem to represent a new approach for the development of functional materials via mechanochemistry, and might open new routes towards the understanding of the mechanisms and pathways of mechanochemical cocrystal formation and polymorphism.



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

Page No. – Page No.

Cocrystal Formation via Mechanochemistry: from Neat and Liquid-Assisted Grinding to Polymer-Assisted Grinding