Electronic Supplementary Material (ESI) for CrystEngComm.

Reducing a Cocrystal to Nanoscale Dimensions Enables Retention of Physical Crystal Integrity upon Dehydration

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Electronic Supporting Information

Contents

1. Materials and Methods

All reagents were purchased from Sigma-Aldrich co. and used as is.

Powder X-ray data were collected on a *Rigaku* XD Ultima II diffractometer (Serial No. AD20971) equipped with a NaI scintillation detector using Cu *K*α radiation (λ=1.54056 Å).

SEM images were collected using *Hitachi* S-4800 scanning electron microscope operated at a range of 5–10 kV. Prior to imaging, samples were coated with gold for approximately 3 minutes using *Emitech K550* sputter coater.

Thermal analysis of samples (nano- and microsized crystals) was performed using Differential Scanning Calorimetry (DSC) (TA® Q2000 V 24.2). Samples of 6 – 8 mg were weighed and hermetically sealed in an aluminum pan. Measurements for thermal events (ie., melting point) were obtained in a temperature range of 30 – 250 °C using a 20 °C/min heating rate.

Water content was measured by Thermal Gravimetric Analysis (TGA) (TA® Q50) in a 100 μL pan by heating to 130 °C using a 10 °C/min heating rate. The heating cycle was repeated twice on the tested sample. Samples of 8 – 10 mg for dehydration were heated to 130 °C using a 10 °C/min heating rate and upon equilibration at room temperature, were transferred to an aluminum pan with a lid that was crimp sealed.

Pore mapping was conducted using Mercury® (v 3.7) to determine solvent-contact volumes. The void volume was estimated for the caf:24DBA:H_2O cocrystal based on space occupied by a spherical probe with a radius ranging from 1.2 – 1.7 Å.L. Barbour, *Chem. Commun*., 2006, **11,** 1163.[1] The results indicated no void space existed within the crystal structure that could accommodate a probe within the specified radial range of 1.2 – 1.7 Å.

2 Microsized Cocrystal

2.1 Synthesis of caf:24DBA:H2O

Microsized cocrystals formation of 2,4-dihydroxybenzoic acid (≥98.0%) (24DBA) with caffeine (anh., ≥ 99.0%) (caf) employed the reported SMPT-based suspension approach.[2] Equimolar amounts of caffeine (60 mg) and 2,4DBA (48 mg) were mixed in 4 mL of acetonitrile and vortexed. The resulting slurry was equilibrated at ambient conditions for ~ 18 hour and filtered. The dried solid was collected for further analysis. Single crystals were obtained through slow evaporation (~ 5 days) at RT from acetonitrile.

2.2 Powder X-ray diffractometry data

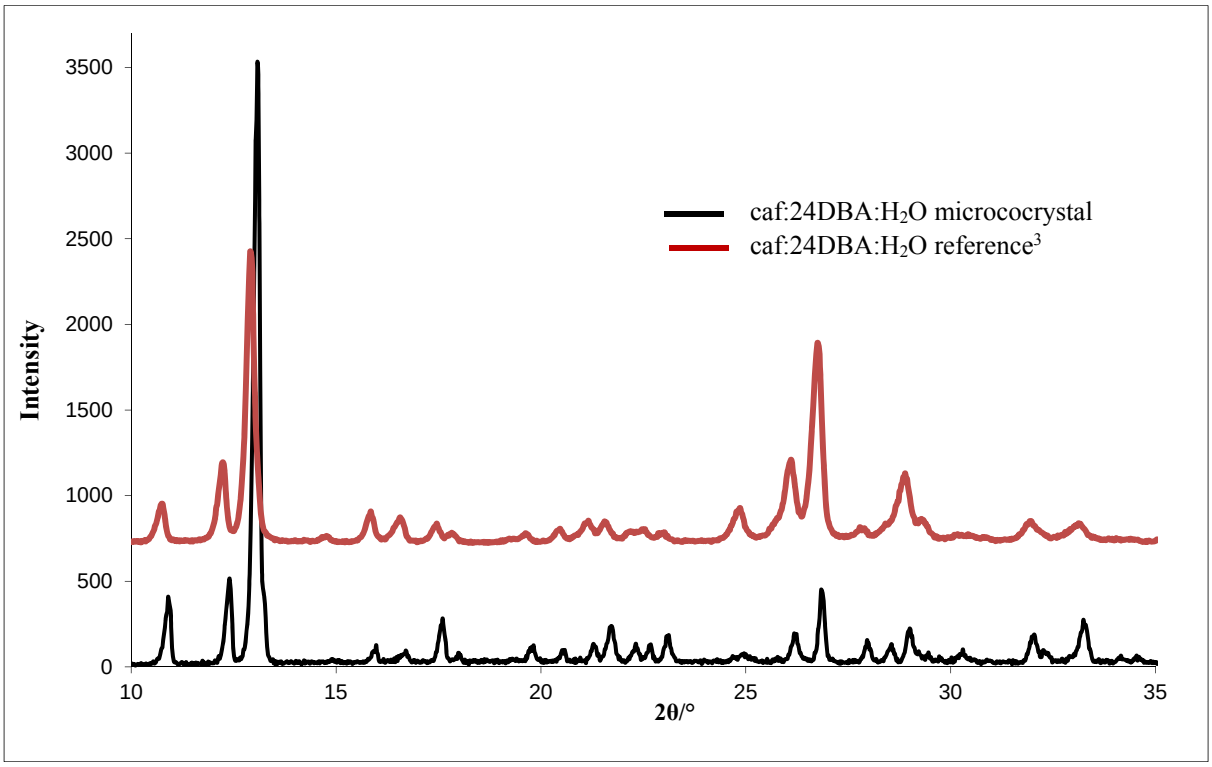

Figure S - 1. PXRD diffractogram of caf:24DBA:H_2O micro-cocrystal compared to previous reported PXRD data

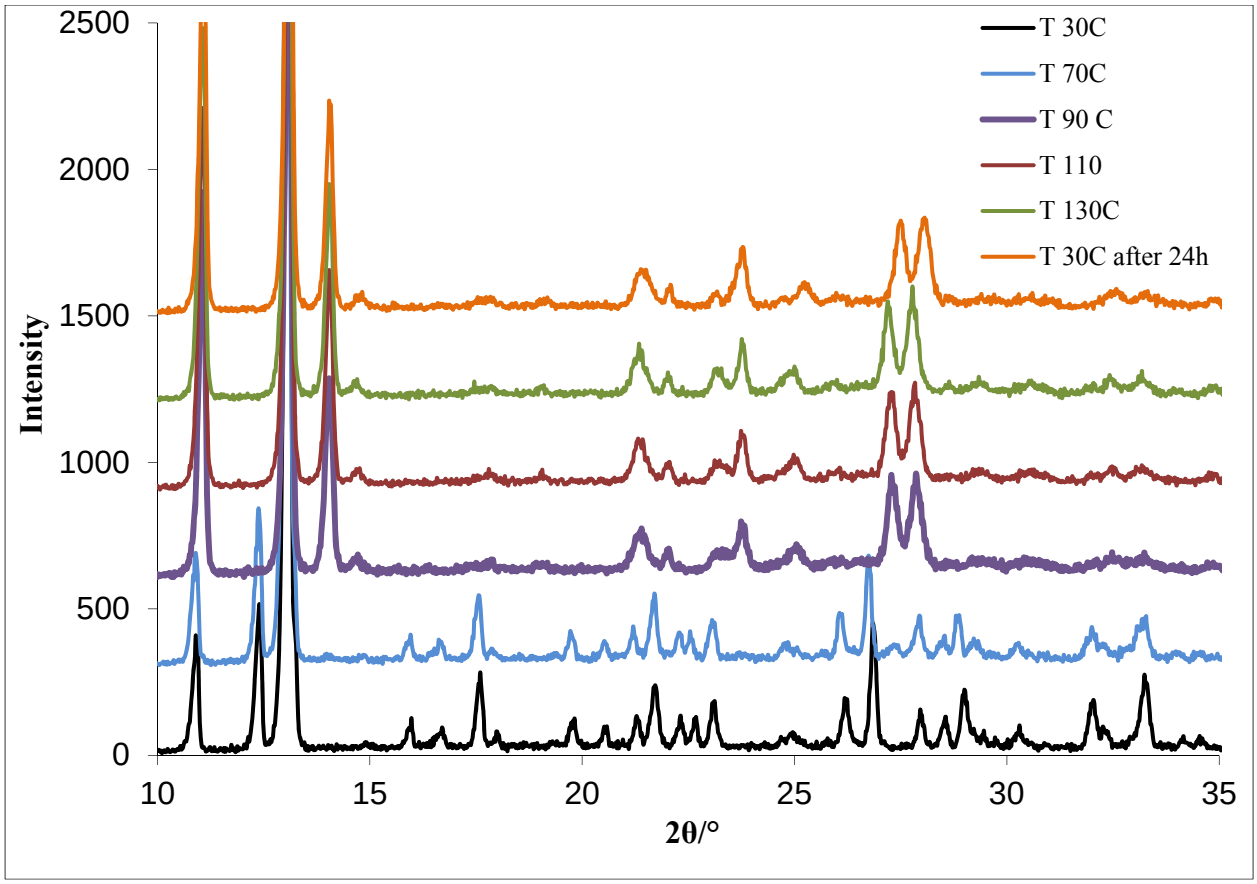

Figure S - 2 PXRD Diffractogram collected of caf:24DBA:H_2O micrococrystals across temperature range of 30 – 130 °C and after 24 h at 30 °C. Conversion from monohydrate cocrystal to the dehydrated cocrystal is observed between 70 – 90 °C

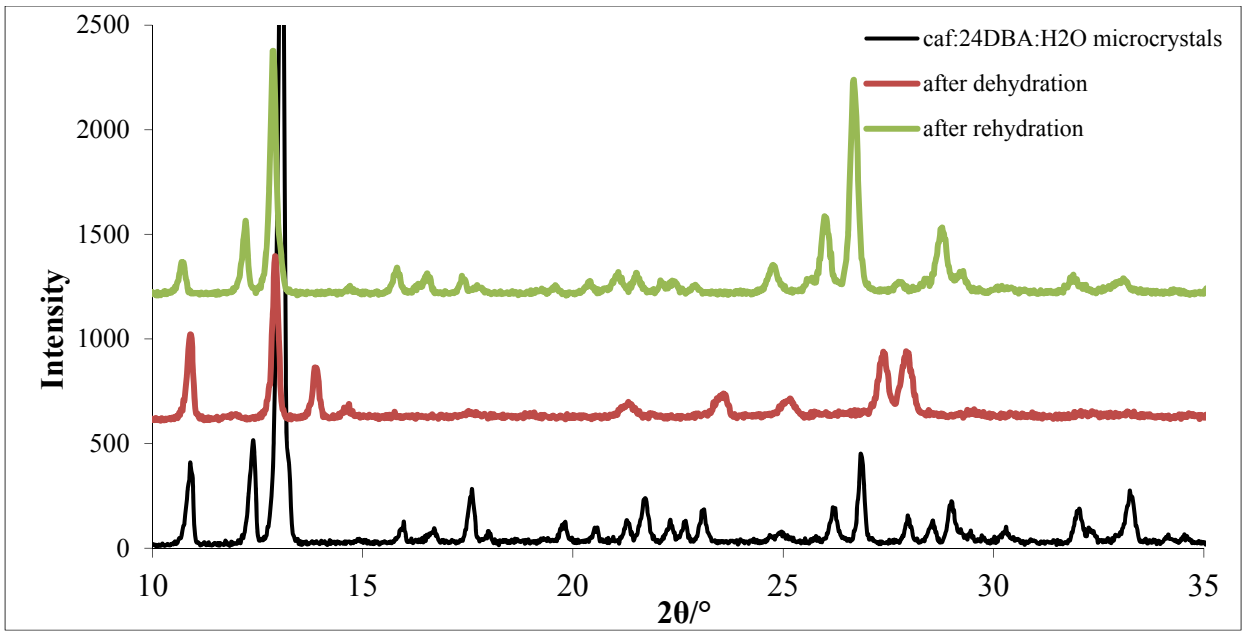

Figure S - 3 PXRD diffractogram comparison of the initial caf:24DBA:H_2O cocrystal (black) to the pattern after dehydration (red) and to the pattern after rehydration (green) by exposure to 98% RH at RT for 24 h

2.3 SEM imaging

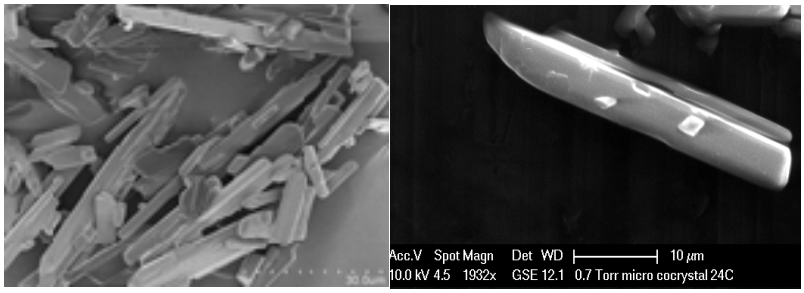

Figure S - 4 SEM images of micro-sized caf:24DBA:H_2O cocrystal

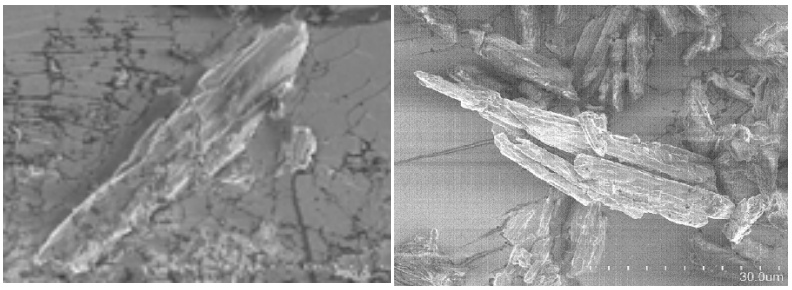

Figure S - 5 SEM images of micro-sized caf:24DBA:H_2O cocrystal after dehydration. Cracking and striations apparent in the micro-sized crystals

2.4 Thermal Analysis Data

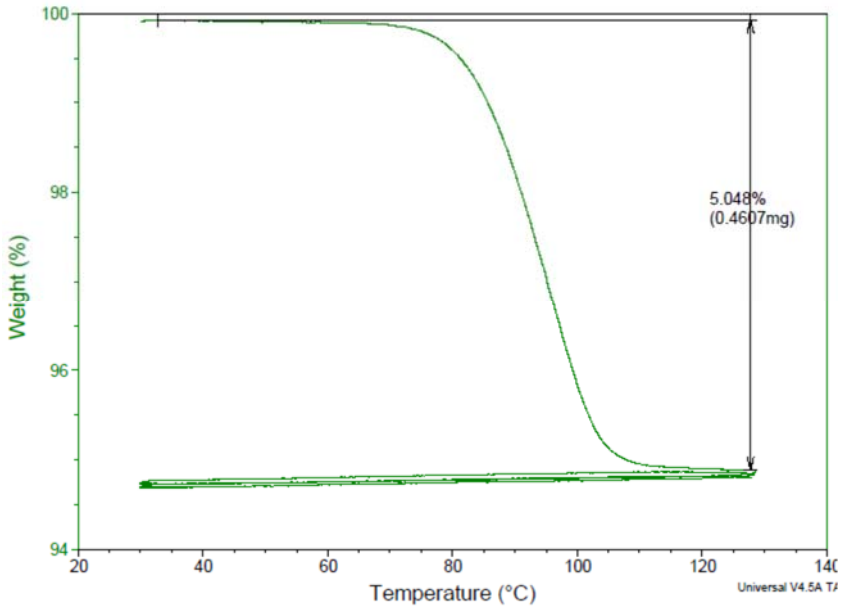

Figure S - 6 Example water content determination measurement by TGA for micro-sized caf:24DBA:H_2O. Sample was heated to 130 °C at 10 °C/min. The cycle was repeated twice on the sample. No water loss observed after the first heating cycle.

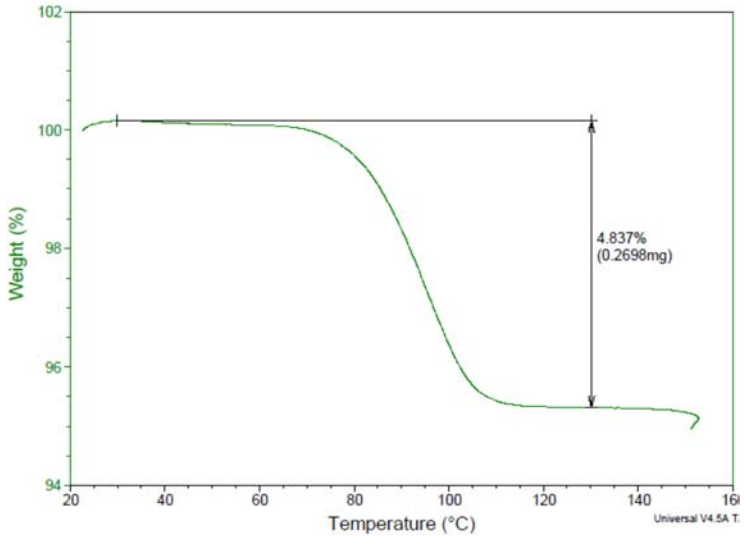

Figure S - 7 Water content determination measurement by TGA for micro-sized caf:24DBA:H_2O after rehydration at 98%RH exposure at RT.

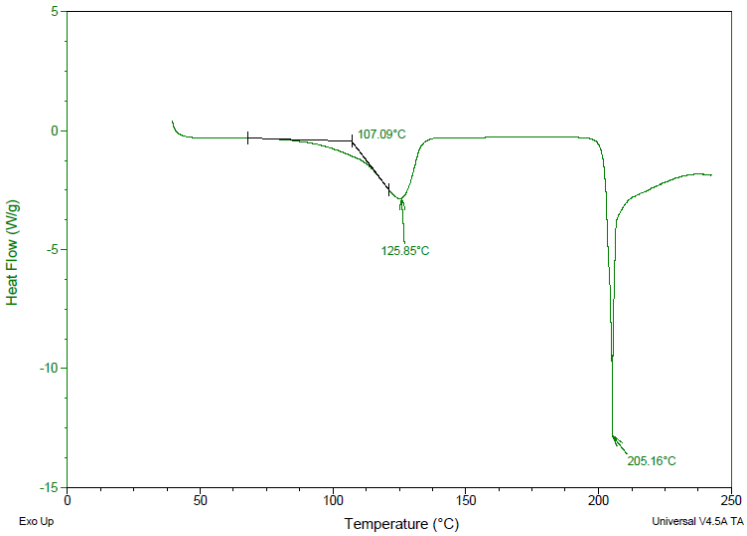

Figure S - 8 Thermal analysis by DSC for micro-sized caf:24DBA:H_2O. Onset of H_2O loss indicated at < 100 °C with a melt event at 206.2 °C.

3 **Nanosized Cocrystal**

3.1 Synthesis of caf:24DBA:H2O

Nanosized cocrystals formation of 2,4-dihydroxybenzoic acid (≥98.0%) (24DBA) with caffeine (anh., ≥ 99.0%) (caf) employed the reported sonochemical method.[3] Equimolar amounts of caffeine (125 mg) and 2,4DBA (99 mg) were separately dissolved in 1 mL of chloroform and 600 µL of acetone, respectively. Both solutions were then simultaneously and rapidly injected into 100 mL of hexanes at ~ 0 ºC. The resulting suspension was sonicated for 15 s in a cleaning bath (Branson 2510R-DTM) and filtered. The dried solid was collected for further analysis.

3.2 Powder X-ray diffractometry data

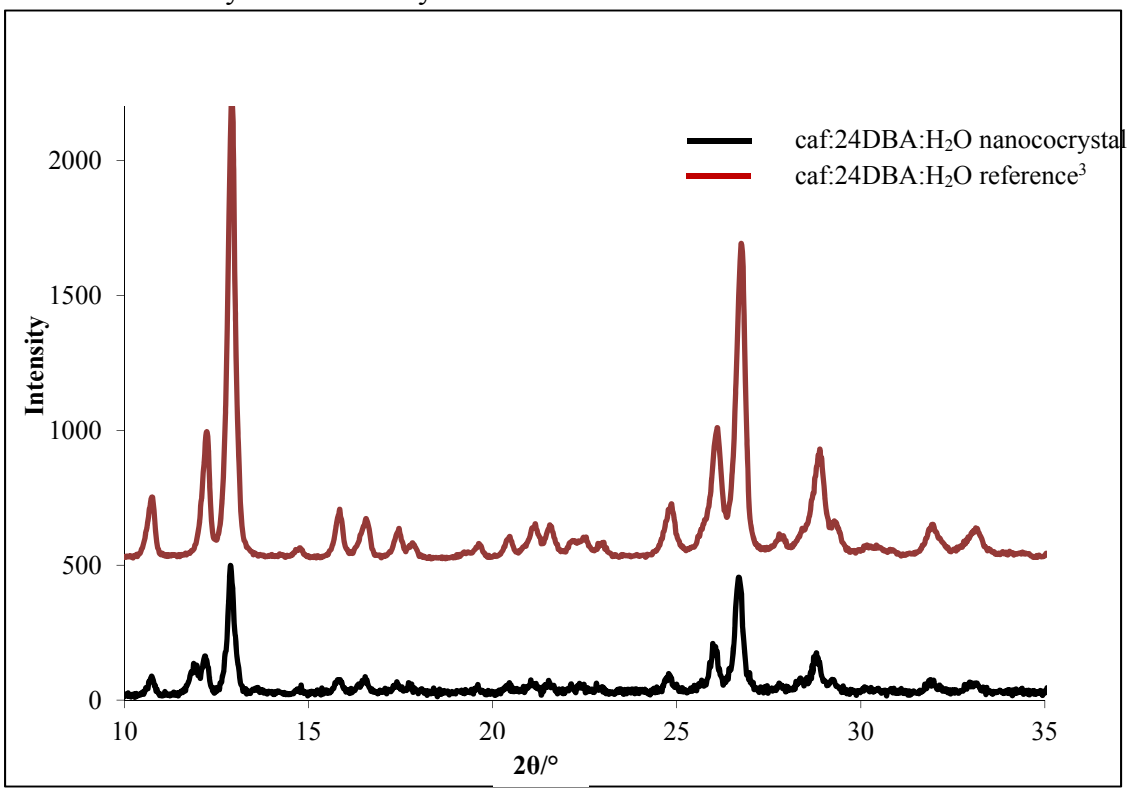

Figure S - 9 PXRD diffractogram of caf:24DBA:H_2O micro-cocrystal compared to previous reported PXRD data

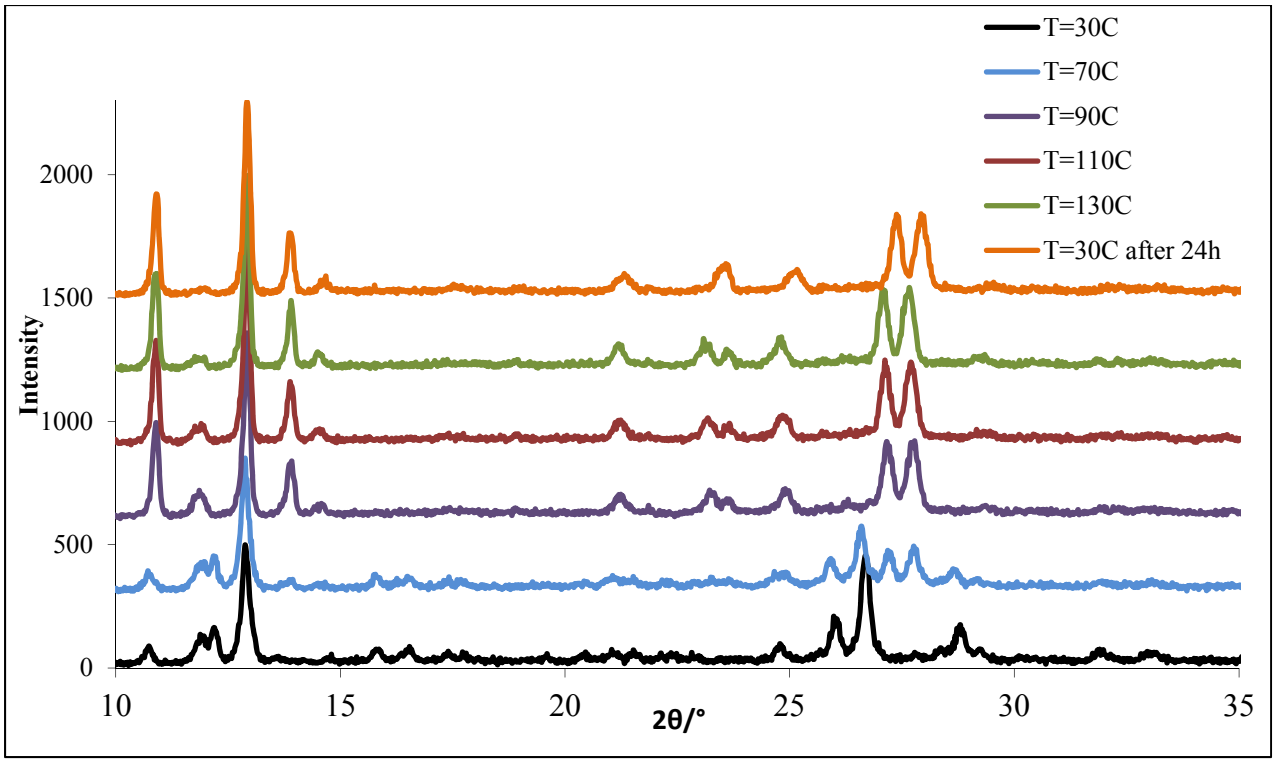

Figure S - 10 PXRD diffractogram collected of caf:24DBA:H_2O nanococrystals across temperature range of 30 – 130 °C and after 24 h at 30 °C. Conversion from monohydrate cocrystal to the dehydrated cocrystal is observed between 70 – 90 °C

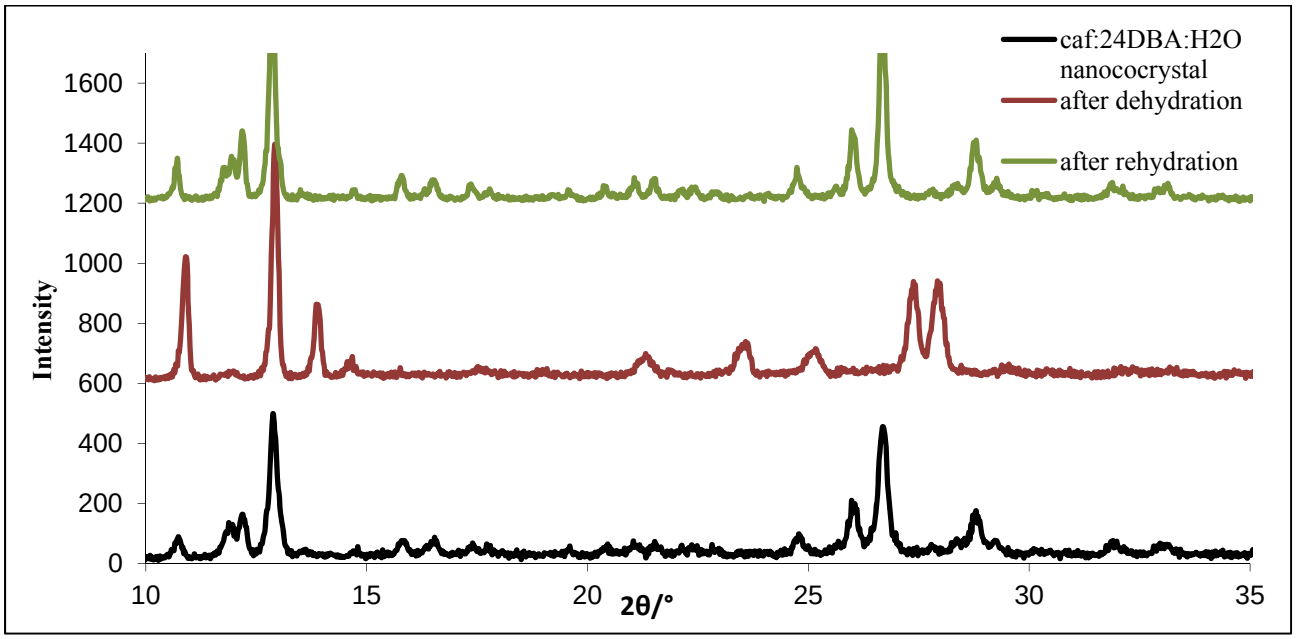

Figure S - 11 PXRD diffractogram comparison of the initial caf:24DBA:H_2O cocrystal (black) to the pattern after dehydration (red) and to the pattern after rehydration (green) by exposure to 98% RH at RT for 24 h

3.3 SEM imaging

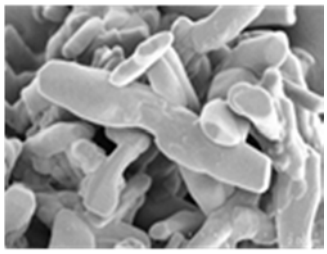

Figure S - 12 SEM image of caf:24DBA:H_2O nanococrystals

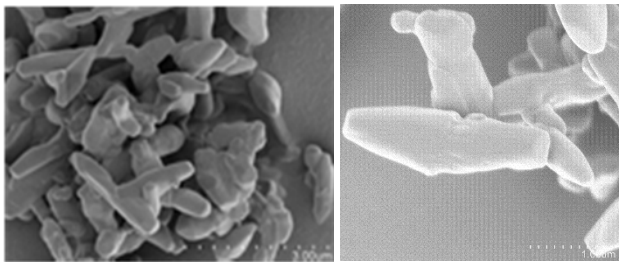

Figure S - 13 SEM images of caf:24DBA:H_2O nanococrystals after dehydration. Crystals are intact and morphology is unchanged from monohydrate crystals

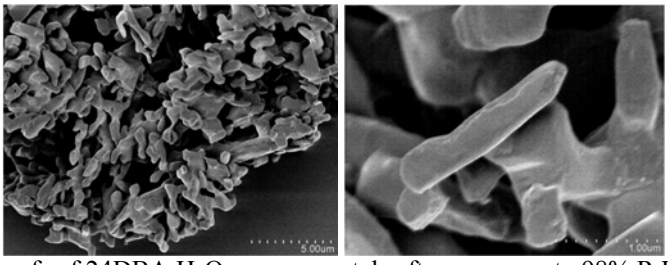

Figure S - 14 SEM images of caf:24DBA:H_2O nanococrystals after exposure to 98% R.H. at RT for 24 h, resulting in conversion from the anhydrate back to the initial monohydrate cocrystal. Physical integrity is preserved in the nanococrystals.

3.4 Thermal Analysis Data

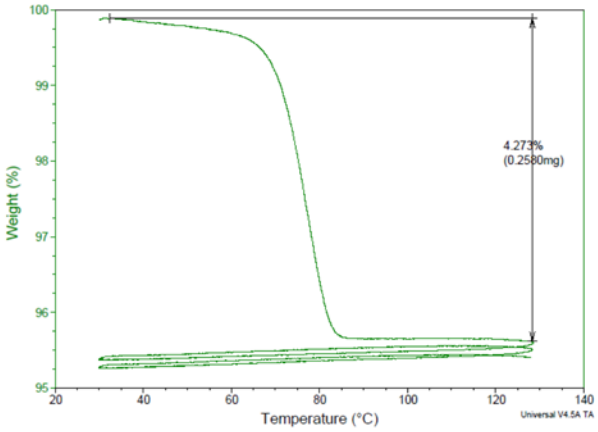

Figure S - 15 Example water content determination measurement by TGA for nano-sized caf:24DBA:H_2O cocrystal. Sample was heated to 130 °C at 10 °C/min. The cycle was repeated twice on the sample. No water loss observed after the first heating cycle.

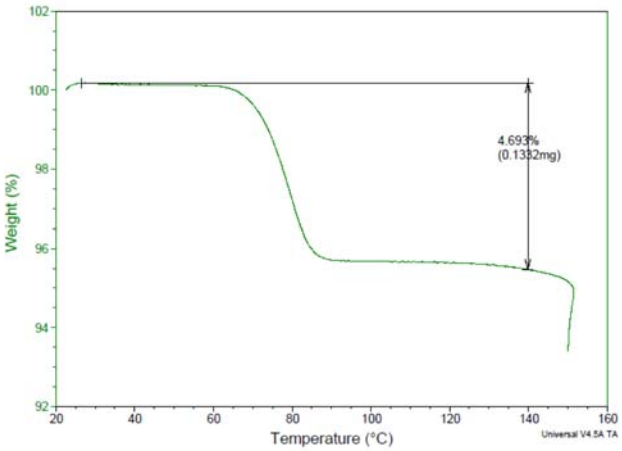

Figure S - 16 Water content determination measurement by TGA for nano-sized caf:24DBA:H_2O cocrystal after rehydration at 98%RH exposure at RT.

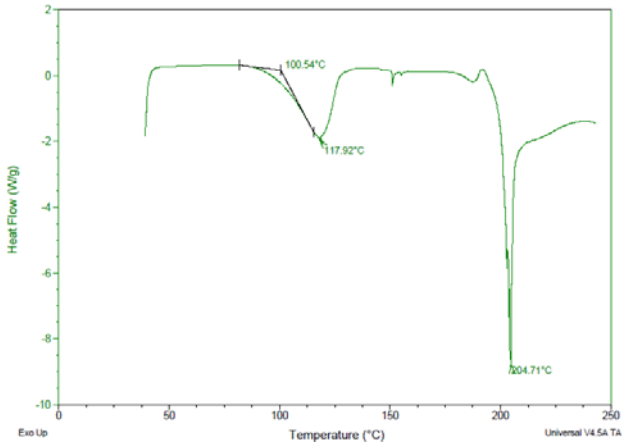

Figure S - 17 DSC thermogram of nano-sized caf:24DBA:H_2O cocrystal. Onset of H_2O loss indicated at < 100 °C with a melt event at 204.7 °C.

4. References

1. L. Barbour, *Chem. Commun*., 2006, **11**, 1163.
2. D.-K. Bučar, R. F. Henry, X. C. Lou, R. W. Duerst, L. R. MacGillivray , G. G. Z. Zhang, *Cryst. Growth Des.* **2009**, *9*, 1932.
3. J. Sander, J. D.-K. Bučar, R. F. Henry, L. R. MacGillivray , G. G. Z. Zhang, *Angewandte Chem. Int. Ed*., 2010, **49**, 7284. 0363561