Chem Soc Rev

RSC Publishing

REVIEW ARTICLE

View Article Online
View Journal | View Issue

Mechanochemical preparation of co-crystals

Dario Braga,* Lucia Maini and Fabrizia Grepioni

Cite this: *Chem. Soc. Rev.*, 2013, **42**, 7638

Received 15th January 2013

DOI: 10.1039/c3cs60014a

www.rsc.org/csr

The preparation of co-crystals *via* mechanochemistry combines the quest for clean and green processes with the investigation of multicomponent new materials, among the currently most fashionable systems in the crystal engineering field: the physico-chemical properties of the components add, merge or transform when co-crystals are formed, giving rise to potentially improved performance in ''old'' solid-state chemistry fields, as in the pharmaceutical industry field, where they represent a way to obtain new formulations and to improve the properties (solubility, thermal stability, compressibility, *etc.*) of both new and existing drugs.

Introduction

This review deals with the crossing of two roads. The road of mechanochemistry, which is an ancient one and has been recently rediscovered to meet the demand for clean processes and environmentally friendly, solvent-free reactions,[1] and the road of co-crystals, which has become popular after discovering that most of the fundamental concepts of crystal engineering can be applied to the making of these multicomponent new materials often of pharmaceutical interest.[2] Undoubtedly, the impetus to the investigation of co-crystals has come mainly from their potential impact on the pharmaceutical field, as a way to improve the properties of existing drugs or as a route to new drugs. Co-crystallization can, in fact, be used to change relevant properties such as dissolution rate, solubility, thermal and hydration stability or compressibility, *etc.*,[3] or to develop entirely new drugs with enhanced/combined properties.[4]

Pharmaceutical co-crystals generally consist of an API and one or more ancillary molecules called co-crystal formers or ''co-formers''. Clearly, a co-former needs to be a GRAS (Generally Recognized As Safe) compound, *i.e.* accepted by the general pharmacopeia.[5]

Typically, co-crystals are prepared by slow solvent evaporation, the limitation being the solubility of the components in a given solvent or solvent mixture, but also the solubility of the co-crystal with respect to that of the single components.[4b] Direct mixing, whether with the intermediacy of small quantities of solvent (see below), or *via* mechanical grinding of the molecular materials, has revealed itself as a more direct and cost effective (no solvent being required) way to prepare molecular and ionic co-crystals. Mechanical mixing works well with active pharmaceutical

Dipartimento di Chimica ''G. Ciamician'', Via Selmi 2, 40126 Bologna, Italy. E-mail: dario.braga@unibo.it; Fax: +39 051 2099456; Tel: +39 051 20995555

Dario Braga

Dario Braga is Professor of Chemistry at the University of Bologna. His main scientific interests are in the study of crystal polymorphism and in the crystal engineering exploitation of hydrogen-bonding interactions between ions and in solvent-free gas–solid and solid–solid reactions. He has published more than 300 papers and reviews and organized several international conferences and schools on crystal engineering. He was the first scientific editor of CrystEngComm. He is member of the international editorial board of Chem. Commun.

Lucia Maini

Lucia Maini received a PhD in Chemistry, under the supervision of Prof. Dario Braga, at the University of Bologna, where she became Research Assistant in 2006. She has published about 70 papers and contributions to books. Her main interests are in solvent-free chemistry, crystal engineering, polymorphism, luminescent MOFs, thin-films and OLED.

ingredients (API) which form molecular crystals,[6] but also with ionic crystals and with organometallic systems. Planetary milling can for example be used in high-throughput solid-state screening methods for the detection of co-crystalline forms.[7] The ability to scale mechanochemical co-crystal formation is of course important for industrial applications. This was recently addressed by Medina *et al.*, who described a scalable continuous flow solvent-free process for pharmaceutical co-crystallization using twin screw extrusion.[8]

Before proceeding, we deem appropriate to point out that the subjects of mechanochemistry and mechanochemical methods have been reviewed recently.[9] On the other hand, a book on pharmaceutical co-crystals has recently been published.[10] This review aims to bridge the two subjects, focusing on the mechanochemical preparation of co-crystals, with the aim to demonstrate that the mechanochemical approach can be the method of choice for approaching co-crystals preparation.

Mechano crystal chemistry: grinding, milling, liquid assisted grinding, *kneading*

The term mechanochemistry is usually associated with the breaking and forming of covalent bonds. Early studies based on manual grinding or ball milling were conducted by Boldyrev, Fernandez-Bertran, and Kaupp.[1,11] Solid-state techniques are commonly used at an industrial level, mainly with inorganic solids and materials,[12] also to produce amorphous phases.[13] More recently, under the impetus of the supramolecular chemistry paradigm, the idea of using mechanical methods to induce chemical transformations has been extended to include the breaking and forming of non-covalent interactions, those responsible for crystal structure and stability in molecular solids.

Early successful experiments between molecular crystals and between crystals and gases were carried out by Rastogi and others[14] and further extended by Curtin and Paul in the 1970s.[15] However, to the best of the authors knowledge, the first mechanochemically prepared crystalline materials that would be, by today's perception, called co-crystals were crystalline host–guest inclusion compounds prepared by Toda and collaborators.[16]

Fabrizia Grepioni

Fabrizia Grepioni is Associate Professor of Chemistry at the University of Bologna. She has published about 300 papers and book contributions. Her scientific interests are in the fields of crystal engineering of metal-containing systems, solid-state reactivity, photoluminescent solids, polymorphism and crystal forms.

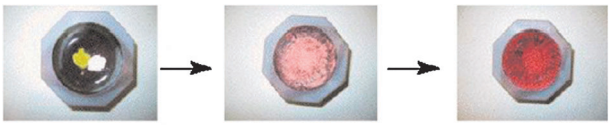

Fig. 1 Colour change of the co-ground crystals of *rac*-BN and BQ, (a) before grinding, (b) during the grinding and (c) the final product (reproduced from ref. 18*b*, copyright RSC).

Charge-transfer systems were further investigated by Toda's group[17] and by Kuroda *et al.*[18] Kuroda obtained three-component co-crystals based on racemic bis-β-naphthol, benzoquinone and anthracene (see Fig. 1); importantly, the resulting co-crystals could not be obtained from solution and so required structure determination from X-ray powder diffraction.[19] Sada *et al.* prepared colored charge-transfer complexes by mixing electron donor and electron acceptor molecules.[20]

Direct mixing of molecular compounds is not only the easiest way to have access to new co-crystals,[21] but also to reproduce existing co-crystals previously obtained by solution methods.[22]

Etter and collaborators investigated formation of hydrogen-bonded co-crystals by grinding of the solid components.[23] The same product could be obtained even in the presence of a third solid component.[24] In the case of 2-aminobenzoic acid, Etter also showed that grinding could determine polymorph interconversion.[25]

Molecular crystals are ''soft'' and often soluble in water or common organic solvents. Moreover, molecular components are highly mobile within the crystal[26] and on the surface of the grains, because they are held in place by a web of intermolecular interactions. The strength of these interactions resides in their number and cooperative action, but individual links are easily broken and easily replaced as the molecules ''move'' around or are captured by solvent molecules, or the whole crystal rearranges from one given packing to another, as is the case with polymorphic transformations. It has been argued by Kaupp that mobility accounts for most molecular processes taking place in the solid state.[27]

While it is possible, if not to guarantee, at least to explore the feasibility of a co-crystal formation on the basis of solubility data and/or knowledge of the most common supramolecular synthons,[28] it is still difficult to predict whether the resulting co-crystal will be more or less stable with respect to the component molecules.[29]

"Softness" is the reason why molecular crystals can be reacted directly by mechanochemical mixing/grinding of the solid materials in their polycrystalline form. Mechanical mixing can be done either in "dry" conditions, *i.e.* by mixing polycrystalline samples of the solid reactants without the presence of moisture or solvent, or in "wet" conditions, *viz.* in the presence of moisture or minimal amount of solvents. It is by now well known that very small amounts of solvent can dramatically accelerate, and even enable, mechanochemical reactions between solids. Since moisture is difficult to exclude in a grinding process unless special precautions are adopted, the distinction between truly "dry" and "wet" conditions is difficult to establish.

The "wet" conditions for grinding have been described with different epithets, though essentially with the same meaning: terms like "wet grinding", "solvent-drop grinding", "liquid assisted grinding" and "*kneading*" (which might be slightly confusing in the literature and indexing) all imply that a solvent is involved, whether by intention or not (as in the case of grinding in humid air), but only in very tiny quantity.[30]

"Wet grinding", "liquid-assisted" and "kneading" are all terms which have long been employed in industrial and technological processes concerning polymers, minerals, pharmaceutics, ceramics (among others). In particular, *kneading* is an industrially relevant process that can also be applied in a small-scale research lab,[31] and is commonly employed in the preparation of cyclodextrin inclusion compounds, which also have pharmaceutical uses.[31,32]

In the context of crystal engineering both LAG and *kneading* have also been described as a sort of "solvent catalysis process" of the solid-state process, whereby the small amount of solvent provides a lubricant for molecular diffusion.[30a] As far as terminology is concerned it might be interesting to note – for the curious reader – that in 2002 Shan *et al*. reported on "a significant increase in kinetics by the appropriate use of very small quantities of solvent".[30b] In 2004, between April and July, Trask *et al*. used for the first time the expression "solvent-drop grinding",[30d] while Braga *et al.* chose the term "kneading" both for a Suzuki-coupling reaction in the solid-state[33] and for the preparation of a supramolecular organometallic–inorganic system.[34] In 2006 Friščić *et al.* changed the solvent-drop grinding into "liquid-assisted grinding",[35] which *via* the acronym "LAG" has rapidly rooted in the crystal engineering community and has become the most frequently used expression to indicate a grinding process with a tiny amount of solvent. The term LAG has the intrinsic advantage of being a clear succinct descriptor, which is important for indexing of journal articles. In 2008 "solvent-assisted mechanochemistry" was also employed specifically for reactions involving coordination compounds.[36]

In an attempt to both summarize and generalize, we might say that "kneading" refers to the process of grinding one, two or more components together with an intentional, small amount of liquid (which could also be one of the reagents), while "liquid-assisted grinding" can be used in a more general sense to comprise reactions occurring *via* intervention of a liquid phase, be it added intentionally (tiny drops of solvent or a liquid reagent) or present at some stage during the process (capture of moisture from the air, melting of one component due to increased local pressure and/or temperature, formation of a eutectic phase, or extrusion of water molecules from the crystalline edifice of a hydrated solid). In this broader sense, therefore, the term "liquid-assisted grinding" will be used in what follows.[37]

As for the use of the term "grinding", it should be noted that "dry grinding" and "neat grinding" have also been utilized, but we reckon that the simple noun is sufficient to denote all mechanical processes for which no liquid is either added or present at some reaction stage.

In general liquid-assisted grinding processes are preferred to simple grinding, because they are generally faster and more often produce crystalline solids instead of amorphous materials.[38] For example, while caffeine and citric acid do not form a co-crystal upon neat grinding, LAG with water or organic solvents gives the pharmaceutical solid (caffeine)·(citric acid).[39]

As mentioned above, one cannot properly describe reactions between two solid phases carried out in liquid-assisted grinding conditions as *bona fide* solid-state processes, because of the role played by the liquid. Whether acting as a lubricant, providing a supersaturation condition on the surface of the grains or facilitating molecular mobility by "peeling off" external layers of molecules from the grains, it is inconceivable that the solvent is merely an innocent bystander, playing no role in the process.

On the other hand, it is often difficult – at least on a lab scale, and even when using ball-milling – to control exact reaction conditions such as temperature and pressure exerted.

The very heat generated by friction during a grinding process can, for example, induce local melting of crystals or melting at the interface between the different crystals, so that the reaction takes place in the liquid phase even if the final product is a solid. The same reasoning applies to the possible formation of eutectic phases between two solids[40] or of an amorphous intermediate phase.[41] Neither should one forget the possibility of an intermediacy through a vapour phase.[14b,42]

It has been noted that the nature of the solvent utilized in the liquid-assisted grinding process may be relevant in the choice of product obtained, which seems to indicate that solvation (and therefore solubility effects) can be significant.[30d,42b]

Regarding molecular scale rearrangements, some crystalline intermediate phases have been observed and structurally characterised,[43] while correlations of reactivity with reactant solubility have been noted in some cases.

It is also worth noting that higher reactivity of hydrates with respect to anhydrous forms has been reported in several cases, *e.g.* the hydrates of caffeine and citric acid[39] but also that of hydrated carbamazepine compared to the anhydrous form in the mechanical preparation of (carbamazepine)·(nicotinamide) co-crystals.[44]

Molecular co-crystals

What is a co-crystal then? We have described methods to prepare co-crystals but have not yet quite decided what they are. The matter is still somewhat controversial, and different authors have provided different definitions depending on the view point.

For the scope of this review we regard co-crystals as multi-component crystals formed by two or more different chemical entities, each one possessing a stable solid phase at STP conditions.[5c,45] Thus a co-crystal is a multi-component molecular crystal formed by otherwise separately stable crystalline or amorphous solids. Therefore simple solvates and hydrates are excluded from the category of co-crystals but co-crystal solvates and hydrates are not. Furthermore, we will not discriminate between formally charged systems (molecular salts) and neutral molecular systems when hydrogen bonded acid–base systems are involved, while we will treat differently co-crystals in which the co-formers are ion pairs that would form a stable ionic material on their own (see below).

When hydrogen bonds are involved, the distinction between a salt and a molecular crystal becomes often "semantic". It is well known that in many instances the salt-neutral nature depends only on the position of the proton along the D–H–A vector, which, in turn, depends on the acid/base relative strength and on the temperature.[5c,46,47] This has been demonstrated in a series of studies on the dependence of melting point on the carbon atom chain length and on the proton position along the O–H–N hydrogen bond in acid–base co-crystals. In mechanochemically prepared 1:1 co-crystals of the dicarboxylic acids $HOOC(CH_2)_nCOOH$ (n = 1–7) with 1,4-diazabicyclo[2.2.2]octane (dabco) the melting points of the co-crystals were found to alternate as in the corresponding diacids, irrespective of the salt/molecular nature of the co-crystals, as investigated by X-ray diffraction and solid state NMR spectroscopy.[48] This behaviour is also exhibited by co-crystals of the diacids with dipyridyl molecules 4,4′-bipyridine (bipy), 1,2-bis(4-pyridyl)ethane (bpa), and 1,2-(di-4-pyridyl)ethylene (bpe) which contain an even number of C atoms between the two N atoms, while it is reversed in co-crystals with 1,2-bis(4-pyridyl)propane (bpp), which contains an odd number of (CH_2) groups (Fig. 2).[49]

Examples of variations and/or anomalies in melting points of co-crystals, with respect to those of pure acids, have also been reported by A. Bond[50] for 2:1 co-crystals of *n*-alkylcarboxylic acids with pyrazine, and by Callear *et al.*[51] for co-crystals of imidazole derivatives with α,ω-alkanedicarboxylic acids ($HOOC–(CH_2)_n–COOH$, n = 0–6).

Formation and polymorphic transformation by grinding have been studied for 4,4′-bipyridine (bipy)/pimelic acid (H_2pma) co-crystals.[52]

The first examples of co-crystals involving biologically active molecules were reported in 1993 by Etter[24] for the solid-state co-crystallization of 9-methyladenine and 1-methylthymine, driven by hydrogen-bonding formation between the base pairs.[53] Also in 1993 Caira[54] reported that grinding sulfadimidine with carboxylic acids, such as benzoic, anthranilic, salicylic, and acetylsalicylic (aspirin) acid, yielded co-crystals identical to those previously obtained by solution methods. Interestingly, Caira evaluated the stability of the sulfadimidine-anthranilic acid co-crystal by reacting the preformed co-crystal of sulfadimidine-salicylic acid with anthranilic acid and observing exchange of the acid (Fig. 3).

Competing solid-state exchange between co-crystal components by grinding has also been recently reported on co-crystals of *R*,*R*, *S*,*S*-, racemic and *R*,*S*-tartaric acid (ta) with pyrazine (py). "Supramolecular metathesis" was carried out both *via* kneading with methanol and in methanol slurry by reacting the co-crystal products, (*R*,*R*-ta)·(py), (*S*,*S*-ta)·(py), (*R*,*S*-ta)$_2$·(py) and (*R*,*R*/*S*,*S*-ta)·(py), with the different forms of tartaric acid, showing that co-former exchange could take place according to the sequence of stability (*R*,*S*-ta)$_2$·(py) > (*R*,*R*/*S*,*S*-ta)·(py) > (*R*,*R*-ta)·(py) or (*S*,*S*-ta)·(py).[55]

Zaworotko explored the mechanochemical formation of several co-crystals previously obtained from solution.[22] In each case, the co-crystal was successfully obtained using only 4–20 μL of liquid per 100 mg of solid. Karki *et al.* demonstrated that mechanochemistry was more effective than solution and melt-based methods

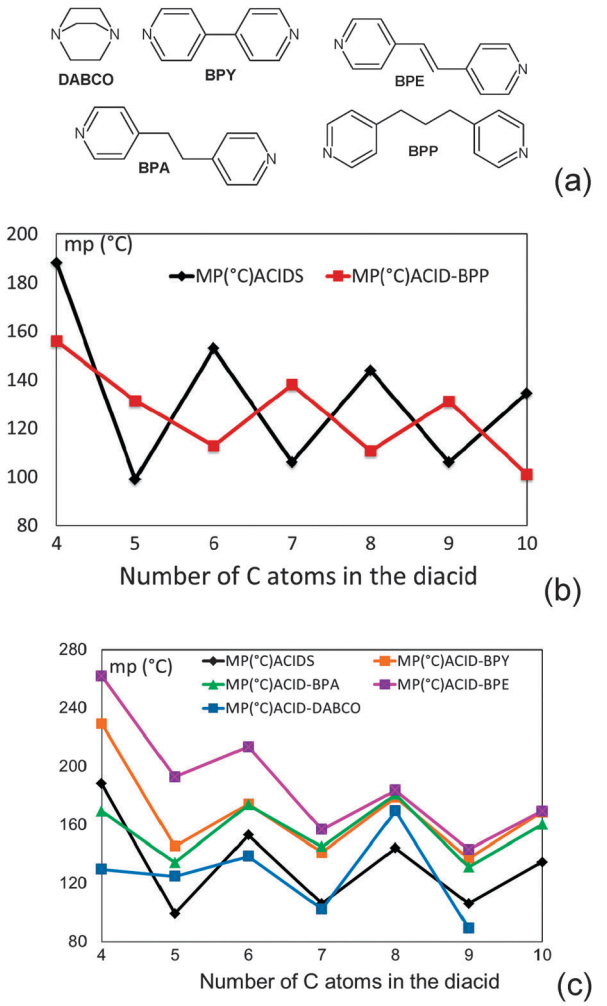

Fig. 2 Comparison of alternating melting points for pure dicarboxylic acids and for co-crystals of dicarboxylic acids with dinitrogen bases (a) containing an odd (b) or an even (c) number of carbon atoms.

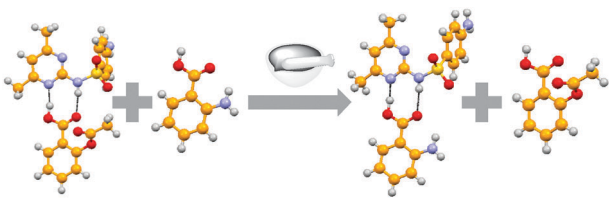

Fig. 3 The sulfadimidine–salicylic acid co-crystal is ground in the presence of anthranilic acid. The final product is a mixture of the sulfadimidine–anthranilic acid co-crystal and salicylic acid.

in screening for co-crystals of nicotinamide.[56] Rodríguez-Hornedo studied mechanochemical co-crystal formation of carbamazepine with saccharin (Fig. 4) *via* formation of an intermediate amorphous phase.[57]

The interaction between the components of a pharmaceutical co-crystal is generally based on hydrogen bonds, and these are likely to be disrupted when interacting with a solvent; therefore, co-crystal screening using conventional solution-based methods often fails to produce co-crystals of low-solubility compounds.

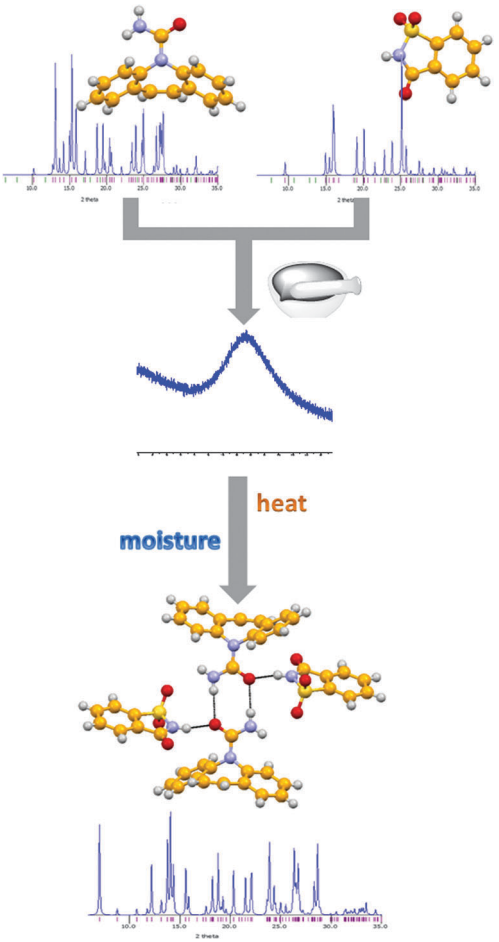

Fig. 4 The co-crystal carbamazepine-saccharin is obtained *via* the formation of an amorphous intermediate. The amorphous phase crystallizes in the presence of moisture or *via* heating.

Crystallization from solution usually leads to the separation of the less soluble component, leaving the more soluble one in solution.[35,58]

Liquid-assisted grinding proved to be superior to grinding in many instances. Some representative examples are described in the following.

Co-crystals of piroxicam[59] and carbamazepine,[60] as well as co-crystals of theobromine with trifluoroacetic or malonic acids could only be obtained by LAG.[39] This was also the case of co-crystals of theobromine with acetic acid[61] and of theophylline with chiral and racemic malic acids,[62] of co-crystals of dihydrocarbamazepine,[63] indomethacin[64] and the drug candidate AMG 517.[65]

LAG was also shown to be advantageous in screening for co-crystals of the model API nicotinamide with dicarboxylic acids[66] and of nicotinamide with the low melting APIs *S*-ibuprofen and *RS*-ibuprofen (see Fig. 5). Single crystals were subsequently grown from solution and structurally characterized, showing network formation.[67]

Co-crystallization of caffeine with glutaric acid in chloroform solution yielded two concomitant polymorphs of the co-crystal (caffeine)·(glutaric acid), while the two polymorphs could be

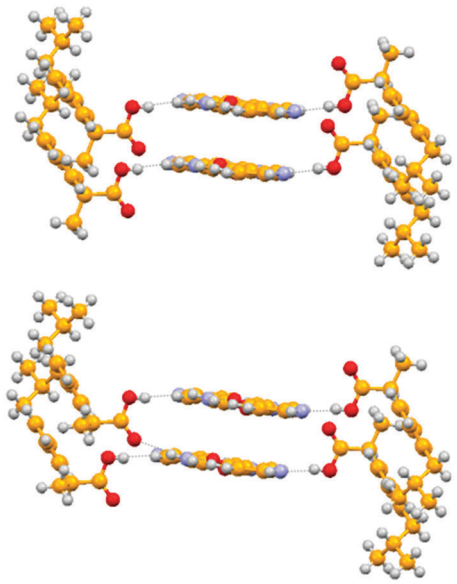

Fig. 5 Nicotinamide co-crystals with *RS*- (top) and *S*-ibuprofen (bottom).

obtained separately if co-crystallization was performed by LAG with different solvents (chloroform or cyclohexane).[68]

Another potentially interesting role for liquid-assisted grinding in the context of pharmaceutical solids is that of carrying out co-crystal–co-crystal reactions involving chiral and racemic solid forms. In particular, LAG reactions between left- and right-handed pharmaceutical co-crystals of theophylline with tartaric acid were found to give a racemic pharmaceutical co-crystal. In contrast, LAG of left- and right-handed co-crystals of caffeine with tartaric acid showed separation of the co-crystal into the components.[69] Recently, the formation of two distinct diastereomeric co-crystals was observed by LAG of racemic malic acid with a single enantiomer of tartaric acid.[70]

Mechanochemical mixing of molecular crystals can often yield co-crystals containing the same constituents in different stoichiometric ratios,[71] depending on the amount of starting materials. Indeed, crystallization of caffeine from liquid acetic acid gives co-crystals of composition (caffeine)·(acetic acid)$_2$. The same product is obtained by grinding the two components in the appropriate ratio. Grinding equimolar amounts of caffeine and acetic acid, however, gives a co-crystal with composition (caffeine)·(acetic acid).[72]

Stoichiometric variations have also been investigated in the cases of co-crystals of nicotinamide with dicarboxylic acids whose preparation, while readily accomplished mechanochemically, could not be easily achieved from solution or a melt.[73]

Mechanochemical co-crystallization has also been exploited in the synthesis of readily compressible and thermodynamically stable forms of paracetamol. Screening by LAG revealed four co-crystals of paracetamol with improved ability to compress into tablets. While tablet formation using the thermodynamically stable paracetamol polymorph is difficult, the metastable orthorhombic polymorph yields tablets much more readily. This effect has been associated with the layered crystal structure of this latter polymorph. Structural characterization and

DFT calculations revealed that enhanced compressibility was indeed related to sheet structures.[74]

Ionic co-crystals

Thus far we have discussed mainly cases of co-crystals where the co-formers are neutral molecules, which interact with each other on the basis of their ability to form supramolecular aggregates or charge transfer complexes. Recently, the mechano-chemical approach has been extended to the preparation of ionic co-crystals (ICCs) formed by an organic molecule and an inorganic alkaline or alkaline earth salt. This class of hybrid organic–inorganic co-crystals has new potentialities, as ionic co-crystals combine the characteristics of molecular crystals with those typical of ionic salts (thermal stability, solubility in water, *etc.*). The convolution of the different properties of organic and inorganic components results in materials with specific characteristics in terms of solubility, dissolution rates and thermal stability.

While the stability of molecular co-crystals depends on the overall contribution of intermolecular interactions of various nature, including, of course, those between molecular ions of opposite charges or permanent dipoles, the formation and stability of ionic co-crystals depend on the interactions established between an organic moiety and the mono-atomic cations and anions with specific localized charge densities. Since the interaction between the organic molecule and the ions is usually based on the presence of oxygen or nitrogen atoms which donate electrons towards the cation and often by hydrogen bonds between hydrogen donor groups on the organic moiety and the anions, the principal interactions in ionic co-crystals resemble those between a solvent molecule and ions in solution. For this reason, the interactions in ICCs have been described as a solvent–solute interaction taking place in the solid state.

ICCs are easily prepared (actually more easily with respect to crystallization from solution) by grinding or liquid-assisted grinding of classical ionic crystalline materials (*e.g.* NaBr, KBr, CsI, RbBr *etc.*) with organic molecules.

The first example reported was that of the ICCs formed between solid barbituric acid, BA, and alkali salts (KBr, RbBr, CsBr).[75] Depending on the alkali metal, the anhydrous or the hydrated product could be obtained, or both. All ionic co-crystals are characterized by higher thermal stability and dissolution rates with respect to pure barbituric acid. The structure of (BA)·(KBr)·$(H_2O)_2$ is shown in Fig. 6.

As the authors report, the beginning of this work was serendipitous. Griesser *et al.* had observed that the IR-spectrum of the anhydrous form II of barbituric acid in KBr showed an additional absorption band at 3500 cm^{-1}, which could only be explained by assuming that some solid state transformation had occurred.[76] It was then shown that upon grinding, with or without the help of MeOH, a solid was obtained that presented the same IR band, and corresponding to the structure of the dihydrated ionic co-crystal (BA)·(KBr)·$(H_2O)_2$. The same co-crystal could also be obtained if barbituric acid in its anhydrous form III or dihydrated form was employed as starting reagent. In all these ionic co-crystals the barbituric acid is present as a neutral molecule.[75]

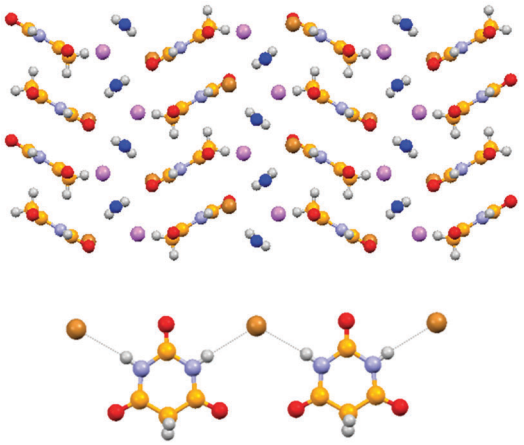

Fig. 6 Crystalline (BA)·(KBr)·$(H_2O)_2$ (top) and the hydrogen bonded chain made of alternating BA molecules and Br^- anions (potassium in violet, bromide in gold).

The hydrated co-crystals BA·MBr·$2H_2O$ (M = Na, K, Rb) are isomorphous, and isomorphism is also observed for the two anhydrous BA·MBr (M = Rb, Cs) co-crystals, while the third anhydrous form observed, BA·CsI, shows a slightly different structure (see Fig. 7). The Rb^+ cation clearly represents a borderline condition, because with it both the hydrated and the anhydrous co-crystals can be obtained.

These ionic co-crystals have different thermal stability with respect to the pure components.[75] Although all crystals show incongruent melting followed by decomposition of the organic moiety, for the solid forms containing sodium and potassium, decomposition is observed at a temperature close to the melting point of pure barbituric acid (onset values 255 and 249 °C, respectively, *versus* 245 °C), while for the co-crystals containing RbBr, CsBr and CsI the value is much higher (307, 298 and 308 °C, respectively).

Furthermore, the co-crystals show dissolution rates that are higher than that of pure barbituric acid [dissolution rates for

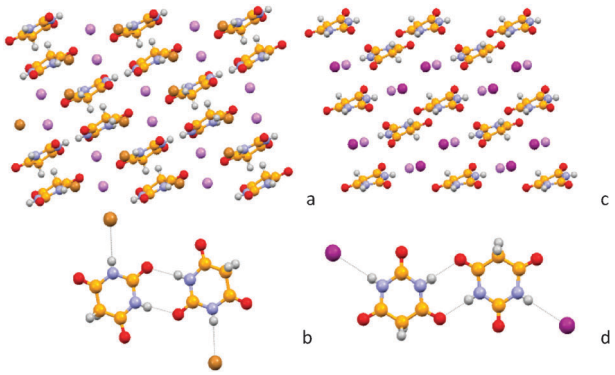

Fig. 7 (a) Packing view of BA·CsBr along the *b*-axis and (b) hydrogen bond interactions between two BA molecules and two bromide anions; (c) packing view of BA·CsI along the *b*-axis and (d) hydrogen bond interactions between two BA molecules and two iodide anions. (Caesium cations in violet, bromide and iodide anions in gold and purple, respectively).

BA and its anhydrous co-crystals are 21(2), 22(3), 27(1) and 29.1(0.3) mol L^{-1} min^{-1} for BA, BA·RbBr, BA·CsBr and BA·CsI, respectively], thus confirming that co-crystallization can represent a strategy to alter the dissolution properties of an organic molecule.[77]

In yet another recent example, mechanical treatment of piracetam with the lithium salts LiCl and LiBr has also generated new ICCs.[78] Since piracetam is a known drug used to treat psycho-organic syndromes or cognitive decline (marketed as Nootropil® by UCB)[79] and lithium ion is used as a mood stabilizing drug in patients affected by bipolar disorder,[80] the combination in a single material of both APIs results in a co-drug.

Co-drugs, also known as ''drug–drug conjugates'' or dual-acting complexes, are usually formed by two or more drug compounds linked to one another *via* a labile covalent or coordination bond.[81,82]

PIR·LiCl·$2H_2O$ can be easily obtained *via* grinding; the lithium cation is tetracoordinated by two water molecules and two piracetam molecules. The packing can be described as an alternation of inorganic and organic layers (light blue and orange, respectively, in Fig. 8a). Upon heating the anhydrous phase was obtained. PIR·LiCl is unstable and reconverts quickly into PIR·LiCl·$2H_2O$ if left in the air. In the crystal structure of PIR·LiCl, characterized *via* powder diffraction, the lithium cations are coordinated by chloride anions and piracetam molecules (Fig. 8b).

Ionic co-crystals were also obtained from solution and *kneading* (see Fig. 9) of barbituric acid, diacetamide, malonamide, nicotinamide and piracetam with the inorganic salt $CaCl_2$,[83] which is known for its non-toxicity. The structures of ICCs were determined either from single crystal diffraction data or from

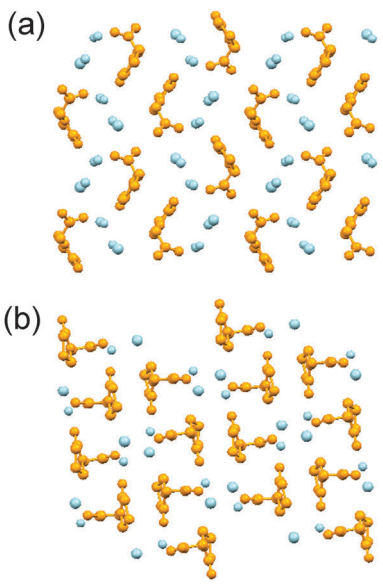

Fig. 8 (a) Crystalline PIR·LiCl·$2H_2O$ (top, view along the *a*-axis) and (b) PIR·LiCl (bottom, view along the *c*-axis). Organic part in orange (piracetam molecules) and inorganic part in light blue (lithium and chloride ions and water molecules). Hydrogen atoms are not shown.

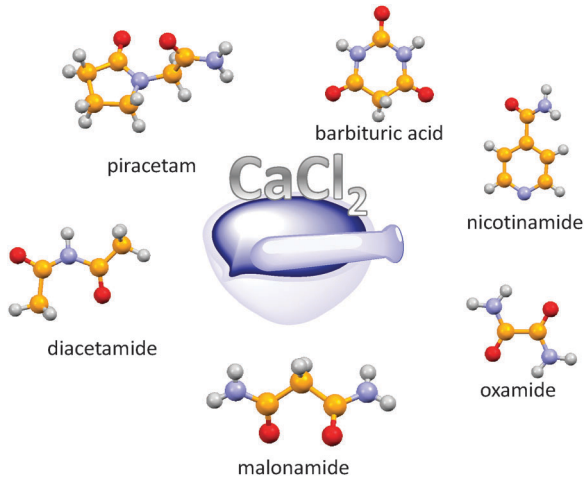

Fig. 9 Screening for ICC formation: *kneading* of barbituric acid, diacetamide, malonamide, nicotinamide and piracetam with the inorganic salt $CaCl_2$.

powder diffraction data, using simulated annealing procedures. Crystalline products were analyzed by DSC, TGA and variable temperature XRPD. Intrinsic dissolution rate measurements were also performed on nicotinamide and piracetam ICCs.

Intrinsic dissolution rate measurements show that ICCs of piracetam and nicotinamide have a lower IDR in physiological solution than the corresponding pure APIs: 136.4 *vs.* 262.8 mg L^{-1} min^{-1} and 187.7 *vs.* 379.4 mg L^{-1} min^{-1}, respectively. These differences are significant, as ICC formation almost halves the IDR value. Besides the difference in IDR, thermal stability of both APIs is enhanced in ICCs with respect to the pure components. While pure nicotinamide melts at 132 °C, nicotinamide·$CaCl_2$·H_2O is stable up to 142 °C, as shown by variable temperature powder XRPD analysis. At this temperature nicotinamide·$CaCl_2$·H_2O converts into another crystalline form, presumably the corresponding anhydrous nicotinamide·$CaCl_2$, which is still stable at 240 °C.

Analogously, while pure piracetam melts at 127 °C, the ICC piracetam$_2$·$CaCl_2$·$2H_2O$ transforms at around 140 °C into another crystalline compound (possibly the anhydrous form), which is still stable at 180 °C.

In the pharmaceutical field the design of co-crystals where the co-former is an inorganic salt is still an almost unexplored subject and no reference to pharmaceutically active inorganic is available except for some recent patent.[84] A search in the Cambridge Structural Database has shown that the number of ionic co-crystals (ICCs) containing lithium salts and molecules potentially interesting for pharmaceutical applications is quite scarce (less than ten): the organic molecule is in most cases an amino acid. More examples of lithium salts co-crystallized with amino acids were reported recently.[85,86]

Organic–organometallic co-crystals

Grinding or liquid-assisted grinding have also been used to investigate co-crystal formation involving organometallic molecules. Expectedly, the behaviour of neutral organometallic

molecules, carrying organic ligands bound to a metal centre, does not differ from that of purely organic ones.

An example is the family of organometallic–organic co-crystals of the pyridyl ferrocene derivative $Fe(\eta^5\text{-}C_5H_4\text{–}C_5H_4N)_2$ with dicarboxylic acids $HOOC(CH_2)_nCOOH$ of variable chain length (n = 4–7). The co-crystals, of general formula $Fe(\eta^5\text{-}C_5H_4\text{–}C_5H_4N)_2\cdot$(diacid), were prepared by liquid-assisted grinding of solid mixtures with MeOH. All compounds are organized in discrete macrocycles rather than extended networks, except for the pimelic acid adduct (n = 5) (Fig. 10).

In the search for polymorphs of the pimelic acid adduct, vapour digestion of the solid mixture was attempted. The stoichiometry of the products was affected by the protic or aprotic nature of the solvent. The co-crystal with 1 : 1 stoichiometric ratio, as observed in the solid-state synthesis, was obtained by exposure to vapours such as CH_2Cl_2, $CHCl_3$, $(CH_3CH_2)_2O$, CH_3NO_2 and ethyl lactate, while the 1 : 2 co-crystal was formed in the presence of protic solvents, such as CH_3OH, CH_3CH_2OH, H_2O and isopropyl alcohol. This indicates that the solvent used in the mechanochemical process is not an innocent spectator, nor simply a lubricant helping in the diffusion process, but takes an active part in the reaction, very likely *via* slight supersaturation levels over the grain surfaces, *i.e.* dissolution, and therefore solubility, in the added liquid could be a key factor.

To explore the effect of the preparation method on the nature of the product, co-crystallisation of $Fe(\eta^5\text{-}C_5H_4\text{–}C_5H_4N)_2$ and anthranilic acid, $(C_6H_4)NH_2COOH$, was also investigated.[87] It was shown that the same product can be obtained, quantitatively, by four different processes, namely *kneading* with methanol, wet compression (*i.e.* pressure without mixing in the presence of MeOH), vapour digestion (*i.e.* placing a mixture of the solid reactants in an atmosphere of MeOH vapour), and heating of a mixture of the two solid reactants. In contrast, no reaction was observed by dry mixing or dry compression. This demonstrates not only the ability of small amounts of added liquids in the grinding process to direct the course of a co-crystallization, but to actually *enable* co-crystallization.

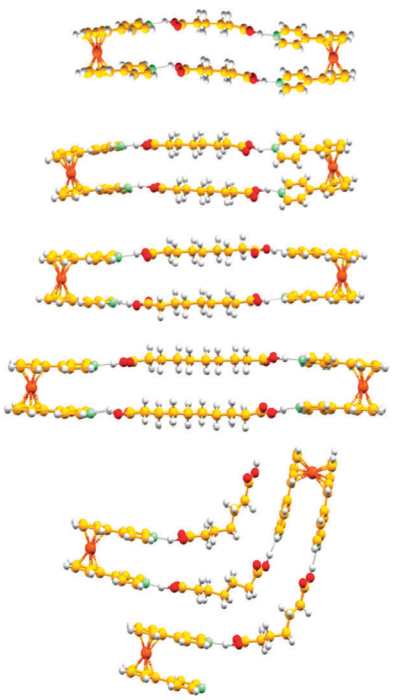

Fig. 10 The macrocycles of formula $\{Fe(\eta^5\text{-}C_5H_4\text{–}C_5H_4N)_2\cdot(HOOC(CH_2)_nCOOH_2)\}_2$ (n = 4, 6, 7, 8) and the zig-zag chain found for n = 5.

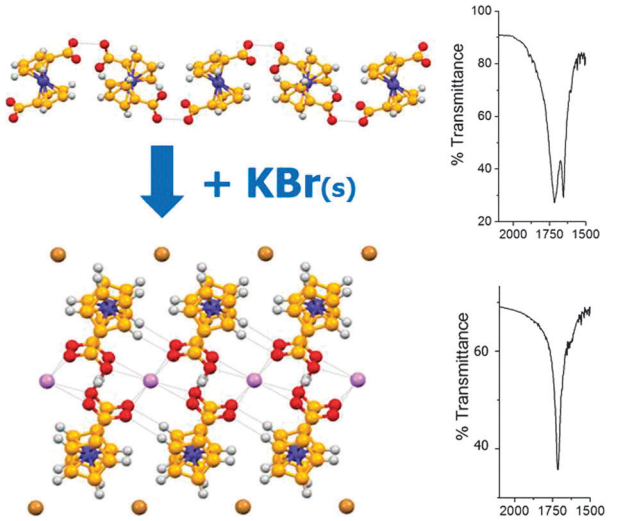

Fig. 11 A graphical description of the process leading from $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]$ and KBr to $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]_2\cdot$KBr, with relevant portions of the corresponding IR spectra.

Ionic co-crystals are also possible with organometallic systems. The investigation of the co-crystallization product of the reaction both in solution and in the solid state between the organometallic molecules and KBr revealed quantitative formation of the co-crystal $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]_2\cdot$KBr.[34a] The extension of this reaction to the family of alkali halides afforded a wealth of new co-crystals of general formula $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]_2\cdot$MX, with M^+ = K^+, Rb^+, Cs^+, NH_4^+ and X^- = Cl^-, Br^-, I^-, PF_6^-, characterized by the presence of a supramolecular cage formed by four organometallic molecules, which encapsulate the alkali or ammonium cations *via* O···M^+ or O···H–N interactions.[34b] The cage is sustained by O–H···O hydrogen bonds between carboxylic –COOH and carboxylate $-COO^{(-)}$ groups, and by C–H···O bonds between $-CH_{Cp}$ and –CO groups, while the anions are layered in between the cationic complexes, as shown in Fig. 11 in the case of $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]_2\cdot$KBr.

Conclusions

In this review article we have addressed the application of solvent-free mechanochemical reactions to obtain new co-crystalline materials. Besides the academic relevance, both aspects have great utilitarian implications, especially in the pharmaceutical field, as solvent-free processes are in general cheaper and environmentally friendly, as they minimize the problem of solvent disposal, while co-crystals are attractive new materials,

which might lead to the discovery of new drugs or to improved properties of existing APIs.

Via a series of examples coming from recently published papers it has been demonstrated that mechanochemistry is often preferable to solution or melt-based approaches as a more efficient and general way to screen for new co-crystal forms. The recently opened new avenue of ionic co-crystals also promises to deliver interesting new findings and innovation. All is well then? There are downsides, of course. We need to mention some; first of all reproducibility of the experimental conditions. As mentioned in the introduction, mechanical methods, as compared to more traditional solution methods, are more difficult to operate under exact and reproducible conditions. Manual grinding, mortar-and-pestle for example, is highly dependent on the "human factor", *i.e.* the skill and strength of the operator. As manual grinding essentially induces molecular diffusion and contact by working on a polycrystalline sample generating heat by friction, local temperature can rise considerably, well above melting point of the "soft" molecular crystals, and this depends of course on the nature of the compounds under investigation but also on the pressure exerted. Ball milling allows more control as the heat produced by the mechanical shaking can be dissipated/absorbed, and yet the quantities required are larger than by manual grinding. LAG/*kneading* on the other hand, when applied on a lab scale (and this was the case for most of the examples discussed in this article) also depend on the "human factor" and it is not unusual to see in real life that different people can obtain different products, or fail to obtain compounds that were previously accessed easily.

Another point to consider is that the polycrystalline nature of mechanochemically produced co-crystals makes impossible the use of the, by now, straightforward single-crystal diffraction method, indispensable for a precise description of the structure of the co-crystals. In general one has to resort to the *a posteriori* preparation of single crystals starting from the powdered product. In some cases, single crystals can be grown from solution by seeding, *i.e.* by using a small portion of the polycrystalline sample to "instruct" the crystallization process. Once the single-crystal structure is known, an X-ray powder pattern can be calculated and compared with the measured powder patterns of products obtained from subsequent preparations. Fortunately, structure determination from powder diffraction is becoming increasingly accessible and many of the compounds whose structures are shown/reported in this review have been structurally characterised from powder diffraction data.[88]

One should not forget that grinding or liquid-assisted grinding tends to produce amorphous material. There is almost no co-crystalline powder that can be considered amorphous-free. Since amorphous phases are less stable thermodynamically than crystalline phases, it is often the case that they also differ in physico-chemical properties; hence it is of importance to be able to characterize these properties and to determine the amount of amorphous phase accompanying the desired polycrystalline product. The characterization of the amorphous phase is still a substantial challenge for X-ray diffraction, and the contribution of spectroscopic methods, mainly solid state NMR but also IR/Raman spectroscopies, as well as of thermodynamic methods (DSC, TGA, *etc.*,) becomes essential.

Acknowledgements

We thank MIUR and the University of Bologna for financial support.

Notes and references

1 G. Kaupp, *CrystEngComm*, 2003, **5**, 117–133.
2 P. Vishweshwar, J. A. McMahon, M. L. Peterson, M. B. Hickey, T. R. Shattock and M. J. Zaworotko, *Chem. Commun.*, 2005, 4601–4603.
3 (*a*) D. Braga, S. d'Agostino, E. Dichiarante, L. Maini and F. Grepioni, *Chem.–Asian J.*, 2011, **6**, 2214–2223; (*b*) S. Aitipamula, R. Banerjee, A. K. Bansal, K. Biradha, M. L. Cheney, A. R. Choudhury, G. R. Desiraju, A. G. Dikundwar, R. Dubey, N. Duggirala, P. P. Ghogale, S. Ghosh, P. K. Goswami, N. R. Goud, R. R. K. R. Jetti, P. Karpinski, P. Kaushik, D. Kumar, V. Kumar, B. Moulton, A. Mukherjee, G. Mukherjee, A. S. Myerson, V. Puri, A. Ramanan, T. Rajamannar, C. M. Reddy, N. Rodríguez-Hornedo, R. D. Rogers, T. N. G. Row, P. Sanphui, N. Shan, G. Shete, A. Singh, C. C. Sun, J. A. Swift, R. Thaimattam, T. S. Thakur, R. Kumar Thaper, S. P. Thomas, S. Tothadi, V. R. Vangala, N. Variankaval, P. Vishweshwar, D. R. Weyna and M. J. Zaworotko, *Cryst. Growth Des.*, 2012, **12**, 2147–2152.
4 (*a*) D. P. McNamara, S. L. Childs, J. Giordano, A. Iarriccio, J. Cassidy, M. S. Shet, R. Mannion, E. O'Donnell and A. Park, *Pharm. Res.*, 2006, **23**, 1888–1897; (*b*) D. J. Good and N. Rodríguez-Hornedo, *Cryst. Growth Des.*, 2009, **9**, 2252–2264; (*c*) A. V. Trask, W. D. S. Motherwell and W. Jones, *Int. J. Pharm.*, 2006, **320**, 114–123; (*d*) A. V. Trask, W. D. S. Motherwell and W. Jones, *Cryst. Growth Des.*, 2005, **5**, 1013–1021.
5 (*a*) N. Shan and M. J. Zawarotko, *Drug Discov. Today*, 2008, **13**, 440; (*b*) W. Jones, W. D. S. Motherwell and A. V. Trask, *MRS Bull.*, 2006, **31**, 875; (*c*) P. Vishweshwar, J. A. McMahon, J. A. Bis and M. J. Zaworotko, *J. Pharm. Sci.*, 2006, **95**, 499–516.
6 (*a*) A. Delori, T. Friscic and W. Jones, *CrystEngComm*, 2012, **14**, 2350–2362; (*b*) S. L. Childs and M. J. Zaworotko, *Cryst. Growth Des.*, 2009, **9**, 4208–4211.
7 S. R. Bysouth, J. A. Bis and D. Igo, *Int. J. Pharm.*, 2011, **411**, 169–171.
8 C. Medina, D. Daurio, K. Nagapudi and F. Alvarez-Nunez, *J. Pharm. Sci.*, 2010, **99**, 1693–1696.
9 (*a*) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friscic, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413–447; (*b*) T. Friscic, *Chem. Soc. Rev.*, 2012, **41**, 3493–3510.
10 *Pharmaceutical Salts and Co-crystals*, ed. J. Wouters and L. Quéré, The Royal Society of Chemistry, 2012.
11 (*a*) V. V. Boldyrev and K. Tkacova, *J. Mater. Synth. Process.*, 2000, **8**, 121–132; (*b*) J. F. Fernandez-Bertran, *Pure Appl. Chem.*, 1999, **71**, 581–586.
12 (*a*) J. M. Cairney, S. G. Harris, L. W. Ma, P. R. Munroe and E. D. Doyle, *J. Mater. Sci.*, 2004, **39**, 3569–3575; (*b*) Y. A. Kim,

T. Hayashi, Y. Fukai, M. Endo, T. Yanagisawa and M. S. Dresselhaus, *Chem. Phys. Lett.*, 2002, **355**, 279–284; (*c*) K. Wieczorek-Ciurowa, K. Gamrat and K. Fela, *Solid State Ionics*, 2003, **164**, 193–198.

13 J. F. Willart, V. Caron, R. Lefort, F. Danede, D. Prevost and M. Descamps, *Solid State Commun.*, 2004, **132**, 693–696.

14 (*a*) T. P. Rastogi and N. B. Singh, *J. Phys. Chem.*, 1966, **70**, 3315–3324; (*b*) R. P. Rastogi and N. B. Singh, *J. Phys. Chem.*, 1968, **72**, 4446–4449; (*c*) R. P. Rastogi, P. S. Bassi and S. L. Chadha, *J. Phys. Chem.*, 1963, **67**, 2569–2573.

15 (*a*) I. C. Paul and D. Y. Curtin, *Acc. Chem. Res.*, 1973, **6**, 217–225; (*b*) I. C. Paul and D. Y. Curtin, *Science*, 1975, **187**, 19–26; (*c*) C. C. Chiang, C. T. Lin, H. J. Wang, D. Y. Curtin and I. C. Paul, *J. Am. Chem. Soc.*, 1977, **99**, 6303–6308; (*d*) A. O. Patil, D. Y. Curtin and I. C. Paul, *J. Am. Chem. Soc.*, 1984, **106**, 348–353.

16 F. Toda, K. Tanaka and A. Sekikawa, *J. Chem. Soc., Chem. Commun.*, 1987, 279–280.

17 (*a*) F. Toda, *Acc. Chem. Res.*, 1995, **28**, 480–486; (*b*) F. Toda and H. Miyamoto, *Chem. Lett.*, 1995, 861.

18 (*a*) Y. Imai, N. Tajima, T. Sato and R. Kuroda, *Chirality*, 2002, **14**, 604–609; (*b*) R. Kuroda, Y. Imai and N. Tajima, *Chem. Commun.*, 2002, 2848–2849; (*c*) F. Toda, M. Senzaki and R. Kuroda, *Chem. Commun.*, 2002, 1788–1789.

19 E. Y. Cheung, S. J. Kitchin, K. D. M. Harris, Y. Imai, N. Tajima and R. Kuroda, *J. Am. Chem. Soc.*, 2003, **125**, 14658–14659.

20 (*a*) D. R. Trivedi, Y. Fujiki, Y. Goto, N. Fujita, S. Shinkai and K. Sada, *Chem. Lett.*, 2008, 550–551; (*b*) D. R. Trivedi, Y. Fujiki, N. Fujita, S. Shinkai and K. Sada, *Chem.–Asian J.*, 2009, **4**, 254–261.

21 J. Lu and S. Rohani, *Org. Process Res. Dev.*, 2009, **13**, 1269–1275.

22 D. R. Weyna, T. Shattock, P. Vishweshwar and M. J. Zaworotko, *Cryst. Growth Des.*, 2009, **9**, 1106–1123.

23 M. C. Etter, *J. Phys. Chem.*, 1991, **95**, 4601–4610.

24 M. C. Etter, S. M. Reutzel and C. G. Choo, *J. Am. Chem. Soc.*, 1993, **115**, 4411–4412.

25 W. H. Ojala and M. C. Etter, *J. Am. Chem. Soc.*, 1992, **114**, 10288–10293.

26 A. I. Kitaigorodskii, *Molecular Crystals and Molecules*, Academic Press, New York, 1973.

27 G. Kaupp and M. R. Naimi-Jamal, *CrystEngComm*, 2005, **7**, 402–410.

28 G. R. Desiraju, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2311–2327.

29 (*a*) N. Schultheiss and A. Newman, *Cryst. Growth Des.*, 2009, **9**, 2950–2967; (*b*) R. R. Schartman, *Int. J. Pharm.*, 2009, **365**, 77–80.

30 (*a*) D. Braga and F. Grepioni, *Angew. Chem., Int. Ed.*, 2004, **43**, 4002–4011; (*b*) N. Shan, F. Toda and W. Jones, *Chem. Commun.*, 2002, 2372–2373; (*c*) A. V. Trask, N. Shan, W. D. S. Motherwell, W. Jones, S. H. Feng, R. B. H. Tan and K. J. Carpenter, *Chem. Commun.*, 2005, 880–882; (*d*) A. V. Trask, W. D. S. Motherwell and W. Jones, *Chem. Commun.*, 2004, 890–891; (*e*) T. Friscic and W. Jones, *Cryst. Growth Des.*, 2009, **9**, 1621–1637; (*f*) D. Braga, S. L. Giaffreda, F. Grepioni, A. Pettersen, L. Maini, M. Curzi and M. Polito, *Dalton Trans.*, 2006, 1249–1263.

31 (*a*) S. Watano, T. Okamoto, M. Tsuhari, I. Koizumi and Y. Osako, *Chem. Pharm. Bull.*, 2002, **50**, 341–345; (*b*) S. Watano, J. Furukawa, K. Miyanami and Y. Osako, *Adv. Powder Technol.*, 2001, **12**, 427–441.

32 (*a*) N. Morin, A. Chilouet, J. Millet and J. C. Rouland, *J. Therm. Anal. Calorim.*, 2000, **62**, 187–201; (*b*) G. Bruni, A. Marini, V. Berbenni, R. Riccardi and M. Villa, *J. Inclusion Phenom. Macrocyclic Chem.*, 1999, **35**, 517–530; (*c*) F. Taneri, T. Gueneri, Z. Aigner and M. Kata, *J. Inclusion Phenom. Macrocyclic Chem.*, 2002, **44**, 257–260; (*d*) R. Saikosin, T. Limpaseni and P. Pongsawasdi, *J. Inclusion Phenom. Macrocyclic Chem.*, 2002, **44**, 191–196; (*e*) H. M. C. Marques, *Flavour Fragrance J.*, 2010, **25**, 313–326.

33 D. Braga, D. D'Addario, M. Polito and F. Grepioni, *Organometallics*, 2004, **23**, 2810–2812.

34 (*a*) D. Braga, L. Maini, M. Polito and F. Grepioni, *Chem. Commun.*, 2002, 2302–2303; (*b*) D. Braga, L. Maini, S. L. Giaffreda, F. Grepioni, M. R. Chierotti and R. Gobetto, *Chem.–Eur. J.*, 2004, **10**, 3261–3269.

35 T. Friščić, A. V. Trask, W. Jones and W. D. S. Motherwell, *Angew. Chem., Int. Ed.*, 2006, **45**, 7546–7550.

36 (*a*) G. A. Bowmaker, J. V. Hanna, R. D. Hart, B. W. Skelton and A. H. White, *Dalton Trans.*, 2008, 5290–5292; (*b*) G. A. Bowmaker, *Chem. Commun.*, 2013, **49**, 334–348.

37 If one of the reagents is liquid, one might object, we should more properly talk of ''solid–liquid'' reactions, but we think that ''encasing'' reactions involving solids in too narrow nomenclature boxes goes in the opposite direction of crystal engineering, which expands horizontally and across solid-state chemistry.

38 K. Lien Nguyen, T. Friscic, G. M. Day, L. F. Gladden and W. Jones, *Nat. Mater.*, 2007, **6**, 206–209.

39 S. Karki, T. Friscic, W. Jones and W. D. S. Motherwell, *Mol. Pharmaceutics*, 2007, **4**, 347–354.

40 (*a*) G. W. V. Cave, C. L. Raston and J. L. Scott, *Chem. Commun.*, 2001, 2159–2169; (*b*) G. Rothenberg, A. P. Downie, C. L. Raston and J. L. Scott, *J. Am. Chem. Soc.*, 2001, **123**, 8701–8708; (*c*) K. Chadwick, R. Davey and W. Cross, *CrystEngComm*, 2007, **9**, 732–734.

41 A. Jayasankar, A. Somwangthanaroj, Z. Shao and N. Rodríguez-Hornedo, *Pharm. Res.*, 2006, **23**, 2381–2392.

42 (*a*) R. Kuroda, K. Higashiguchi, S. Hasebe and Y. Imai, *CrystEngComm*, 2004, **6**, 464–469; (*b*) D. Braga, S. L. Giaffreda, F. Grepioni, M. R. Chierotti, R. Gobetto, G. Palladino and M. Polito, *CrystEngComm*, 2007, **9**, 879–881.

43 D. Cincic, T. Friscic and W. Jones, *J. Am. Chem. Soc.*, 2008, **130**, 7524–7525.

44 N. Chieng, M. Hubert, D. Saville, T. Rades and J. Aaltonen, *Cryst. Growth Des.*, 2009, **9**, 2377–2386.

45 O. Almarsson and M. J. Zaworotko, *Chem. Commun.*, 2004, 1889–1896.

46 A. D. Bond, *CrystEngComm*, 2007, **9**, 833–834.

47 (*a*) S. Mohamed, D. A. Tocher, M. Vickers, P. G. Karamertzanis and S. L. Price, *Cryst. Growth Des.*, 2009, **9**, 2881–2889; (*b*) S. L. Childs, G. P. Stahly and A. Park, *Mol. Pharmaceutics*, 2007, **4**, 323–338; (*c*) G. P. Stahly, *Cryst. Growth Des.*, 2007, **7**, 1007–1026; (*d*) C. B. Aakeroy and D. J. Salmon, *CrystEngComm*, 2005, **7**, 439–448.

48 D. Braga, L. Maini, G. de Sanctis, K. Rubini, F. Grepioni, M. R. Chierotti and R. Gobetto, *Chem.–Eur. J.*, 2003, **9**, 5538–5548.
49 D. Braga, E. Dichiarante, G. Palladino, F. Grepioni, M. R. Chierotti, R. Gobetto and L. Pellegrino, *CrystEngComm*, 2010, **12**, 3534–3536.
50 A. D. Bond, *CrystEngComm*, 2006, **8**, 333–337.
51 S. K. Callear, M. B. Hursthouse and T. L. Threlfall, *CrystEngComm*, 2010, 898–908.
52 D. Braga, G. Palladino, M. Polito, K. Rubini, F. Grepioni, M. R. Chierotti and R. Gobetto, *Chem.–Eur. J.*, 2008, **14**, 10149–10159.
53 M. N. Frey, T. F. Koetzle, M. S. Lehmann and W. C. Hamilton, *J. Chem. Phys.*, 1973, **59**, 915–925.
54 M. R. Caira, L. R. Nassimbeni and A. F. Wildervanck, *J. Chem. Soc., Perkin Trans. 2*, 1995, 2213–2216.
55 D. Braga, F. Grepioni and G. I. Lampronti, *CrystEngComm*, 2011, **13**, 3122–3124.
56 S. Karki, T. Friscic and W. Jones, *CrystEngComm*, 2009, **11**, 470–481.
57 (*a*) C. Maheshwari, A. Jayasankar, N. A. Khan, G. E. Amidon and N. Rodríguez-Hornedo, *CrystEngComm*, 2009, **11**, 493–500; (*b*) A. Jayasankar, D. J. Good and N. Rodríguez-Hornedo, *Mol. Pharmaceutics*, 2007, **4**, 360–372.
58 (*a*) T. Friscic, S. L. Childs, S. A. A. Rizvi and W. Jones, *CrystEngComm*, 2009, **11**, 418–426; (*b*) T. Friscic and W. Jones, *Faraday Discuss.*, 2007, **136**, 167–178; (*c*) T. Friscic, A. V. Trask, W. D. S. Motherwell and W. Jones, *Cryst. Growth Des.*, 2008, **8**, 1605–1609.
59 S. L. Childs and K. I. Hardcastle, *Cryst. Growth Des.*, 2007, **7**, 1291–1304.
60 S. L. Childs, N. Rodríguez-Hornedo, L. S. Reddy, A. Jayasankar, C. Maheshwari, L. McCausland, R. Shipplett and B. C. Stahly, *CrystEngComm*, 2008, **10**, 856–864.
61 A. J. Cruz-Cabeza, S. Karki, L. Fabian, T. Friscic, G. M. Day and W. Jones, *Chem. Commun.*, 2010, **46**, 2224–2226.
62 T. Friscic, L. Fabian, J. C. Burley, D. G. Reid, M. J. Duer and W. Jones, *Chem. Commun.*, 2008, 1644–1646.
63 A. J. C. Cabeza, G. M. Day, W. D. S. Motherwell and W. Jones, *J. Am. Chem. Soc.*, 2006, **128**, 14466–14467.
64 S. Basavoju, D. Boström and S. Velaga, *Pharm. Res.*, 2008, **25**, 530–541.
65 (*a*) M. K. Stanton, S. Tufekcic, C. Morgan and A. Bak, *Cryst. Growth Des.*, 2009, **9**, 1344–1352; (*b*) M. K. Stanton and A. Bak, *Cryst. Growth Des.*, 2008, **8**, 3856–3862; (*c*) A. Bak, A. Gore, E. Yanez, M. Stanton, S. Tufekcic, R. Syed, A. Akrami, M. Rose, S. Surapaneni, T. Bostick, A. King, S. Neervannan, D. Ostovic and A. Koparkar, *J. Pharm. Sci.*, 2008, **97**, 3942–3956.
66 L. Orola and M. V. Veidis, *CrystEngComm*, 2009, **11**, 415–417.
67 D. J. Berry, C. C. Seaton, W. Clegg, R. W. Harrington, S. J. Coles, P. N. Horton, M. B. Hursthouse, R. Storey, W. Jones, T. Friscic and N. Blagden, *Cryst. Growth Des.*, 2008, **8**, 1697–1712.
68 (*a*) C. B. Aakeröy, M. Fasulo, N. Schultheiss, J. Desper and C. Moore, *J. Am. Chem. Soc.*, 2007, **129**, 13772–13773; (*b*) C. B. Aakeröy, A. M. Beatty and B. A. Helfrich, *J. Am. Chem. Soc.*, 2002, **124**, 14425–14432; (*c*) C. B. Aakeröy, N. Schultheiss, J. Desper and C. Moore, *Cryst. Growth Des.*, 2007, **7**, 2324–2331.
69 T. Friscic, L. Fabian, J. C. Burley, W. Jones and W. D. S. Motherwell, *Chem. Commun.*, 2006, 5009–5011.
70 M. D. Eddleston, M. Arhangelskis, T. Friscic and W. Jones, *Chem. Commun.*, 2012, **48**, 11340–11342.
71 A. V. Trask, J. van de Streek, W. D. S. Motherwell and W. Jones, *Cryst. Growth Des.*, 2005, **5**, 2233–2241.
72 A. V. Trask, J. van de Streek, W. D. S. Motherwell and W. Jones, *Cryst. Growth Des.*, 2005, **5**, 2233–2241.
73 C. C. Seaton, A. Parkin, C. C. Wilson and N. Blagden, *Cryst. Growth Des.*, 2008, **9**, 47–56.
74 S. Karki, T. Friscic, L. Fábián, P. R. Laity, G. M. Day and W. Jones, *Adv. Mater.*, 2009, **21**, 3905–3909.
75 D. Braga, F. Grepioni, L. Maini, S. Prosperi, R. Gobetto and M. R. Chierotti, *Chem. Commun.*, 2010, **46**, 7715–7717.
76 N. Zencirci, E. Gstrein, C. Langes and U. J. Griesser, *Thermochim. Acta*, 2009, **485**, 33–42.
77 C. B. Aakeröy, S. Forbes and J. Desper, *J. Am. Chem. Soc.*, 2009, **131**, 17048–17049.
78 D. Braga, F. Grepioni, L. Maini, D. Capucci, S. Nanna, J. Wouters, L. Aerts and L. Quere, *Chem. Commun.*, 2012, **48**, 8219–8221.
79 (*a*) J. Wouters, A. Tilborg and L. Quere, in *Pharmaceutical Salts and Co-crystals*, The Royal Society of Chemistry, 2012, pp. 330–337; (*b*) S. D. Shorvon, in *The treatment of Epilepsy*, ed. S. D. Shorvon, E. Perucca, D. Fish and W. E. Dodson, Wiley–Blackwell, 2004, pp. 489–495.
80 (*a*) P. Grof and B. Müller-Oerlinghausen, *Bipolar Disord.*, 2009, **11**, 10–19; (*b*) J. K. Rybakowski, *World J. Biol. Psychia.*, 2011, **12**, 340–348.
81 W. M. Lau, A. W. White, S. J. Gallagher, M. Donaldson, G. McNaughton and C. M. Heard, *Curr. Pharm. Des.*, 2008, **14**, 794–802.
82 L. Feng, P. H. Karpinski, P. Sutton, Y. Liu, D. F. Hook, B. Hu, T. J. Blacklock, P. E. Fanwick, M. Prashad, S. Godtfredsen and C. Ziltener, *Tetrahedron Lett.*, 2012, **53**, 275–276.
83 D. Braga, F. Grepioni, G. I. Lampronti, L. Maini and A. Turrina, *Cryst. Growth Des.*, 2011, **11**, 5621–5627.
84 L. Quéré, *WO*2007/141002, 2007.
85 T. T. Ong, P. Kavuru, T. Nguyen, R. Cantwell, Ł. Wojtas and M. J. Zaworotko, *J. Am. Chem. Soc.*, 2011, **133**, 9224–9227.
86 T. T. Ong, PhD Thesis, University of South Florida, 2011, http://gradworks.umi.com/34/50/3450427.html.
87 D. Braga, S. L. Giaffreda, K. Rubini, F. Grepioni, M. R. Chierotti and R. Gobetto, *CrystEngComm*, 2007, **9**, 39–45.
88 (*a*) A. Altomare, M. Camalli, C. Cuocci, C. Giacovazzo, A. G. G. Moliternia and R. Rizzi, *J. Appl. Cryst.*, 2009, **42**, 1197–1202; (*b*) W. I. F. David and K. Shankland, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2008, **64**, 52–64; (*c*) W. I. F. David, K. Shankland, J. van de Streek, E. Pidcock, W. D. S. Motherwell and J. C. Cole, *J. Appl. Crystallogr.*, 2006, **39**, 910–915; (*d*) A. Coelho, *J. Appl. Crystallogr.*, 2000, **33**, 899–908; (*e*) A. Coelho, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2007, **63**, 400–406.

