

Introductory Lecture: Mechanochemistry, a versatile synthesis strategy for new materials

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Mechanochemistry deals with reactions induced by the input of mechanical energy – for example by impacts within a vibratory ball mill. The technique has a long history with significant contributions from Ostwald, Carey Lea and, notably, Faraday. Mechanochemistry has subsequently seen application in a variety of areas of materials science including mechanical alloying in metallurgy, the synthesis of complex organic molecules and, more recently, the discovery and development of new solid forms of active pharmaceutical ingredients. This paper overviews the broad areas of application of mechanochemistry, some key features which make it a particularly attractive approach to materials synthesis and some mechanistic aspects highlighted within the literature. A significant part, however, will focus on recent applications in the area of pharmaceuticals and its important role in exploring the rich variety of solid forms available for small, drug-like, molecules.

1. Introduction

Mechanochemistry is a long-established method for the synthesis of solids and molecules. Its chemical importance was recorded by Faraday, who in 1820 demonstrated the reduction of AgCl to Ag by grinding in a mortar and pestle a mixture of AgCl and Zn.¹ Significant progress followed, especially through the work of Carey Lea (1823–1897),² and the position of mechanochemistry within the framework of chemistry as a whole was established by Ostwald who noted the equivalency of electrochemistry, thermochemistry, photochemistry and mechanochemistry.^{3–5}

Long held as an efficient process for the synthesis of metallic alloys, a recent extensive review by James *et al.*⁶ has highlighted several of the emergent areas now being actively pursued with regard to the application of mechanical energy in driving various transformations – indeed a working definition from that review is “mechanochemistry refers to reactions, normally of solids, induced by the impact of mechanical energy such as grinding in ball mills”. A formal definition by IUPAC states “a mechano-chemical reaction is a chemical reaction that is induced by

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mechanical energy”.⁷ Although a narrow definition of mechanochemistry may lead to a suggestion that the making and breaking of covalent bonds would be a prerequisite for a process to fall under the definition of “mechanochemistry”,⁸ following the appreciation of the importance of “non-covalent bonds” in supramolecular chemistry it seems reasonable to include changes in crystal packing to be a mechanochemical event. Links to mechanochemical activation by ultrasound have also been proposed.^{9,10}

This paper will briefly summarise recent developments in mechanochemistry, particularly in its application in pharmaceutical materials science and its role in the development of new solid drug dosage forms, to complement earlier literature which has covered extensively metals and alloys and inorganic (ionic) systems. As we will describe later, the amount of energy which can be imparted to a system under mechanical activation can be significant – certainly sufficient to break chemical bonds⁶ – but can also be reduced when working with systems such as soft molecular crystals in order to minimise chemical activation while still enabling processes such as the conversion of a crystalline solid to an amorphous product,¹¹ or the readjustment of molecules within a lattice. Such readjustments may lead to the introduction of lattice imperfections,¹² to polymorphic transformations¹³ or to the intimate mixing of two separate crystalline molecular solids to create a crystalline multicomponent product indistinct from that which would be obtained by a conventional solution crystallisation.¹⁴ Particularly advantageous in mechanochemical transformations is the avoidance of the need for large volumes of solvent (as required, for example, in the recrystallization of poorly soluble molecules), and hence a strong “Green Chemistry” aspect to mechanochemistry is recognised.^{15,16} In terms of commercial interest, the review by James *et al.* describes a search of patent applications for the terms “mechanochemical” and “mechanochemistry” which revealed a significant increase in usage in the patent literature from 1980 onwards.⁶

2. Areas of application and development

The areas in which mechanochemistry has been applied with success are varied and include: catalysts,¹⁷ nanoparticles,^{18–20} organic synthesis,^{21–27} MOFs,²⁸ oxides,²⁹ biomaterials,^{30,31} supramolecular chemistry,^{32–34} process engineering,³⁵ dyes and pigments,³⁶ fluorophores,³⁷ exfoliation of graphene nanosheets³⁸ and modification of fullerenes (see Fig. 1).³⁹ Numerous further examples are given in the review by James *et al.*⁶ and several other reviews on the application of mechanochemistry are available.^{28,40–47} In particular, the contributions of V. V. Boldyrev and his colleagues to both experimental and theoretical aspects of mechanochemistry have been important to the subject.^{3,9,48,49}

From a synthetic chemistry viewpoint an important observation is that substances can react by a significantly different pathway in the solid state than they would in solution, leading to new products or to much higher selectivities.^{50,51} This ability to generate a much broader product-spectrum, as we will demonstrate later, is also particularly important in areas other than chemical transformations *e.g.* in crystal polymorph conversions – and it is to be noted that the addition of very small amounts of liquid may have a significant impact on the outcome of a solid–solid reaction, even though quantities are much less than a conventional solvent-based reaction might require – see later.



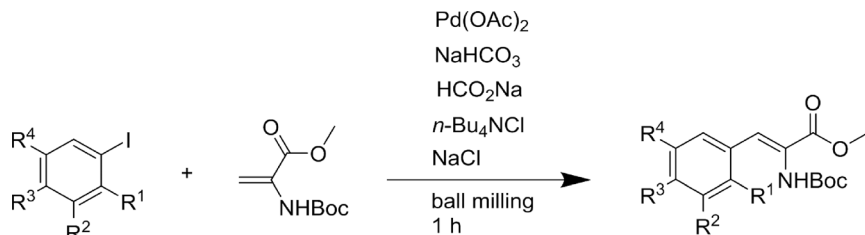


Fig. 1 General scheme for the Heck reaction under ball milling conditions. Reproduced from ref. 6.

A key area of active research remains the understanding of the processes by which mechanically induced reactions occur.⁵² Given the variety of materials of interest, ranging from metals and ceramics to pharmaceuticals, the specific details of how a process occurs will likely be varied and complex.^{3,53,54} Also to be distinguished is the time-scale over which an event is studied. During the few milliseconds following the impact of two solids at high velocity, significant local consequences will ensue. Hot spots, magma–plasma regions, rapid induction of defects (point, linear and planar) and then propagation of these defects through the crystal are some of the concepts which have evolved. The distribution of imparted energy will also be different in those solids with high rigidity and few pathways for energy dissipation (so that the effects at the specific point of impact will be great) than it is in those systems where structural movement (*e.g.* slippage of crystal planes) may allow the energy (and its consequences) to be distributed over a much larger distance.³ During this early stage, the making and breaking of chemical bonds would seem possible. Following the initial short-term consequences, there will also be the longer term events associated with the final energy dissipation and relaxation of the system. The slow crystallisation of an intermediate amorphous phase may be such an example (see Fig. 2 and 3).^{11,52,55,56} It is possible, then, to envisage that an individual particle, for example within a milled pharmaceutical material, may be completely amorphous initially, but over time

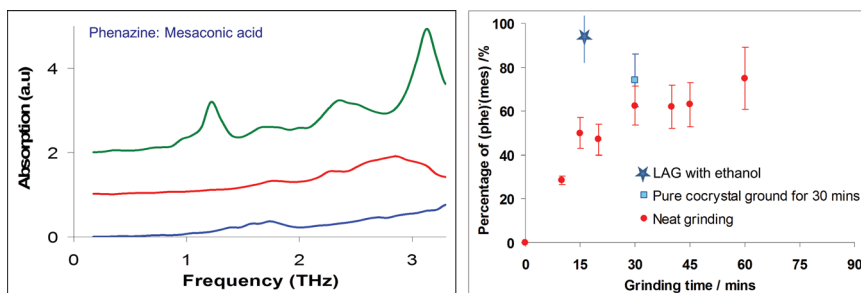


Fig. 2 (a) Terahertz spectra obtained from (top to bottom): a 1 : 1 mesaconic acid–phenazine cocrystal; mesaconic acid; phenazine. (b) Analysis (*ex situ*) of the extent of formation of the cocrystal from a mixture of phenazine and mesaconic acid, as a function of neat grinding time, as measured using the characteristic cocrystal band at 1.1 THz (red circles). The blue star, by comparison, shows close to 100% conversion in 15 minutes as a result of the presence of liquid in a LAG experiment. The blue square represents the percentage of a cocrystal sample that remained crystalline during dry grinding.⁵⁶



may change to consist of domains of crystalline solid embedded within an amorphous shell (or more likely *vice versa* where, for example, humidity from the surrounding atmosphere results in each amorphous particle crystallising from the outside). This model might suggest that a description of a product as 25% amorphous does not mean that 25% of all the particles are amorphous and 75% are not – but that each individual particle within the product consists of domains of crystalline and amorphous in a 3 : 1 ratio.

A key factor for potential commercial exploitation in many instances would seem to be difficulties associated with scale-up. The progression from gram-scale, lab-based synthesis to kilogram-scale or higher outputs is an issue that has been addressed in many industrial applications³ and more recently in the area of pharmaceuticals, where twin extrusion approaches are employed (Fig. 4).^{57,58} Furthermore, it is noteworthy that frequently the generation of a new material (*e.g.* in the case of molecular crystals) at the gram level can allow, through subsequent seeding of a supersaturated solution, production *via* a conventional solvent-based crystallisation route.⁵⁹

It is also necessary to recognise the need for methods of structurally characterising the products of mechanochemical processes. When applied to chemical conversions which may occur, molecular identity can be established by conventional analytical methods (*e.g.* solution NMR and mass spectrometry). For solid–solid transformations, where the identity of crystalline intermediates or final states is required, major improvements in crystal structure determination from powder X-ray diffraction data (frequently coupled with solid-state NMR) have been pivotal.^{60–64} In addition, the structural analysis of individual crystallites that result from mechanochemical processes is possible through utilisation of the electron diffraction facility of the transmission electron microscope.^{65–67}

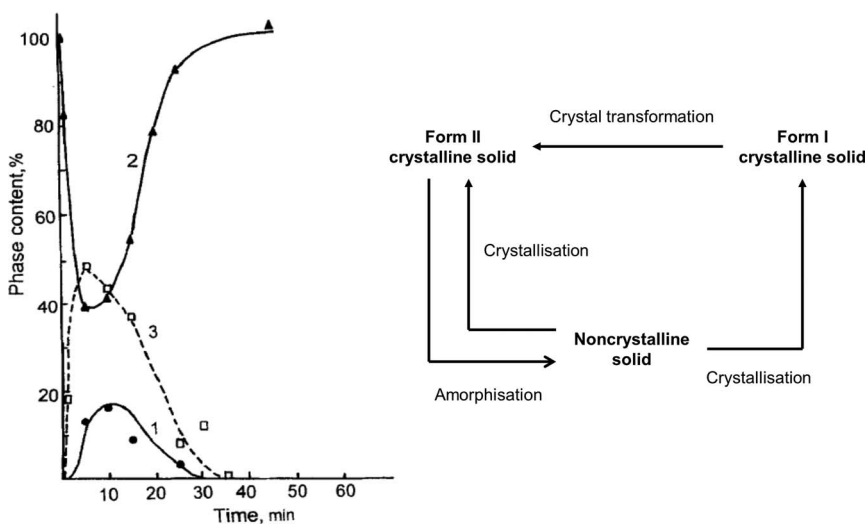


Fig. 3 (a) Schematic of the different pathways occurring during the mechanochemical treatment of sulphathiazole. Mechanical treatment resulted in the partial amorphisation of the drug and the interconversion of Forms I and II. (b) Time profile for the phase interconversion for sulphathiazole: 1 – indicating generation of Form I; 2 – initial loss and subsequent regeneration of Form III; 3 – the existence of a transient amorphous phase. Figure adapted from ref. 55.



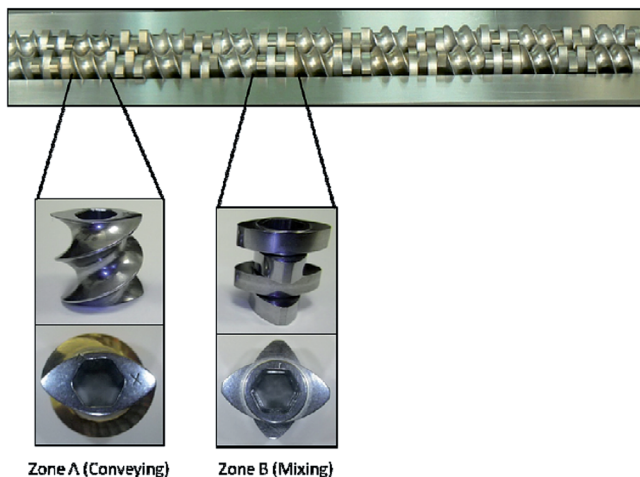


Fig. 4 Typical twin extrusion configuration used for the formation of cocrystals. The conveying and mixing zones are shown. Typical output rate is approximately 0.5 g min^{-1} . PXRD suggests comparable properties for the product to that obtained by conventional solution growth. The possibility of simultaneously blending the cocrystal product within a polymer matrix is an important additional advantage of the method. Reproduced from ref. 58.

3. Pharmaceutical materials

Within various areas of process engineering (including food science, chemicals and pharmaceuticals) particle size reduction is an important step.^{35,68} Approaches to size reduction include compression (*e.g.* rollers) or impact (*e.g.* impact mills and ball mills). All methods involve transfer of varying amounts of energy to the

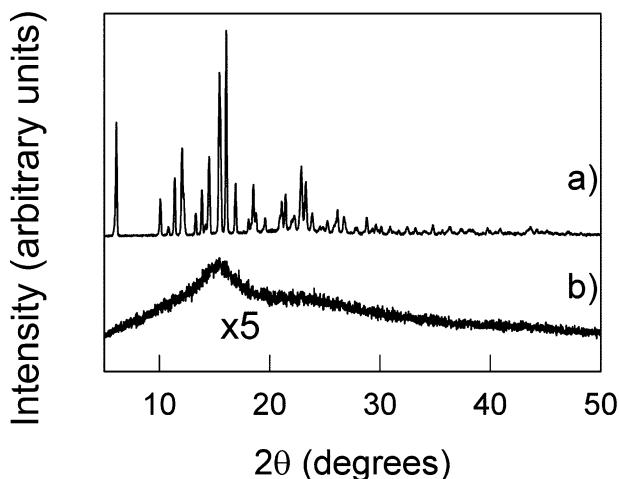


Fig. 5 Demonstration of the amorphisation of trehalose as a result of milling at room temperature within a high energy planetary micro-mill. PXRD patterns (a) before and (b) after milling. Adapted from ref. 11.



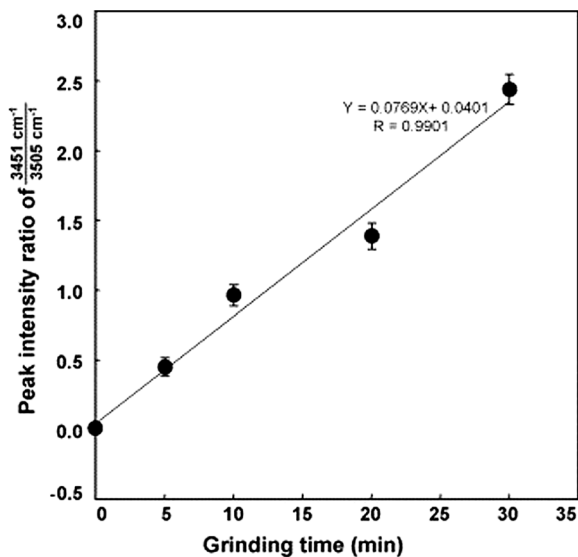
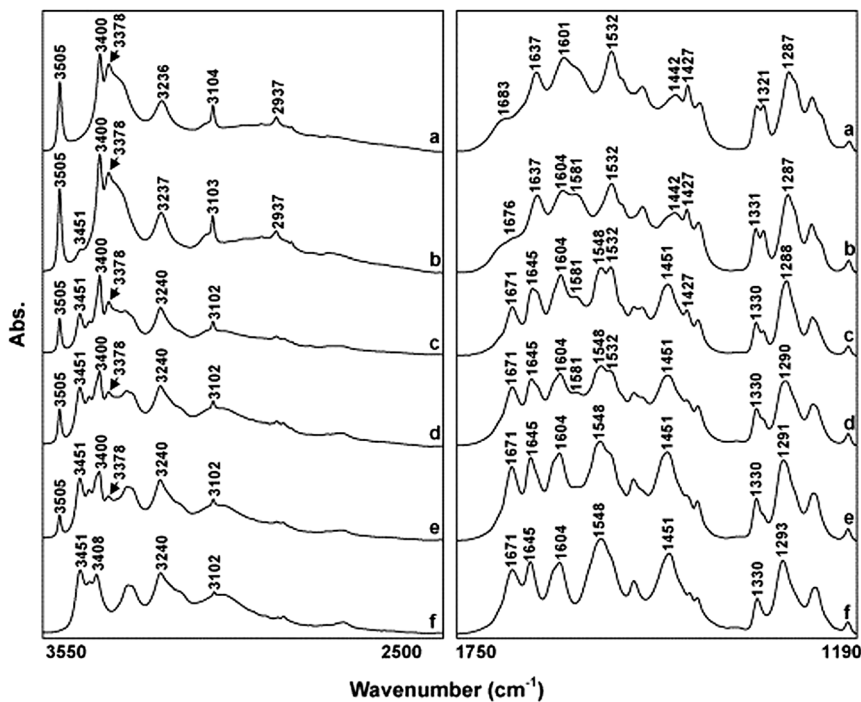


Fig. 6 (a) Grinding-time dependence of the FTIR spectra for famotidine showing from top to bottom the emergence of the absorption at 3451 cm^{-1} which is used to monitor the formation of Form A of the material. (b) Plot of peak intensity ratio (I_{3451}/I_{3505}) for the spectra above indicating a possible zero order rate law for the conversion. Reproduced from ref. 78 with permission from Elsevier.



particle(s), and as a result other consequences can accompany the size reduction including the introduction of defects (such as dislocations, point defects and stacking faults)¹² and in particular amorphisation⁶⁹ or polymorphic transformations.⁷⁰

The work of Descamps and others with regard to pharmaceutical materials has clearly demonstrated the critical role of the glass transition temperature, T_g , in determining whether or not a persistent amorphous phase will be generated.^{11,71–73} The combination of increased milling intensity and the absence of any plasticisers, which might lower T_g (either as liquid or vapour, *e.g.* water, from the surrounding atmosphere), will encourage the formation of an amorphous product (Fig. 5). The distinction between amorphous and crystalline products is particularly important for pharmaceutical applications given the inherent increased transient solubility (and hence improved bioavailability) associated with amorphous compared to crystalline solid forms.^{69,74–76}

Frequently, the amorphisation of a material can be a desirable outcome, especially as a means of increasing the transient solubility of the material or of eliminating compression issues with the crystalline equivalent.⁶⁸ This attribute is frequently used in the pharmaceutical industry, and the complex nature of the resulting solids has been extensively studied (especially with regard to the instability of the amorphous form with respect to the crystalline state).⁷⁴

Polymorphic transformations from the stable to a metastable form (again with increased apparent solubility) can also be a useful consequence of the application of mechanical energy (Fig. 6).^{13,77–79} Jet-milling, a particle-size reduction method frequently used within the pharmaceutical industry where particle–particle collisions occur within a carrier gas (typically air), has, for example, been found to induce polymorph interconversions along with the size reductions.

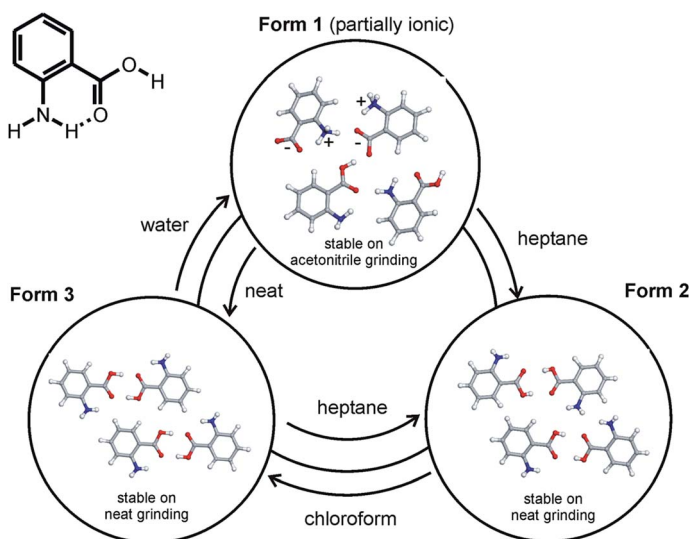


Fig. 7 Schematic of the observed transformations between the three polymorphic forms of anthranilic acid with the pathways depending on the conditions under which mechanochemical treatment was performed.



With grinding experiments, an approach for directing the polymorphic outcome through addition of a small amount of liquid was described by Trask *et al.* for the cases of anthranilic acid and succinic acid (see Fig. 7).⁸⁰ For anthranilic acid, interconversion between the three known polymorphic forms occurred depending upon the choice of the added liquid.⁸¹ In the case of succinic acid, while the β -polymorph appeared stable to neat grinding, addition of a few drops of a low polarity liquid (*e.g.* hexane) caused conversion to the α -polymorph. More polar liquids (*e.g.* water, acetonitrile or methanol) appeared not to induce the transformation. The actual mechanism of the solid–solid transformation is an area of ongoing interest, especially where the change appears to be crystal–crystal in nature.⁸²

An additional reason for interest in mechanochemical processes comes from the fact that the majority of drugs (80–90%) are formulated as tablets, which are seen as a reliable and general way of delivering medicines, and that the tableting process itself requires the application of significant applied pressures (see Fig. 8).^{55,83–90} Importantly, tablets contain other components (excipients), which are added to enhance performance *e.g.* lubricants, dissolving agents and so on. When pressure is applied during compression, there is a risk that surface–surface reactions between the components and drug, such as that between dicalcium phosphate dihydrate and aspirin, will lead to enhanced instability.⁹¹

More recent interest has focused on the formation of cocrystals (see Fig. 9) by milling or grinding.^{92–94} One of the earliest examples of a cocrystal obtained by grinding is that of quinhydrone reported in the work of Wohler published in 1844.⁹⁵ The advantage for this system compared to solution crystallization was shown by Patil *et al.*,⁹⁶ who demonstrated that simple grinding of mixtures was significantly superior to attempted solution growth, where self oxidation–reduction lowered the efficiency of complex formation. Subsequently, numerous examples of host–complex formation by solid–solid mixing were reported by Toda and co-workers.⁵⁰ Work by Etter and colleagues also demonstrated how solid–solid grinding could be used to produce hydrogen bonded cocrystals of adenine and thymine derivatives, where a marked selectivity amongst various base pairs was observed.¹⁴ Hollingsworth *et al.*⁵¹ used grinding as a means of creating cocrystals of dinitriles and urea, as part of a wide study of inclusion crystals, in cases where solution growth was not possible. Pedireddi *et al.* demonstrated that in

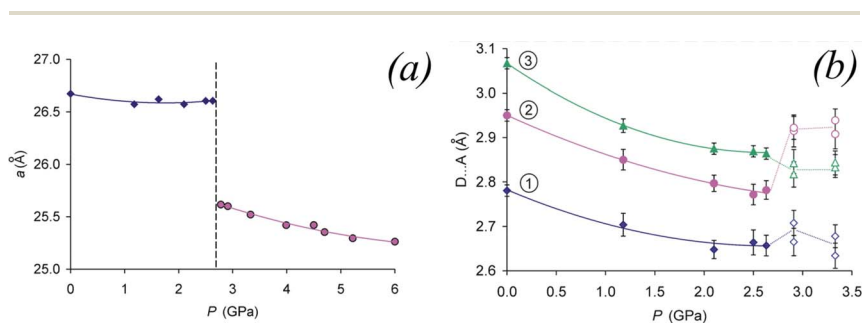

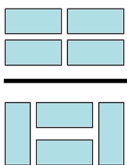


Fig. 8 (a) Hydrostatic pressure induced transition for chlorpropamide in a saturated ethanol solution. The phase change results in a first order change at approximately 3.5 GPa. The change is illustrated for the *a*-axis. (b) Changes in non-hydrogen atom positions as the transition pressure is reached. Adapted from ref. 46.

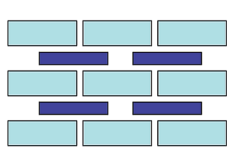


 = Drug molecule

Polymorphs



Multi-component forms







hydrate  = water
 solvate  = solvent
 salt  = counter ion
 cocrystal  = cocrystal former

Fig. 9 Schematic of the characteristics of polymorphs and multicomponent systems. Cocrystals represent a sub-set of the multicomponent group, frequently that characterised by the requirement that the components be neutral and solid at room temperature.

some cases a third component is necessary in order for a cocrystallisation reaction to take place⁹⁷ and Kuroda and her colleagues studied the influence of the addition of a third component on the optical properties of the resulting cocrystals.⁹⁸

Frequently, the solid state properties of a pure drug can present processing or application problems *e.g.* particle flow, thermal stability, stability to moisture or ability to be compacted,⁶⁸ and, increasingly, poor solubility is an issue.^{99,100} The challenge with a badly behaving drug, therefore, is to be able to control the properties of the molecule in the solid state without recourse to chemical modification by covalent chemistry. The use of multicomponent systems, especially pharmaceutical cocrystals, and more recently ionic cocrystals,^{101,102} has been demonstrated to be an effective strategy in such instances.^{103–112} In terms of property improvement with pharmaceutical cocrystals, various examples are known including: enhancing stability against hydration of an anhydrate form (see

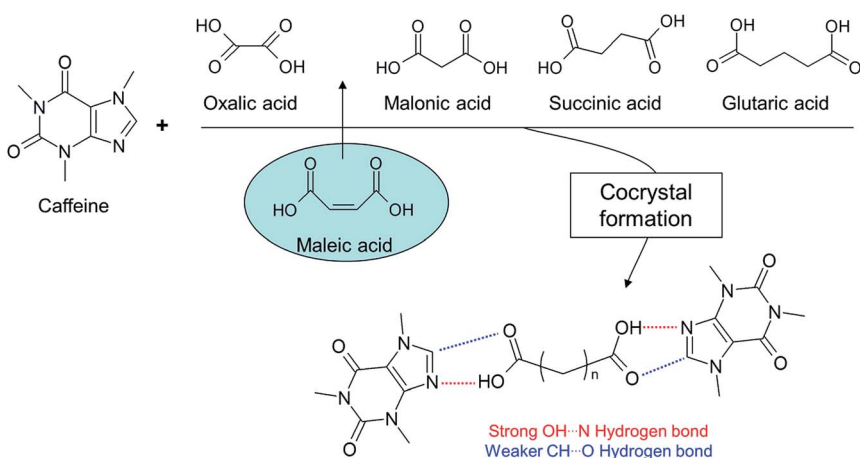


Fig. 10 Supramolecular synthon approach used in the design of cocrystals of caffeine with various dicarboxylic acids. This approach lead to a variety of solid forms of caffeine which could be tested for stability under conditions of high humidity. Mechanochemistry was the technique used to both screen for cocrystal formation and also prepare powders for humidity assessment.



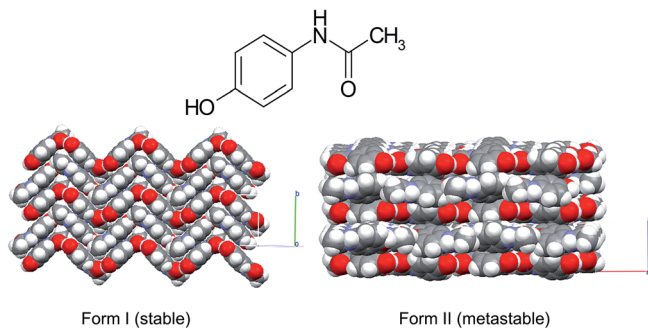


Fig. 11 Packing diagrams for Form I and Form II paracetamol. Whilst Form I is the stable phase it does not compress well during tablet formation. The metastable Form II has a layered structure more appropriate for compression, but readily transforms to Form I.

Fig. 10),^{113–116} developing forms with improved compression properties (for tablet formation) (see Fig. 11 and 12),^{117,118} significantly improving the bioavailability of poorly soluble drugs and controlled release strategies *e.g.* for insulin.¹¹⁹ Trask has reported on the potential intellectual property implications of pharmaceutical cocrystals,¹²⁰ and recent interest has also focused on regulatory guidelines.¹²¹ In non-pharmaceutical applications, benefits of cocrystallisation have been shown for fluorescent materials^{37,122} and explosives.^{123,124}

An early indication of the potential to form pharmaceutical cocrystals by grinding was provided by Caira *et al.* in 1995 who used grinding to prepare a series of crystalline products containing sulfonamide (similar to those obtained from solution) in a facile manner.¹²⁵ They also reported detailed solid state kinetic data based on powder X-ray measurements and were able to show a distinct selectivity between reactants during grinding.

An ongoing challenge, however, is selecting possible cofomers which might cocrystallise with the API rather than remain as a separate and distinct crystalline phase. Whilst various strategies have been developed to predict the likelihood of cocrystal formation,^{126–129} experimental screening for viable cofomers remains vital (Fig. 13).^{130–132} While solution growth remains the ideal approach – especially with regard to scale-up in later stages of development – significant differences in solubility between the drug and cofomer often presents difficulties.^{115,116,133–135} Mechanochemistry has emerged as a powerful tool in the experimental screening area, and has the advantage of minimising the need for large volumes of solvent (Fig. 14). It has also emerged as a powerful way of searching for different



Fig. 12 Micrographs of tablets made from (a) paracetamol Form I and (b) to (d) cocrystals of paracetamol with theophylline, naphthalene and oxalic acid respectively. Tablet (a) is poorly formed as a result of the inappropriate packing of the molecules in the lattice, whereas the cocrystal structures are amenable to deformation during tableting.¹¹⁸



polymorphic forms of cocrystals^{135,136} as well as for various stoichiometric compositions *e.g.* 1 : 1, 1 : 2 and 2 : 1.⁵⁹ Furthermore, mechanochemistry has been used to identify chiral agents suitable for converting a racemate into two distinct diastereomeric cocrystal phases¹³⁷ as well as for cofomer exchange.¹³⁸

An extension to simple (*i.e.* neat or dry) grinding of mixtures was reported by Shan *et al.* who added a few drops of liquid to the reaction mixture (liquid assisted grinding, LAG) (see Fig. 15).¹³⁹ Initial attention focused on LAG as a means of accelerating cocrystallisation kinetics, although it was subsequently shown to provide a means of increasing product diversity. For example, the outcome of mechanochemical formation of cocrystals has been compared with that from using other approaches to cocrystallisation. Trask *et al.* reported three possible

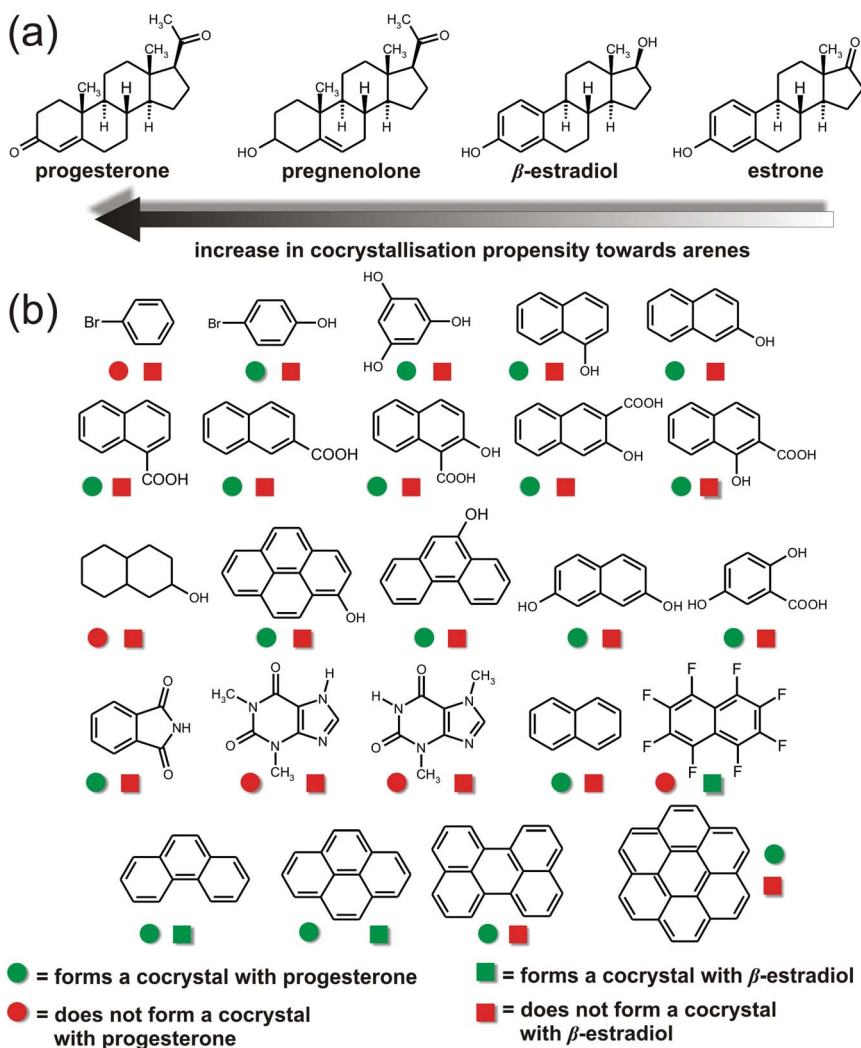


Fig. 13 The use of mechanochemistry to explore the various possible combinations of cofomers for a family of steroid drugs. The various outcomes are delineated by the accompanying legend. See ref. 161 for details.



outcomes in the case of cocrystals with caffeine: (i) solution growth and milling produced identical products; (ii) a different stoichiometric product could be obtained by milling compared to solution; and (iii) different polymorphic forms were possible.⁵⁹ Numerous recent publications have demonstrated that LAG is likely to be the most efficient way of screening for cocrystal formation.^{140–144} The key advantage of LAG over solution based approaches was interpreted by Davey,^{145,146} Childs¹⁴⁷ and others¹⁴⁸ on the basis of solution phase chemistry (Fig. 16). Other developments, such as ion- and liquid-assisted grinding (ILAG)¹⁴⁹ and vapour digestion of solid mixtures,^{150,151} have also been reported.

Further insight has been given by the recent work of Bučar *et al.* for the case of caffeine and benzoic acid.¹⁵² No cocrystals for this pair of molecules were known despite a strong expectation based on studies of analogous systems¹⁵³ and despite extensive experimental efforts to generate such a species over many years. A systematic study using a large range of cocrystallisation methods including neat grinding, liquid assisted grinding, melt crystallization and various solution methods was employed (Fig. 17). All failed to produce the elusive cocrystal even though theoretical work had clearly confirmed a cocrystal was thermodynamically feasible. During grinding experiments, however, the addition of a few seed crystals of an isostructural fluorobenzoic acid cocrystal readily generated the elusive cocrystal, with the inference being that, as in solution crystallisation, a high barrier to nucleation of a particular form can frequently exist.

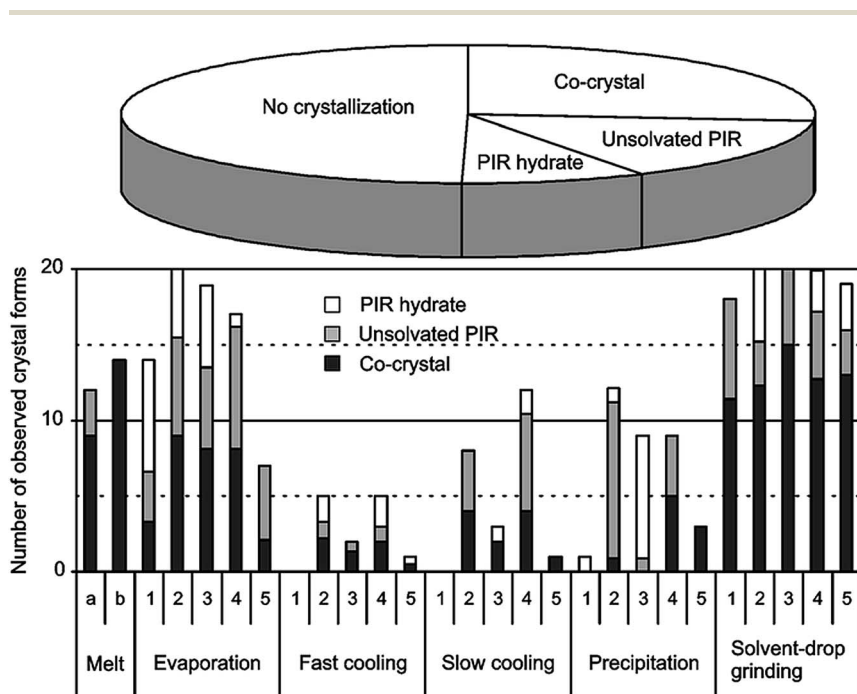


Fig. 14 Overview of the results obtained by various cocrystallisation attempts for piroxicam. Solvent-drop grinding (LAG) is shown in this case to be the most efficient and straightforward screening method. The numbers 1–5 indicate the various solvents used in the experiments. Reproduced with permission from ref. 142.



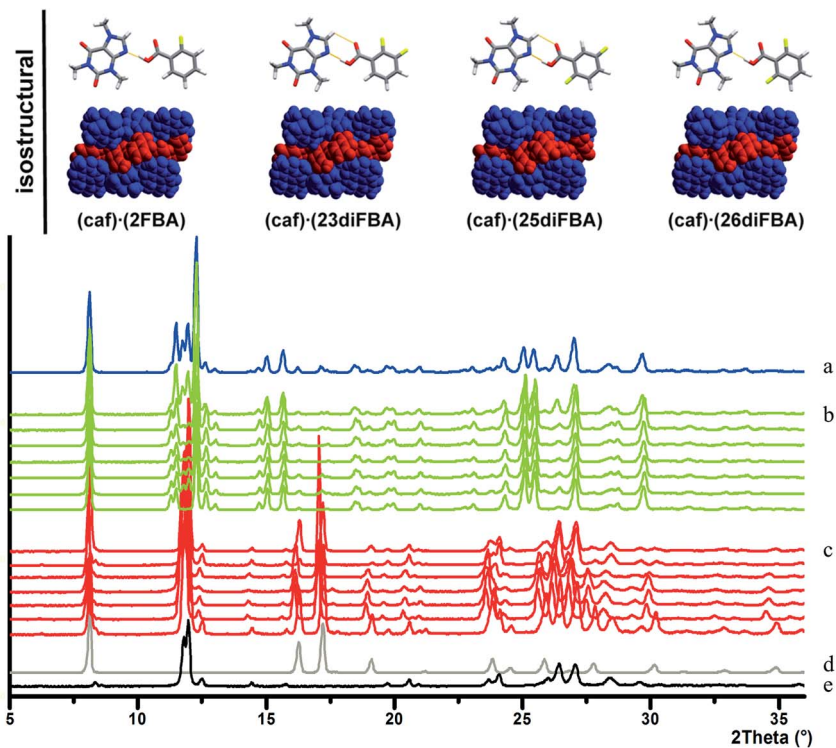


Fig. 17 Top. Isostructural cocrystals of caffeine with various fluorobenzoic acids which have similar packing to that predicted for the likely structure of the caffeine–benzoic acid cocrystal. Bottom. PXRD traces of (a) product without deliberate addition of seeds, but prepared in an environment where the caffeine–benzoic acid cocrystal had previously been obtained, (b) products of various seeding reactions, (c) products of various unseeded reactions, (d) benzoic acid and (e) caffeine. The main points to note include the similarity of the patterns in (a) and (b) and that those in (c) are a simple combination of the starting materials in (d) and (e). See ref. 152 for more details.

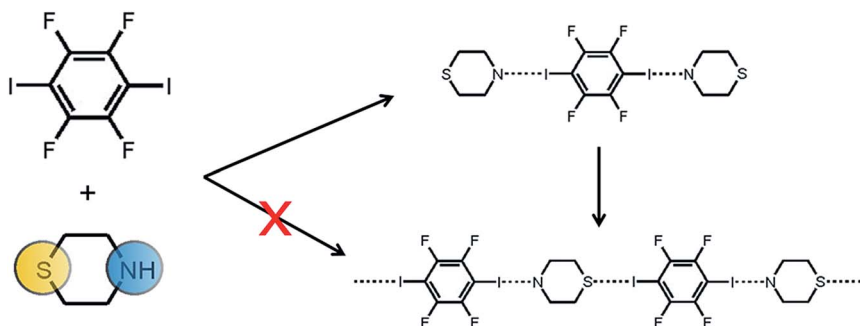


Fig. 18 The discrete trimer units and extended polymer chains (based on halogen bond interactions) believed to be formed during the LAG reaction. When the strength of the halogen bond is weak the product is limited to the trimer unit.



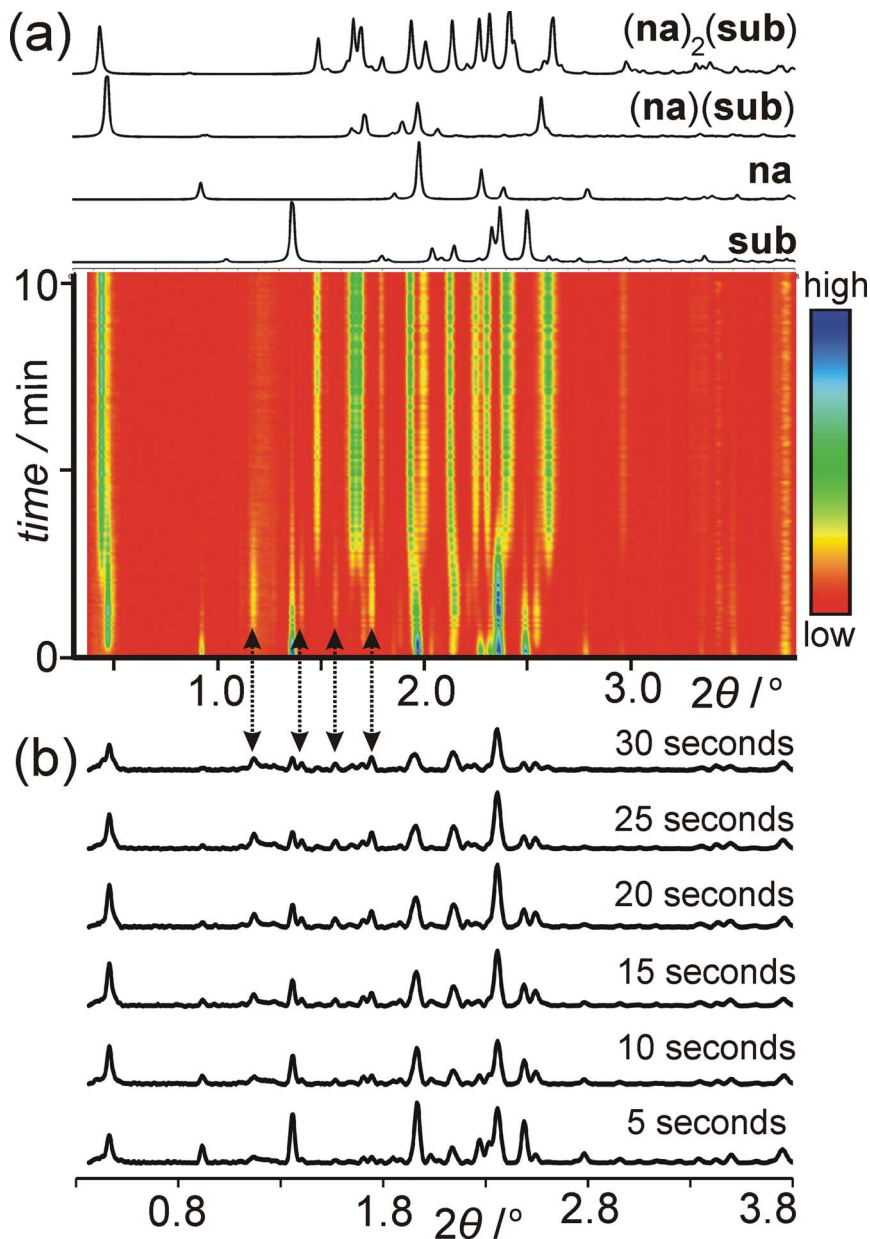


Fig. 19 *In situ* synchrotron data for the milling of suberic acid and nicotinamide in a 2 : 1 ratio. (a) The PXR patterns of the phases expected to be formed during milling along with the data obtained as a function of time. The inset shows the particular region at 0.4 to 0.5 degrees two-theta showing the initial formation of the 1 : 1 cocystal followed by the 2 : 1 product. (b) The specific reflections indicated by arrows indicate the intermediate phase which is not detected by conventional *ex situ* studies. See ref. 157 for further details.

milling, several recent efforts have concerned developing methods to follow *in situ* the course of the reaction. Noteworthy has been the use of synchrotron X-ray diffraction. In a study of the milling of a mixture of carbamazepine and succinic





Fig. 20 (a) Transmission electron micrograph and (b) electron diffraction pattern obtained from a sample of a theophylline:L-malic acid cocrystal prepared by LAG. The method is able to monitor particle size as well as polymorphic form.¹⁶⁰

acid, Halasz *et al.*¹⁵⁷ showed that, in the absence of any added liquid, the outcome was the gradual disappearance of reflections of the two components and apparent amorphisation. A similar experiment, but now with the addition of 50 μL of acetonitrile showed that within 10 seconds of milling, reflections associated with a triclinic (cbz)(sac) cocrystal emerged. The reaction was complete within 4 minutes. Such rapidity was to be compared with other solid–solid grinding systems (*e.g.* the reaction of ZnO with imidazoles) where reaction timescales were much longer. Similar *in situ* studies were conducted for suberic acid and nicotinamide demonstrating that formation of a 2 : 1 cocrystal during grinding proceeds *via* a 1 : 1 cocrystal intermediate (see Fig. 19). Frišćić and his colleagues have also used *in situ* methods, based on the changes in fluorescence¹²² accompanying cocrystallisation, to monitor directly events within the grinding jar.

4. Concluding remarks

In the case of pharmaceutical solids, recent work using atomic force microscopy (AFM), terahertz spectroscopy and transmission electron microscopy (TEM) suggests that these techniques will be important for characterising mechanically treated samples and understanding changes which occur during such processing. For example, there are particle–particle effects – especially important during compression in a tablet containing various components. In the case of aspirin (acetylsalicylic acid) and dicalcium phosphate, when the excipient was attached to the tip of the AFM cantilever and different pressures and contact times under various humidity conditions there was evidence for enhanced reactivity induced by surface contact with excipient.⁹¹ Terahertz spectroscopy has emerged as a sensitive method of monitoring changes in the solid form during mechanical activation,^{56,156} whereas TEM has been shown to be a powerful technique for characterising the size and shape of particulates generated mechanochemically, as well as determining their crystal form (see Fig. 20). TEM can also be used to identify defects in pharmaceutical crystals (see Fig. 21), and will enable a greater understanding of how defects introduced into crystals during mechanical processing influence material properties – for example a link between defects in theophylline crystals and crystal fracture has been established.¹⁶⁰





Fig. 21 Extensive network of dislocations in a sample of theophylline as revealed by transmission electron microscopy. In general, such dislocations can result from the mechanical treatment of crystals.

Mechanochemistry, as mentioned at the outset, provides many opportunities for developing environmentally-friendly processes (especially the avoidance of large volumes of solvent). It also provides routes to materials not readily obtained by other methods. It has a long history and no doubt will continue to demonstrate useful applications whilst at the same time generate considerable activity in rationalising the mechanistic aspects behind the many types of transformations observed.

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