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Electronic Supplementary Information

Ball-Free Mechanochemistry: *In situ* Real-Time Monitoring of Pharmaceutical Co-Crystal Formation by Resonant Acoustic Mixing

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Experimental

Materials. Carbamazepine (ACROS, 98%) and nicotinamide (ACROS, 99%) were used as supplied, without further purification. Distilled water was used for LAG experiments.

Resonant Acoustic Mixing: RAM experiments were performed using a LabRAM-1 (Resodyn). Custom-built Perspex vessels of volume *ca* 0.7 cm^3 (0.8 cm internal diameter, 1.4 cm internal height) were used for all experiments. Equimolar quantities of CBZ and NIC were used in all experiments, with a total mass of 150 mg. A single drop of water (*ca* 20 uL) was added to the surface of the powder, and immediately sealed before loading onto the RAM device. Samples were subjected to RAM treatment at 100 G and 50 G for 30 minutes and monitored in real time by synchrotron X-ray radiation.

Synchrotron X-Ray Powder Diffraction (XRPD). All reactions were monitored *in situ* and in real time using synchrotron radiation at ESRF ID-31. The synchrotron beam (60 um diameter) was aligned along the inside wall of the RAM vessel (0.7 mm from internal wall), to ensure the shortest path length of the beam through the powder. The X-ray source was monochromated to λ=0.1771 Å. Each XRPD pattern was collected for 4 s, allowing for an averaging over the moving sample. A dark scan of 4 s was subsequently measured to ensure no overlapping signals between frames. All patterns were integrated using the pyFAI[1,2] azimuthal integration scheme.

Data Processing: Following integration, the 1D XRPD profiles were Rietveld refined using GSAS with EXPGUI[3,4]. To follow the evolution of individual peaks, powder patterns were background corrected using the Sonnerveld-Visser[5] algorithm in Powder3D[6]. Data were internally normalised to unity and the peak areas obtained using trapezoidal integration in a custom built programme.

Rietveld Refinements

XRPD patterns obtained from *in situ* XRPD experiments were Rietveld refined using GSAS with EXPGUI.[3,4] The large amorphous background is well known, resulting from scattering by the Perspex sample vial. We note slight peak broadening in all cases, due to the thickness of the sample. This broadening has been minimised by reducing the X-ray path length through the sample as much as possible. The combination of a large amorphous background coming from the sample vessel and artificial peak broadening renders determination of any amorphous content very difficult. However, we do not notice any obvious changes to peak shape or the amorphous background over time. Further, previous *ex situ* work on related organic materials did not suggest any amorphisation when analysed by XRD or SEM.[7] This contrasts ball milling, where amorphisation of organic materials is a common occurrence.

Refinements are given for select patterns obtained by RAM treatment at 50 G, Figure S1, spanning the time length of the experiment. There is clear evolution of product phase with continued RAM treatment, as indicated by the growth of Bragg peaks at d-spacing 9.7 Å and 13.10 Å. According to the Rietveld refinements, phase evolution develops as in Figure S2. Carbamazepine (CBZ) reacts with added water to form carbamazepine dihydrate (CBZDH), while nicotinamide (NIC) phase fraction

remains largely constant. Minimal co-crystal (CBZ-NIC) formation is observed. The loss of NIC at the beginning of the experiment seems to be due to some agglomeration in the corners of the vessel.

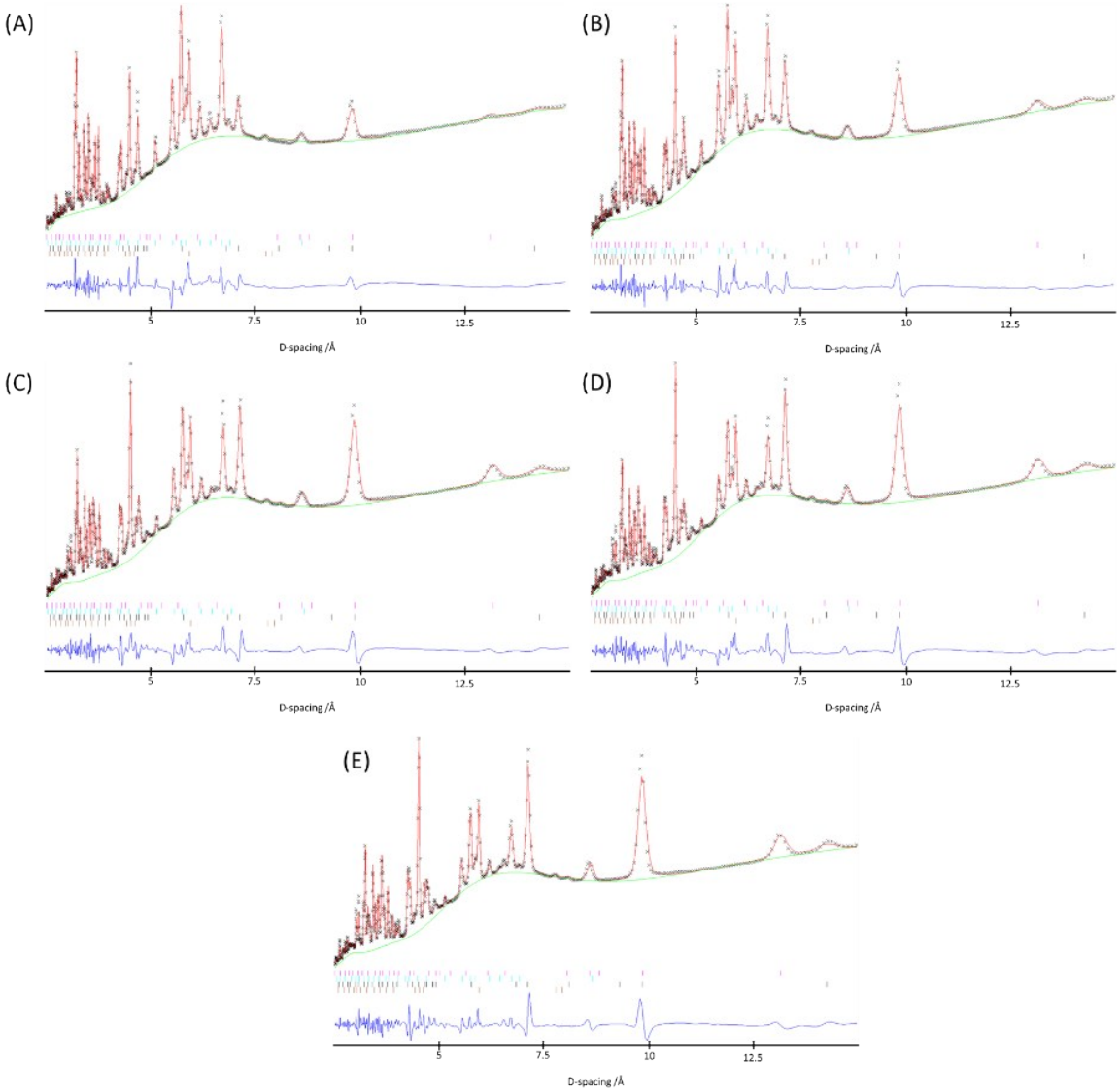

Fig S1: Raw Rietveld refined profiles for the co-crystallisation of NIC and CBZ at 50 G by RAM. Profiles are given for (A) 112 s, (B) 240 s, (C) 400 s, (D) 560 s, and (E) 800 s. Data show (black) raw data, (red) refined pattern, (green) background, and (blue) difference plot. Tick marks correspond to (pink) CBZ-NIC co-crystal, (cyan) CBZ-III, (black) CBZDH, and (brown) NIC.

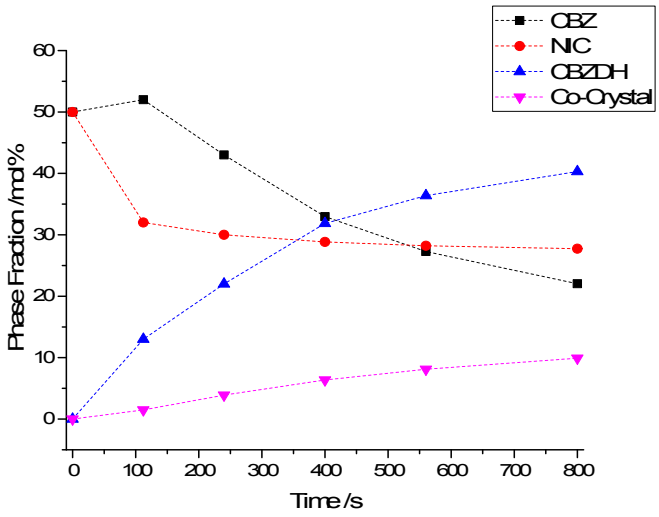

Fig S2: Phase fraction for the co-crystal synthesis by RAM at 50 G.

The higher background associated with the 100 G XRPD profiles rendered reliable Rietveld refinements difficult to achieve. Only the final mixture was therefore analysed to highlight the product differences between the 100 G and 50 G patterns, Figure S3.

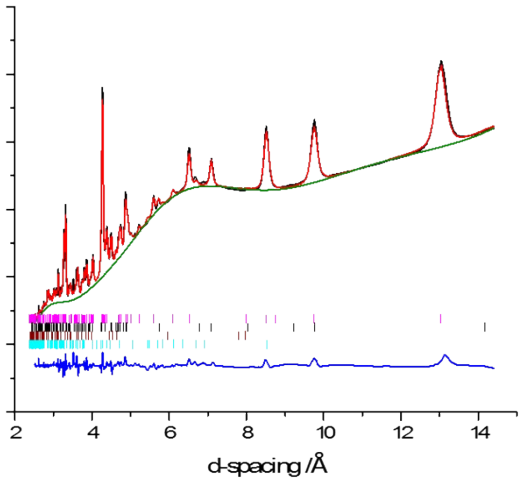

Fig S3: Raw Rietveld refined profiles for the co-crystallisation of NIC and CBZ at 100 G by RAM. Profiles are given for 800 s. Data show (black) raw data, (red) refined pattern, (green) background, and (blue) difference plot. Tick marks correspond to (pink) CBZ-NIC co-crystal, (cyan) CBZ-III, (black) CBZDH, and (brown) NIC.

Time Evolving XRPD

The XRPD profiles collected at each time step clearly identify the evolving phase profile, Figure S4. The evolution of XRPD profiles clearly occurs more slowly in the experiment conducted at 50 G (Fig

S4A) than in that conducted at 100 G (Fig S4B). The time evolved XRPD and monitored peak areas are given in Figure S5.

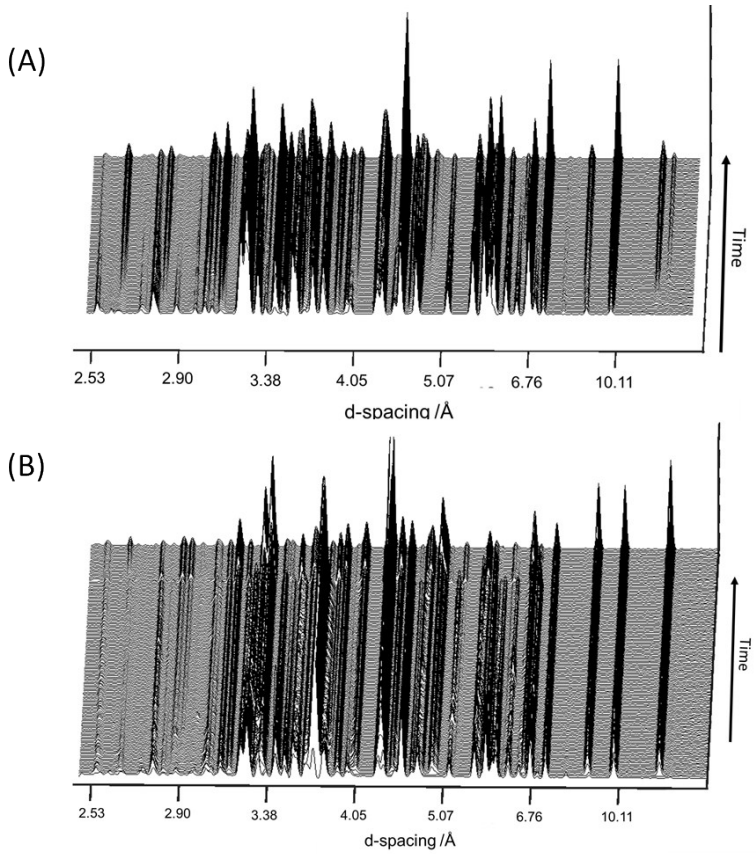

Fig S4: Time evolving, background corrected XRPD profiles for the co-crystallisation of CBZ and NIC at (A) 50 G and (B) 100 G.

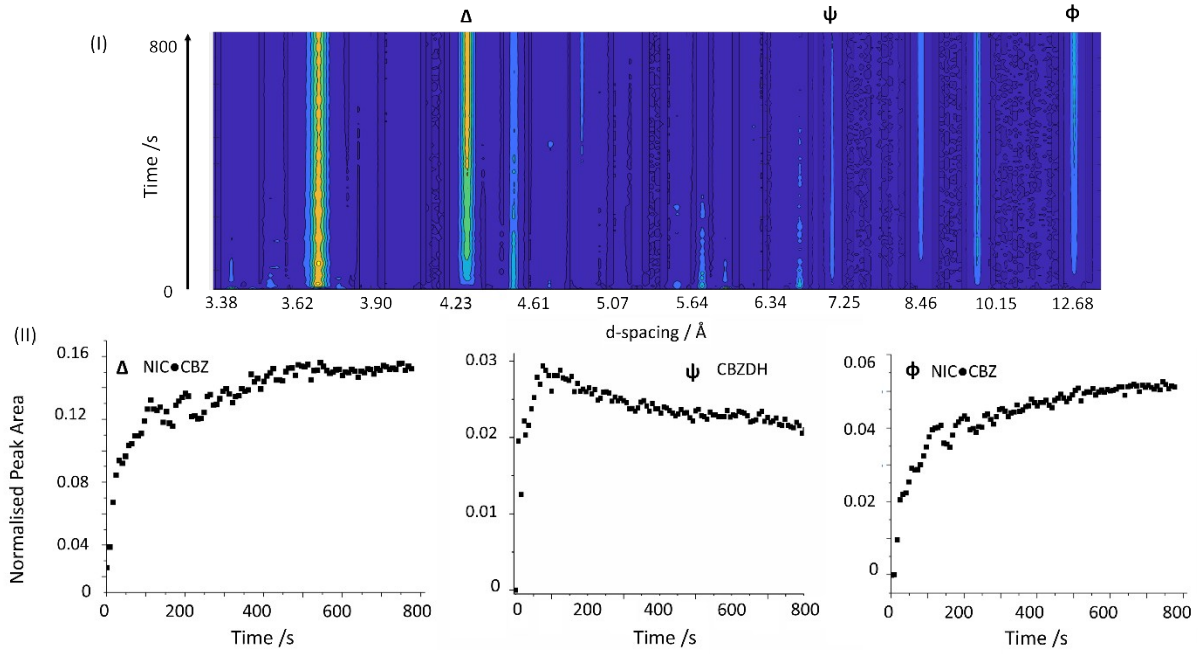

Fig S5: RAM treatment of a 1:1 mixture CBZ and NIC at 100 G. I) time-resolved XRPD profile of RAM treatment. II) Normalised integrated peak intensity of product peaks at d-spacings of *ca* (Δ) 4.30 Å, (Ψ) 7.20 Å and (ϕ) 13.10 Å.

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