Supplementary Material (ESI) for Chemical Communications

Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients.

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Polymorph Screen

Goal:

The goal of the grinding/slurrying screen was to determine if co-crystals **4** and **5** would exhibit polymorphism when ground dry or in the presence of different solvents.

Methods:

Synthesis via grinding. For each co-crystal, a series of 23 solvents was explored. The samples were analyzed using powder X-ray diffraction (See figures 1–4). Powder X-ray diffraction (PXRD) patterns were measured on a Rigaku D/Max Rapid image plate diffractometer (Rigaku/MSC, Woodlands, TX) employing Cu Kα radiation with a 0.3 mm collimator and a 2.0 kW source, operating at 46 kV/40 mA. Preferred-orientation effects were minimized by collecting PXRD data in transmission mode, while oscillating about the *phi*-axis from 0 to 5° and spinning 360° about the ϕ-axis at 2 deg/s. Some PXRD patterns were also measured on a Bruker AXS D8 Discover X-ray Diffractometer. This instrument was equipped with GADDS^{TM} (General Area Diffraction Detection System), a Bruker AXS HI-STAR Area Detector at a distance of 15.05 cm as per system calibration, a copper source (Cu/K_α 1.54056 angstroms), automated x-y-z stage, and 0.5mm collimator.

Synthesis via slurrying. Complete conversion to the Piracetam:p-hydroxybenzoic acid co-crystal was effected by slurrying Piracetam (0.088g, 0.62mmol) and p-hydroxybenzoic acid (0.084g, 0.62mmol) in water (100μL) for 16 hours. Slurrying equimolar amounts of Piracetam (0.088g, 0.62mmol) and gentisic acid (0.096g, 0.62mmol) in water (80μL) for 60 hours resulted in complete conversion to the co-

crystal. PXRD was used to confirm the outcome of these experiments and to observe intermediate degrees of conversion at shorter times.

Materials:

Piracetam (Sigma)

Gentisic acid (Sigma)

p-hydroxybenzoic acid (Sigma)

Solvents used:

Water, acetone, methanol, ethanol, ethyl acetate, n-hexane, toluene, acetonitrile, tetrahydrofuran, isopropyl acetate, benzyl alcohol, nitromethane, dimethyl amine, 2-butanol, ethyl formate, acetic acid, methyl ethyl ketone, methyl tertiary butyl ether, chlorobenzene, N-methyl pyrrolidone, 1,2-dichloroethane, dimethylsulfoxide and dimethoxy ethane.

Conclusion:

Both co-crystals **4** and **5** were obtained from all conditions as a mixture with one or both starting materials and do not exhibit polymorphism based on the series of solvent-mediated grinding experiments.

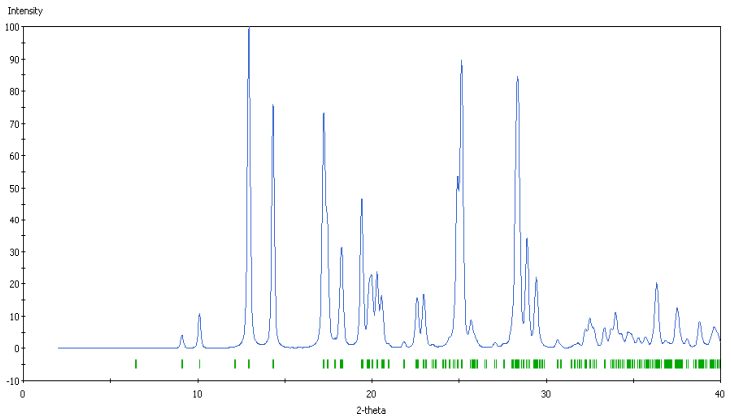

Figure 1. Calculated powder pattern for Piracetam:Gentisic acid co-crystal **4**.

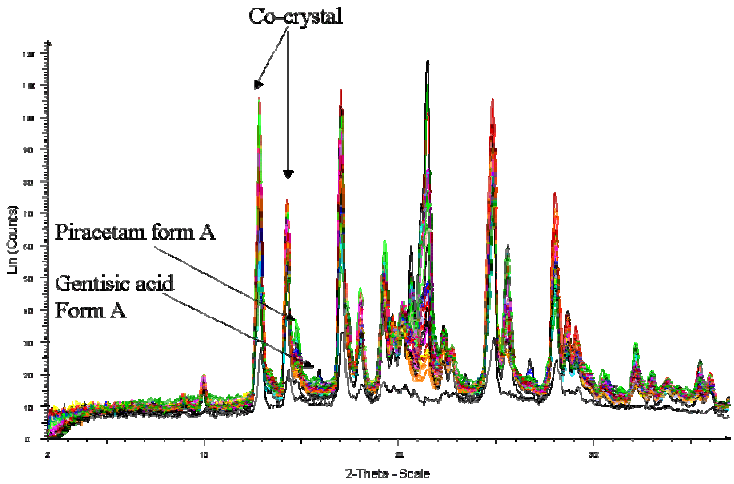

Figure 2. Overlay of powder patterns obtained from solvent drop grinding Piracetam and gentisic acid.

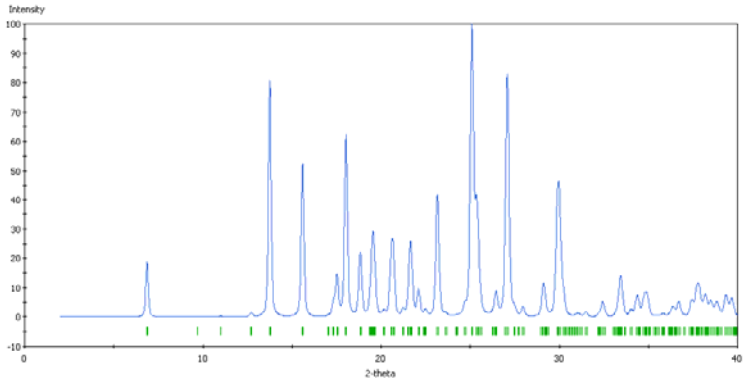

Figure 3. Calculated powder pattern for Piracetam : *p*-hydroxybenzoic acid co-crystal **5**.

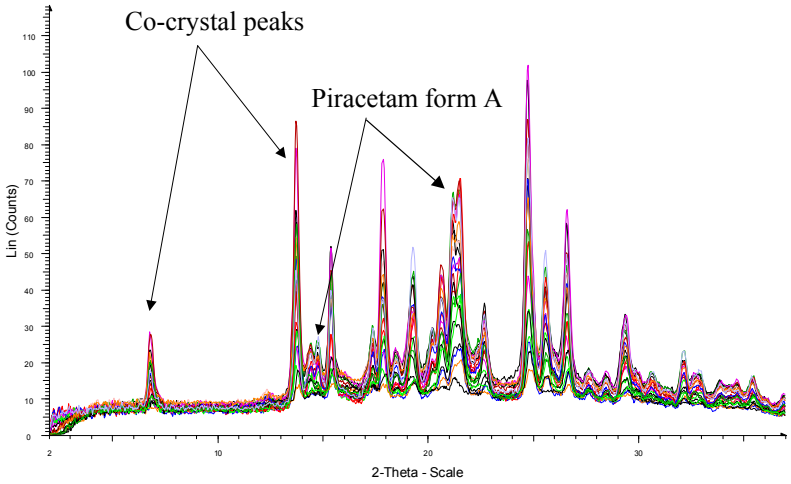

Figure 4. Overlay of powder patterns obtained from solvent drop grinding Piracetam and *p*-hydroxybenzoic acid.

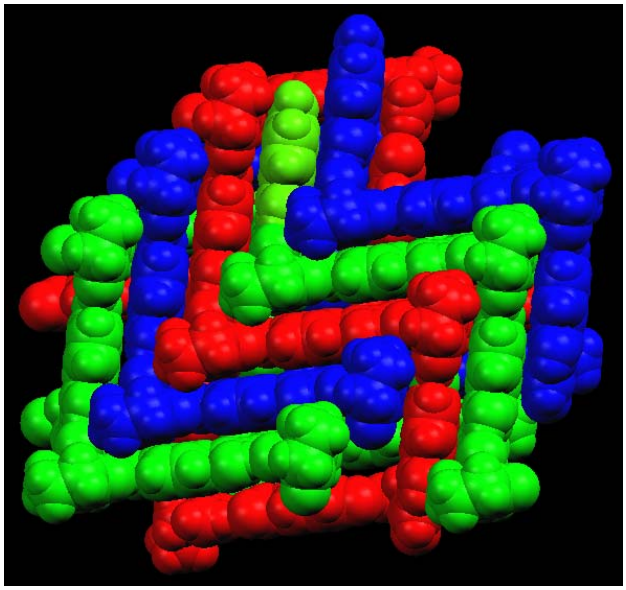

Figure 5. Space filling diagram of the 3-fold interpenetrated network of Piracetam: *p*-hydroxybenzoic acid co-crystal, **5**.