Ball-free mechanochemistry: in situ real-time monitoring of pharmaceutical co-crystal formation by resonant acoustic mixing

Citation for published version:

Digital Object Identifier (DOI):
10.1039/c8cc02187b

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Chemical Communications

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Resonant acoustic mixing (RAM) is a new technology designed for intensive mixing of powders that offers the capability to process powders with minimal damage to particles. This feature is particularly important for mixing impact-sensitive materials such as explosives and propellants. While the RAM technique has been extensively employed for the mixing of powders and viscous polymers, comparatively little is known about its use for mechanochemistry. We present here the first in situ study of RAM-induced co-crystallisation monitored using synchrotron X-ray powder diffraction. The phase profile of the reaction between nicotinamide and carbamazepine in the presence of a small amount of water was monitored at two different relative accelerations of the mixer. In marked contrast to ball-milling techniques, the lack of milling bodies in the RAM experiment does not hinder co-crystallisation of the two starting materials, which occurred readily and was independent of the frequency of oscillation. The reaction could be optimised by enhancing the number of reactive contacts through mixing and comminution. These observations provide new insight into the role of various experimental parameters in conventional mechanochemistry using liquid-assisted grinding techniques.

Mechanochemical techniques (e.g. planetary and vibratory ball milling, grinding, etc.) are a useful method for multi-component, one-pot syntheses of a wide range of compounds and materials. The mechanosynthesis of multi-component organic materials is believed to proceed via fluid-like intermediate phases. These phases may be formed through a eutectic melt, atmospheric moisture, sublimation of one component, or melting due to global temperature rise. The desolvation of solvated reactants has also been suggested to facilitate mechanochemical reactions. While a single general mechanism for liquid-assisted grinding (LAG) is not known, the liquid is believed to enhance molecular mobility, likely through dissolution. Despite the rather limited understanding of the mechanism of LAG, it has proved to be a promising technique for the “solvent-free” production in high yield of novel organic and inorganic compounds and materials, and has been demonstrated to provide control over selection of polymorphic form.

A key feature of traditional mechanochemical experiments is the addition of milling bodies: hard, unreactive masses such as steel or ceramic balls, which introduce mechanical (and often thermal) energy through impact, shear, or a combination thereof. The addition of milling bodies is central to nearly all mechanochemical literature, with explicit discussion about the effects of the number and masses of the milling ball, together with the ratios of balls to the amount of sample. To date, the focus has remained on the amount of energy imparted by these balls on the powder sample at particular milling frequencies, rather than the physical effects of these balls and the associated energy input.

The substantial mechanical energy introduced by the addition of milling bodies can cause considerable damage to particles, and may lead to generation of large numbers of defects into the crystalline lattice or complete amorphisation. This is particularly problematic if the powders being treated are highly sensitive to mechanical stimulus, e.g. energetic materials such as explosives and propellants, or when highly crystalline products are required. Furthermore, issues such as aggregation of particulates, “snowballing”, and compaction can all be encountered during conventional ball milling.

In Resonant Acoustic Mixing (RAM), the sample vessel is placed on a plate connected to a bed of springs, and forced to oscillate at the fixed mechanical resonance frequency of the device. This motion is transferred to the powder, introducing intense, local mixing zones. The RAM technique, Fig. 1, has therefore been proposed as a method to perform mechanochemical processes under significantly more gentle conditions than those experienced during ball milling. For example, the impact-sensitive energetic co-crystal, 2CL-20 HMX,
has been successfully prepared using this technique. A limited number of other co-crystals have also been produced using the RAM technique. The RAM technique offers particular benefits for mechanochemistry on account of its ability to rapidly and thoroughly mix materials.

The monitoring of mechanochemical processes in real time has proved to be highly beneficial in order to identify and understand the correlation between instrument parameters, temperature and reaction rates, together with identification of short-lived intermediate phases and changes in reaction conditions. Real-time and in situ monitoring of mechanochemical processes is therefore vital for gaining an understanding of and hence controlling mechanochemical processes, and can provide different interpretations of reaction mechanisms when compared to ex situ analysis. This is particularly true of novel mechano-reactors that offer new control parameters and RAM technique. Previous investigations have demonstrated that CBZ-NIC is thermodynamically stable under conditions of higher humidities. This indicates that the co-crystal is more thermodynamically stable than CBZDH under normal conditions.

The reaction between form III of carbamazepine (CBZ; ca. 0.4 mmol) and form I nicotinamide (NIC; ca. 0.4 mmol) to form a 1:1 co-crystal CBZ-NIC was investigated according to Fig. 2. This system has been the subject of previous investigations as a model pharmaceutical co-crystal system, and its mechanical ball mill, the LabRAM instrument maintains a constant characteristic Bragg peak appearing at a d-spacing of 7.20 Å were observed. These Bragg peaks indicate the formation of CBZDH and NIC, respectively. Formation of CBZDH occurred at a nearly continuous rate before reaching a final plateau, Fig. 3(I). The continuous and consistent growth of CBZDH before this point, however, suggests that formation of reactive contacts occurred readily, despite the absence of any milling bodies. Some indications of CBZ-NIC were observed, Fig. 3(II), with a characteristic Bragg peak appearing at a d-spacing of ca. 13.10 Å, corresponding to the (011) plane. This peak grew slowly in intensity before reaching a maximum. On mixing at 50 G, the major product peaks do not correspond to the thermodynamically most favourable phase (CBZ-NIC), but instead indicate the formation of CBZDH as the kinetically controlled product. Rietveld refinement, Fig. 3(III), of a subset of the in situ XRPD profiles suggests that >10% conversion to CBZDH was reached after only 90 seconds of mixing and that this phase fraction continued to grow steadily, (see ES1†) up to a limiting value of ca. 40%. Noting that water is present in excess, this conversion is likely limited by hydration of CBZ surfaces, impeding the hydration of deeper particle layers. Rietveld refinement also indicates that no more than 10 mol% of the 1:1 CBZ-NIC co-crystal was formed over the period of the experiment.

The reaction profile was substantially different when a stoichiometric mixture of CBZ and NIC was subjected to mixing at 100 G – see Fig. 4(I) and (II) (full profiles are shown in ES1†). Within the first 30 s of mixing, the reaction proceeded rapidly, leaving only a small amount of the reactants. It should be noted that some Bragg peaks appeared and disappeared somewhat stochastically throughout the first ca. 560 s, suggesting that reactant phases had not been completely eliminated from the mixture, but simply remain undetected. This is most likely due to inhomogeneities in the mixing over the course of the reaction. In marked contrast to the reaction conducted at 50 G, Rietveld
refinement of the XRPD profiles show that the dominant phase at 100 G was indeed the thermodynamically favoured co-crystal CBZ\textsubscript{NIC}, with a final phase fraction of ca. 70 mol%. Some CBZ\textsubscript{DH} was initially formed, followed by partial consumption to a final value of 15–20 mol%, Fig. 4(II). This is consistent with previous reports of the co-crystal being formed on RAM treatment with water, although the presence of CBZ\textsubscript{DH} was not observed in those studies.\textsuperscript{19} The persistence of a small quantity of CBZ\textsubscript{DH}, despite the apparent complete consumption of CBZ, can be attributed to the observation that there was residual powder (CBZ) that had aggregated at the corners of the reaction vessel and which had therefore not been efficiently dispersed into the reaction zone. This reflects the less than ideal geometry of the mixing vessel, which had been optimised for transmission of X-rays rather than for the most efficient mixing.

The XRPD background associated with the 100 G data were notably higher than at 50 G, with Rietveld refinements possible for only a few patterns. Rietveld refinement of the final mixture showed that the major phase at the end of the reaction was CBZ\textsubscript{NIC}. Unfortunately, the most intense Bragg peaks, the (041) and (121) planes at a \(d\)-spacing of ca. 4.30 Å, overlap partially with a minor peak of CBZ. Hence we monitored both the (011) reflection at a \(d\)-spacing of 13.10 Å, as well as the reflections associated with the (041) and (121) planes, Fig. 4(II) and ESI.\textsuperscript{†} For both reflections, a very rapid increase in the intensity of the Bragg peak was observed in the first 100 s of RAM treatment. This is followed by very slow, but continued growth until a final plateau is reached.

It is interesting to observe such a substantial difference in reaction rate when comparing the experiments conducted at two different accelerations. In ball-milling experiments an increased milling frequency generally results in an increasing reaction rate.\textsuperscript{22} In RAM, increasing acceleration affects only the magnitude of the oscillation, with no influence on the frequency of this motion. Previous work on the RAM technique has suggested that higher accelerations are often associated with more thorough and more rapid mixing of the sample.\textsuperscript{21,30} Higher accelerations have also been demonstrated to induce particle comminution\textsuperscript{25} and dissociation of particle aggregates.\textsuperscript{30} These factors all contribute to enhanced mixing, and formation of a larger number of reactive heterogeneous interfaces. While we note that higher mixing can also be associated with heating, earlier measurements suggest these temperature rises to be no higher than ca. 40 °C at both 50 and 100 G.\textsuperscript{17} Based on thermodynamic arguments, NIC and CBZ would be expected to form CBZ\textsubscript{NIC} – this is the product formed in solution. However, in contrast to crystallisation from solution, the reaction zones in mechanochemical processes involving solid are limited to particle–particle interfaces. The composition of the interface is therefore crucial in determining the nature of the associated reaction, with heterogeneous interfaces required for multi-phase reactions to occur. At low accelerations, formation of interfaces between NIC...
and CBZ particles are likely inhibited by agglomeration, insufficient mixing, and by the presence of reaction products coating reactant particles. Thus CBZ particles are more likely to react with liquid water to form CBZDH. Conversely, higher accelerations lead to the disruption of agglomerates, comminution of larger particles, and thus overall more intimate mixing. As a result, a greater number of fresh reactive interfaces are generated and the reaction rate increases.

At lower accelerations in the RAM, CBZDH does not continue to react with NIC; it instead presumably coats unreacted CBZ, which hinders further reaction. This is in stark contrast to ball milling and the co-crystallisation under higher accelerations in the RAM. Indeed, on ball milling, the intensity of impacts does not allow solvate intermediates to be isolated, and highlights the “softness” of the RAM technique. The faster and more complete co-crystallisation under high G-force RAM conditions can be explained by comminution of particles and agglomerates. However, this mechanism does not explain the continued reaction of CBZDH with unreacted NIC. Previous measurements have suggested that the global temperatures obtained in the RAM at 50 and 100 G accelerations vary only slightly, and do not exceed ca. 40 °C.\(^{17}\) Dehydration is therefore not a bulk effect, with CBZDH remaining at the end of the 100 G reaction. To induce comminution, higher accelerations must be associated with increased particle–particle contact energies. These higher energies must therefore lead to surface effects, presumably involving dehydration of CBZDH. Hence the subsequent reaction of CBZDH with residual NIC.

The RAM technique provides a powerful alternative to conventional ball milling technologies, particularly for liquid-assisted mechanochemistry. Co-crystallisation by RAM is not restricted to the present system; in situ real-time XRPD offers great potential to probe a variety of RAM-induced processes. The rate of a mechanochemical co-crystallisation induced by RAM has been followed for the first time, and was found to increase with increasing acceleration. Higher accelerations lead to more intimate mixing (comminution, particle–particle mixing, surface regeneration, etc.) and thus a higher number of reactive interfaces. Moreover, it is possible to alter the pathways of the RAM-induced co-crystallisation using different accelerations. These reactions proceed despite the absence of milling bodies. It is therefore apparent that milling bodies are not always essential in order to obtain the high reaction rates that make mechanochemistry so appealing to the academic and industrial communities. Provided thorough mixing can be achieved, and new reactive interfaces can be formed, mechanochemical reactions can occur.

The authors thank ESRF ID31 (CH4805) for beam time. Thanks to an Edinburgh Global Research Scholarship (AM), EPSRC CMAC EP/1033459/1 (AM), Russian Ministry of Science & Education (AM), an ISIS Facility Development Studentship (KH), WSTC/0047 (SK/CP) and the Russian Academy of Sciences Project 0301-2018-0007 (EB) for funding. Final thanks to Prof. VV Boldyrev for many fruitful discussions.

Conflicts of interest

There are no conflicts to declare.

Notes and references