Electronic Supplementary Material (ESI) for CrystEngComm

A kinetically controlled crystallization process for identifying new co-crystal forms: Fast evaporation of solvent from solutions to dryness

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General Procedure for the Synthesis of Co-crystals by Rotovap Technique: Approximately a total of 100 to 550 mg of the targeted compounds (API and the specified co-former in a definite stoichiometric ratio) was taken in a conical flask and dissolve in the sufficient amount of selected solvent. (In case of the known systems, the same solvent as mentioned in the original reports was used, while, in case of the new systems, the solvent was selected based on the solubility profiles of the individual co-formers.) The flask was heated thoroughly until a clear solution was obtained. The hot solution was filtered into a clean round bottom flask (rbf) by using Whatman filter paper. A little excess of the solvent was added to increase the dilution, followed by gentle warming once again to avoid any precipitations. The clear solution was then rapidly concentrated at rotary evaporator (BÜCHI) by setting the reduced pressure (in mbar) accordingly, as given in Tables S1 to S3, and the water bath temperature at 50 °C. The reduced pressure was allowed to fluctuate between ± 2 mbr from the set pressure. The revolution speed of rbf was always 130 rpm. Upon complete evaporation of the solvent, the vacuum was applied continuously to reach the minimum pressure (9-10 mbar) where it was held for about 5 min. The obtained dry powders were collected from the rbf and characterized by DSC, TGA, powder X-ray diffraction (PXRD) and in some cases, IR. The resulted powders contained small crystalline particles with approximately similar size and with blunt faces as evident from the optical microscopy (Fig. S1).

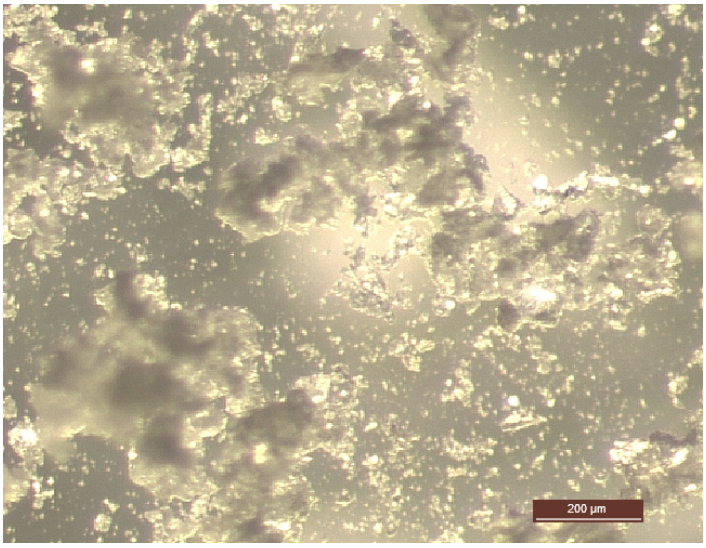


Figure S1. Optical microscopy image of powder sample of (1:1) saccharin (SAC):sulfamethazine (SFZ) co-crystal prepared by the rotovap technique.

Experimental Method:

FT-IR Spectroscopy (KBr): Fourier transmission infrared spectra of the solids were obtained using a Fourier–transform infrared spectrometer (PerkinElmer 502 or SHIMADZU FTIR-8400S). KBr samples (2 mg in 20 mg of KBr) were prepared and 5 scans were collected at 4 cm^{-1} resolution for each sample. The spectra were measured over the range of 4000-400 cm^{-1}.

Powder X-Ray Diffraction (PXRD): The PXRD patterns were collected on a Rigaku SmartLab with a Cu Kα radiation (1.540 Å). The tube voltage and amperage were set at 40 kV and 50 mA respectively. Each sample was scanned between 5 and 50° 2θ with a step size of 0.02°. The instrument was previously calibrated using a silicon standard.

Differential Scanning Calorimetry (DSC): DSC was conducted on a Mettler-Toledo DSI1 STAR^e instrument. Accurately weighed samples (4-6 mg) were placed in hermetically sealed aluminium crucibles (40 µL) and scanned in the range of 30 °C to 300 °C at a heating rate of 5 °C/min under a dry nitrogen atmosphere (flow rate 80 mL/min). The data were managed by STAR^e software.

Thermo gravimetric Analysis: TGA was performed on a Mettler-Toledo TGA/SDTA 851^e instrument. Approximately 6-8 mg of the sample was added to an aluminium crucible and heated from 30 to 350 °C at a rate of 10 °C/min under continuous nitrogen purge.

Hot-Stage Microscopy: Thermomicroscopic investigations were performed on with an optical polarizing microscope (Leica MZ16) equipped with a Linkam hot-stage. Samples were heated over the temperature range of 30 to 190 °C at a constant heating rate of 2-3 °C min^{-1}.

Table S1. Rotary evaporator conditions used for the preparation of 1:1 saccharin (SAC) co-crystals. In the milligram scale batches, equal amount of SAC (100 mg; 0.5459 mmol; Sigma-Aldrich) was used in all cases for preparing the co-crystals. The weight of SAC used in the large scale batches was 2 gm (10.92 mmol).

co-former	chemical source	wt. taken	mmol	solvent (volume)	conditions at rotovap*
carbamazepine	Sigma-Aldrich	128.98 mg	0.5459	acetone (20 mL)	500 mbar, 130 rpm, 50°C
Indomethacin	Sigma-Aldrich	195.32 mg	0.5459	acetone (20 mL)	500 mbar, 130 rpm, 50°C
-do-	-do-	3.9 gm	10.92	acetone (400 mL)	500 mbar, 130 rpm, 50°C
Sulfamethazine	Sigma-Aldrich	151.94 mg	0.5459	acetone (20 mL)	500 mbar, 130 rpm, 50°C
-do-	-do-	3 gm	10.92	acetone (300 mL)	500 mbar, 130 rpm, 50°C

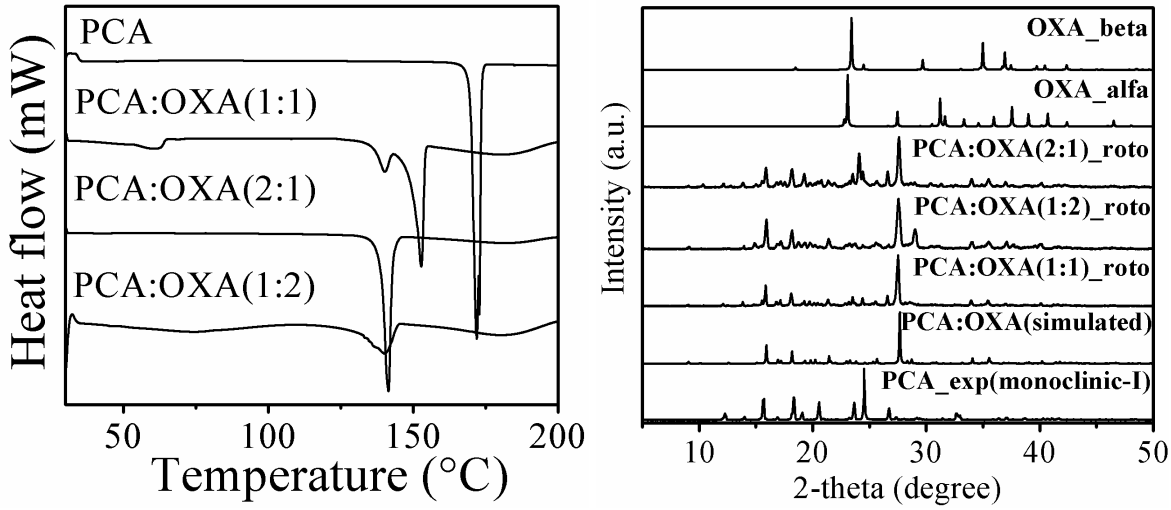
* Set vacuum pressure (mbar), revolution speed of rbf (rpm) and the water bath temperature (°C).

Table S2. Rotary evaporator conditions used for the preparation of 1:1 paracetamol (PCA):oxalic acid (OXA) co-crystals. Equal amount of PCA (50 mg; 0.331 mmol; Bharat Chemicals, Mumbai) was used in all cases for preparing the co-crystal.

co-former	chemical source	wt. taken	mmol	solvent (volume)	conditions at rotovap
oxalic acid	Sigma-Aldrich	29.80 mg	0.331	$CHCl_3$:MeOH (1:1) (10 mL)	360 mbar, 130 rpm, 50 °C

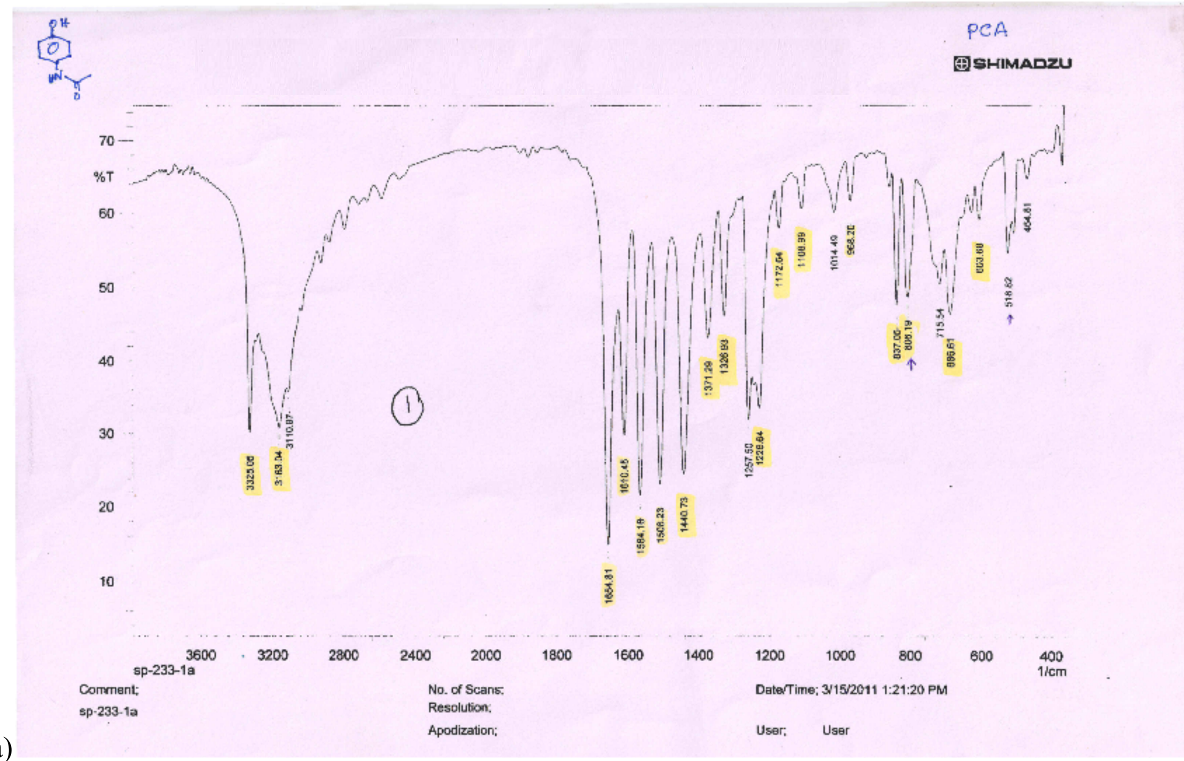
Table S3. Conditions used for the preparation of 1:1 ascorbic acid (ASC) co-crystals. Equal amount of ASC (250 mg; 1.419 mmol; Signa-Aldrich) was used in all cases for preparing the co-crystals.

co-former	chemical Source	wt. taken	mmol	Solvent (volume)	conditions at rotovap
carbamazepine	Sigma-Aldrich	335.2 mg.	1.419	methanol (15 mL)	423 mbar, 130 rpm, 55°C
nicotinamide	Loba Chemie Indstr. Co., Bombay	173.28mg.	1.419	Water (10 mL)	129 mbar, 120 rpm, 55°C
nicotinic acid	Fluka Analytical	174.96 mg	1.419	methanol (15 mL)	437 mbar, 130 rpm, 55°C
isonicotinic acid	Fluka Analytical	174.96 mg	1.419	water (21 mL)	84 mbar, 120 rpm, 55°C



(a) (b)

Figure S2. Paracetamol:oxalic acid: (a) DSC of the solids, obtained from the screening with PCA to OXA ratio 1:1, 2:1 and 1:2, show a common endotherm at nearly 140 °C. In the DSC, the PCA monoclinic form I is also shown. (b) The PXRD of the experimentally obtained samples (roto) and the simulated PXRD patterns of the solid forms of free PCA (monoclinic-I) and OXA (alfa and beta). Although the analysis becomes complicated as the obtained mixture can contain a number of possible forms of the two co-formers, the 1:1 PCA:OXA can be matched well with the corresponding simulated pattern. From PXRD, notice that the 2:1 contains the mixture of PCA forms and OXA–alfa.

(a) 
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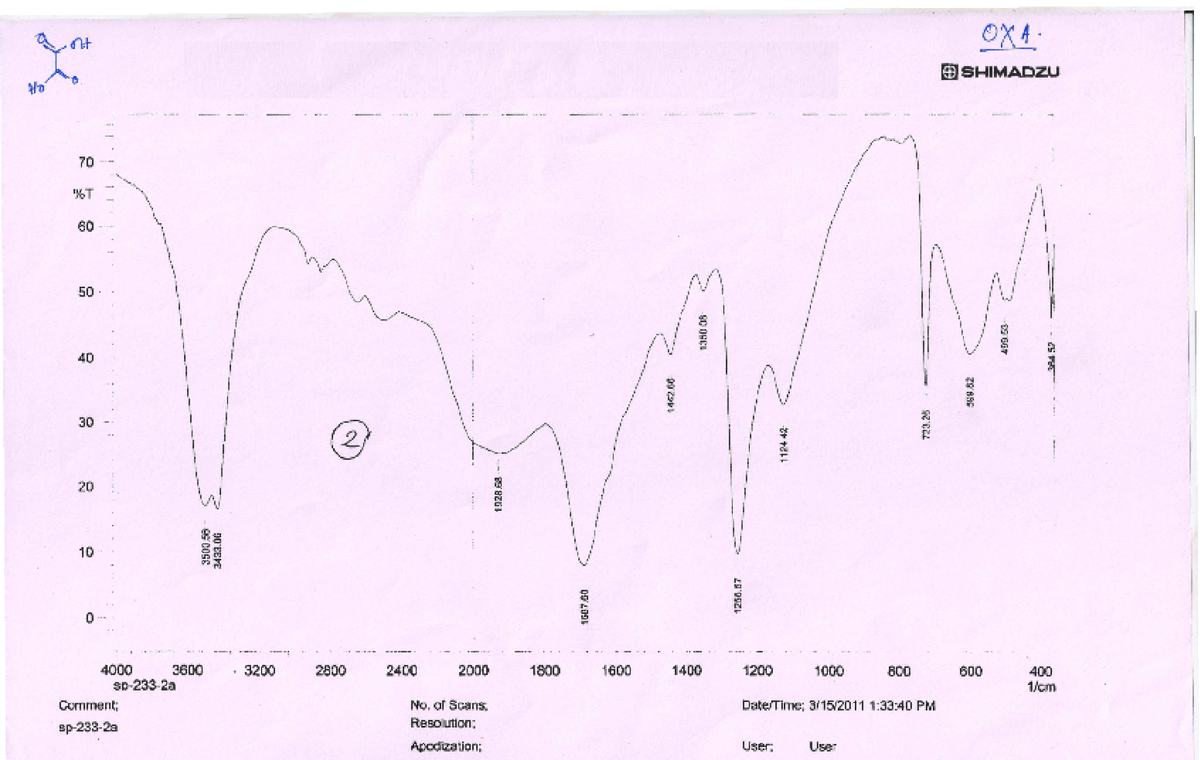
(b) 
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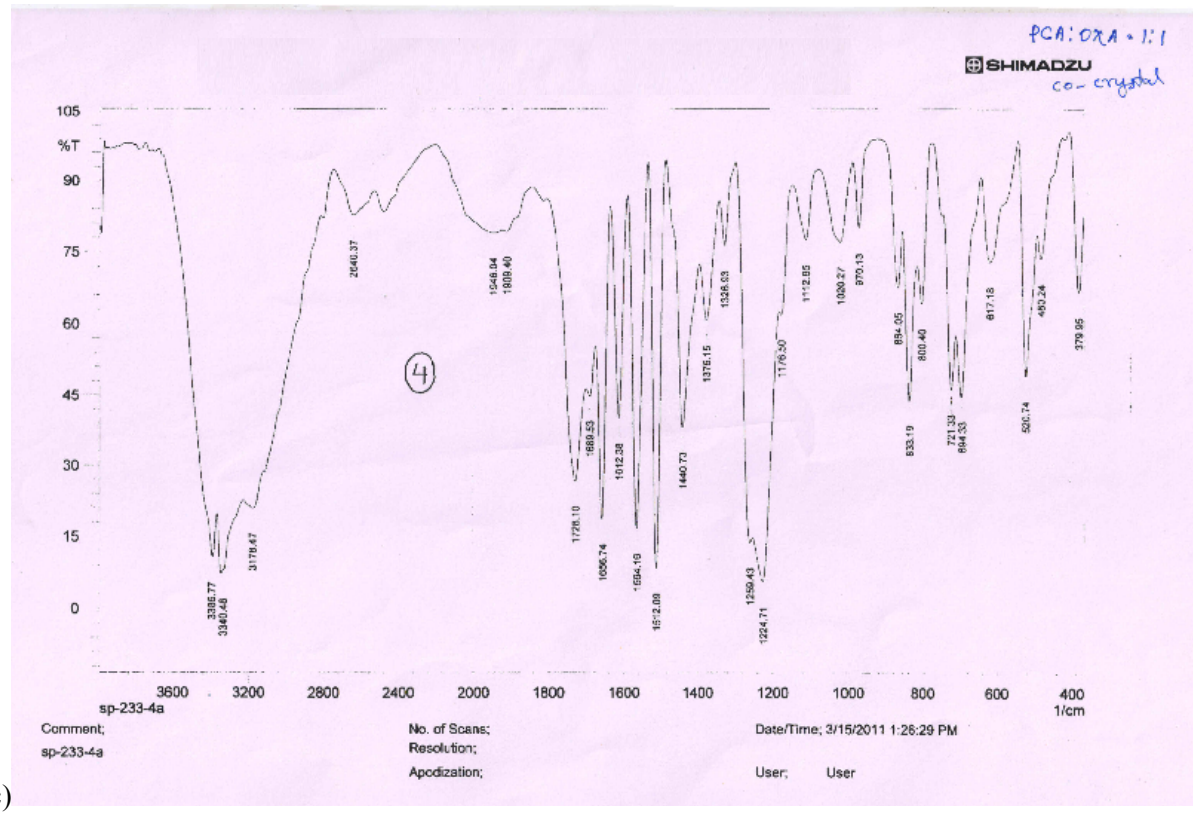
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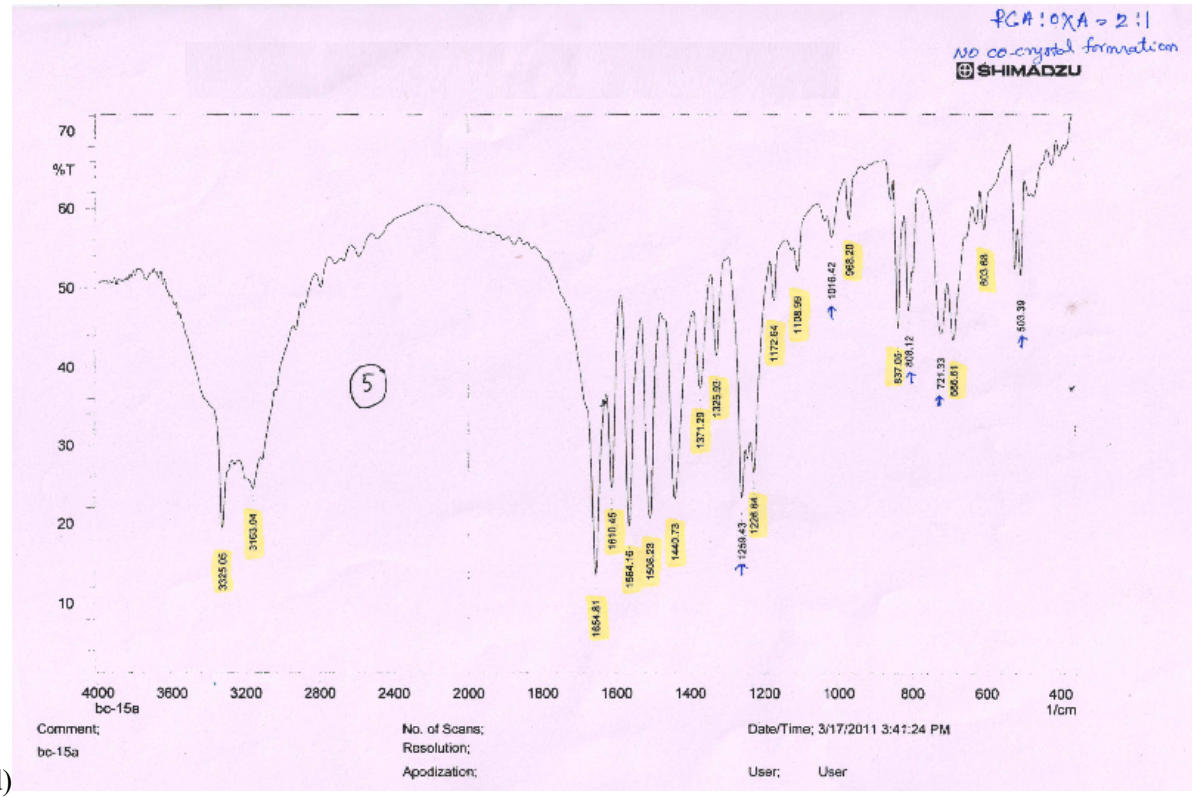
(d) 

Figure S3. IR spectra of (a) commercial free paracetamol (b) free oxalic acid (c) 1:1 PCA:OXA co-crystal obtained by rotovap technique and (d) the 2:1 mixture of PCA and OXA. The comparison of the 1:1 PCA:OXA with the corresponding free PCA and OXA solids shows the clear shift of the observed frequencies (c), while in case of the 2:1 mixture, most of the frequency bands match to the free PCA, indicating no co-crystal formation. The peaks that are matched in (a) and (d) are highlighted with yellow marking while those did not match are indicated with a blue arrow. The frequency peaks corresponding to the OXA could not be detected, due to its lower ratio of amount.

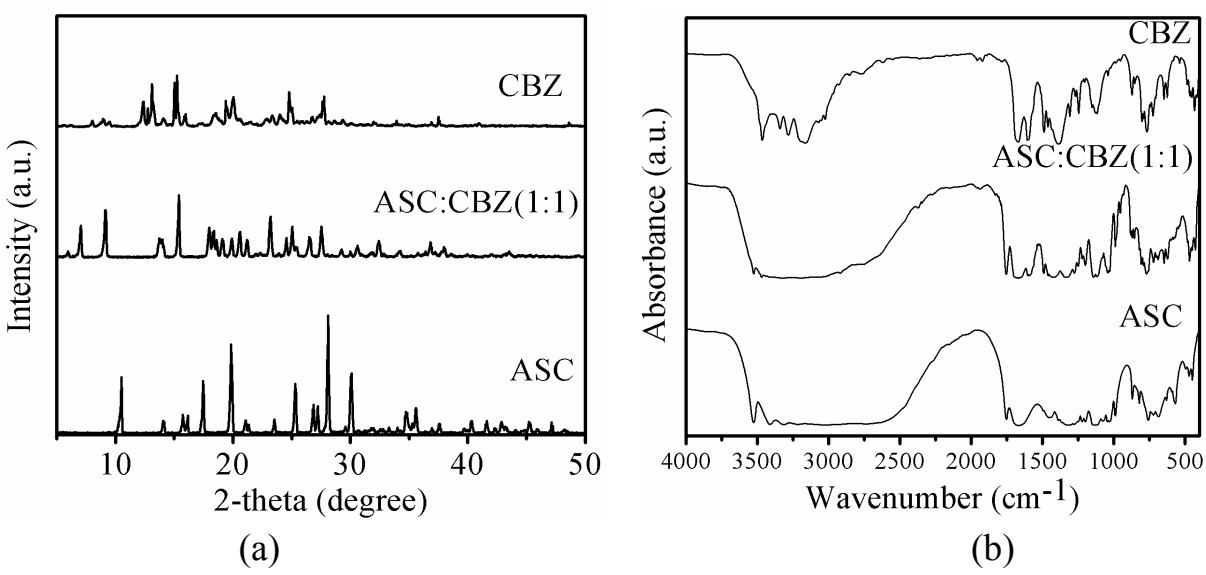


Figure S4. New solid form of ascorbic acid:carbamazepine, ASC:CBZ, (1:1). The comparison of the PXRD (a) and IR (b) plots of the experimental product and the free co-formers readily confirm the formation of the new solid form, ASC:CBZ (1:1).

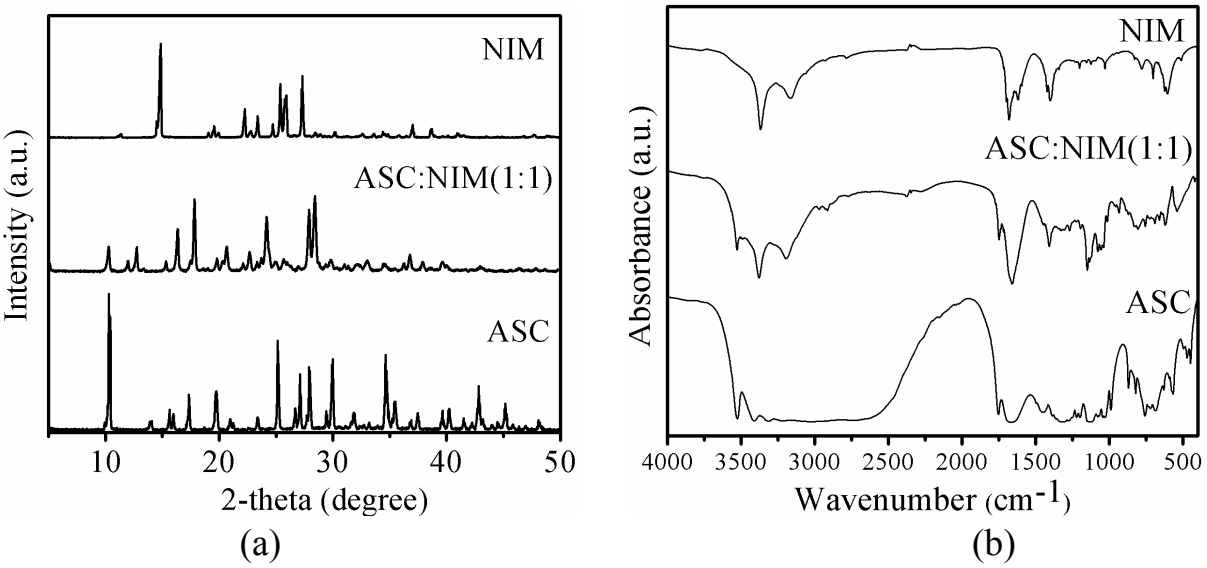


Figure S5. New solid form of ascorbic acid:nicotinamide, ASC:NIM, (1:1). The comparison of the PXRD (a) and the IR (b) plots of the experimental product and the free co-formers readily confirm the formation of the new solid form, ASC:NIM (1:1).

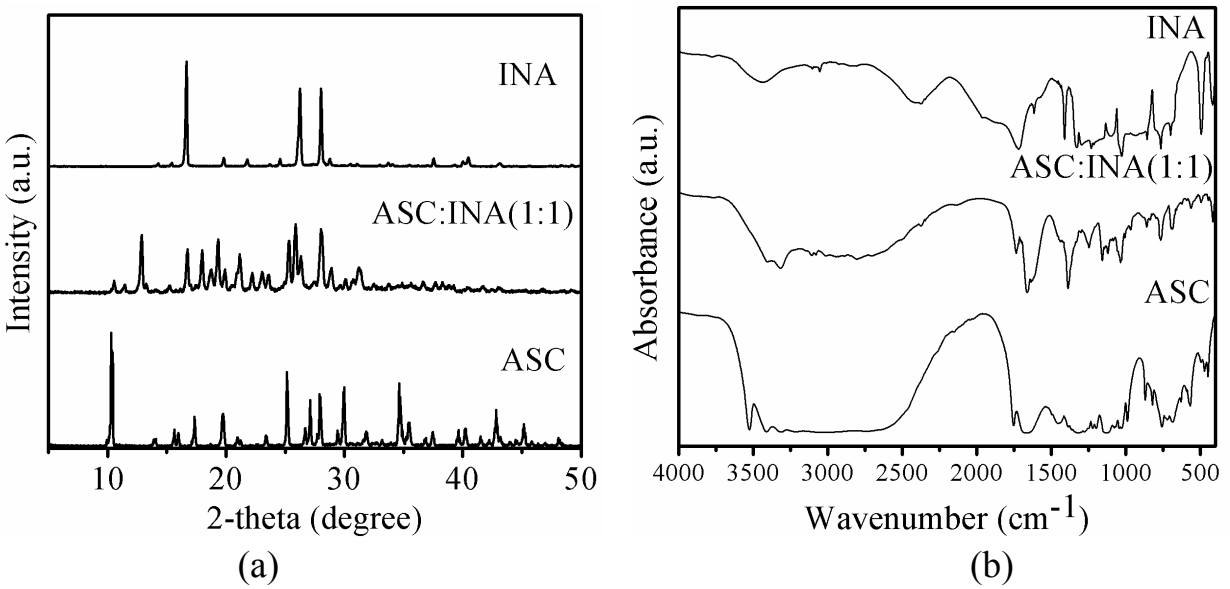


Figure S6. New solid form of ascorbic acid:isonicotinic acid, ASC:INA, (1:1). The comparison of the PXRD (a) and the IR (b) plots of the experimental product (from water) and the free co-formers readily confirm the formation of the new solid form, ASC:INA (1:1).

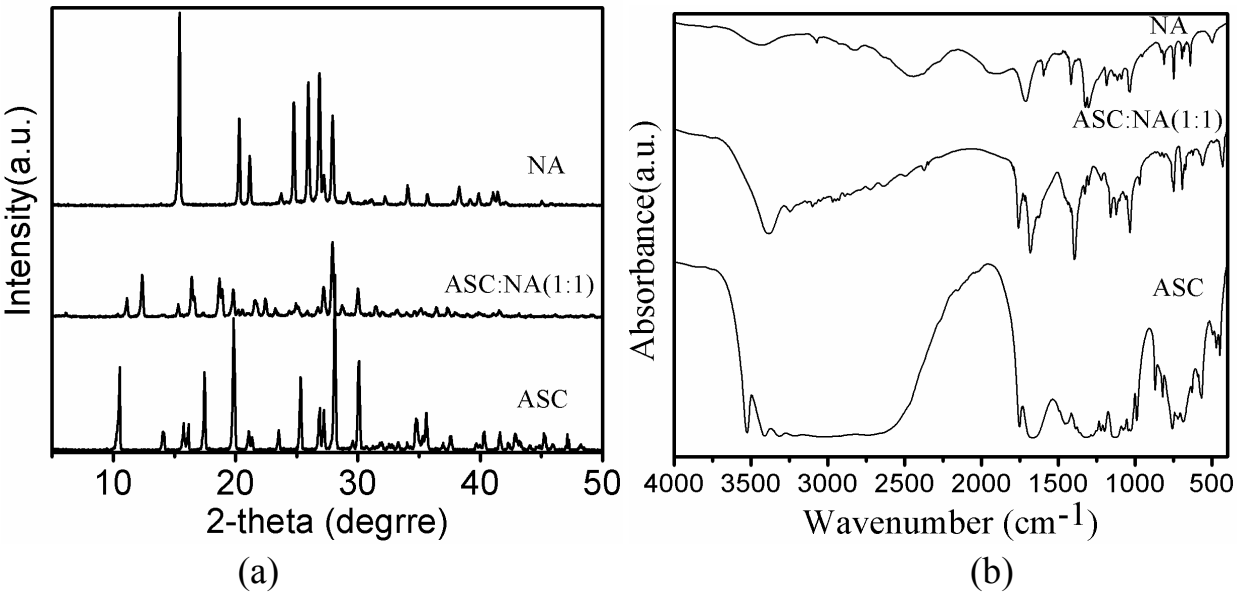


Figure S7. Recently reported solid form of ascorbic acid:nicotinic acid, ASC:NA, (1:1). The comparison of the PXRD (a) and the IR (b) plots of the experimental product (from methanol) and the free co-formers readily confirm the formation of the new solid form, ASC:NA (1:1). The comparison of the experimental and the simulated PXRD plots also showed a good agreement (not shown).

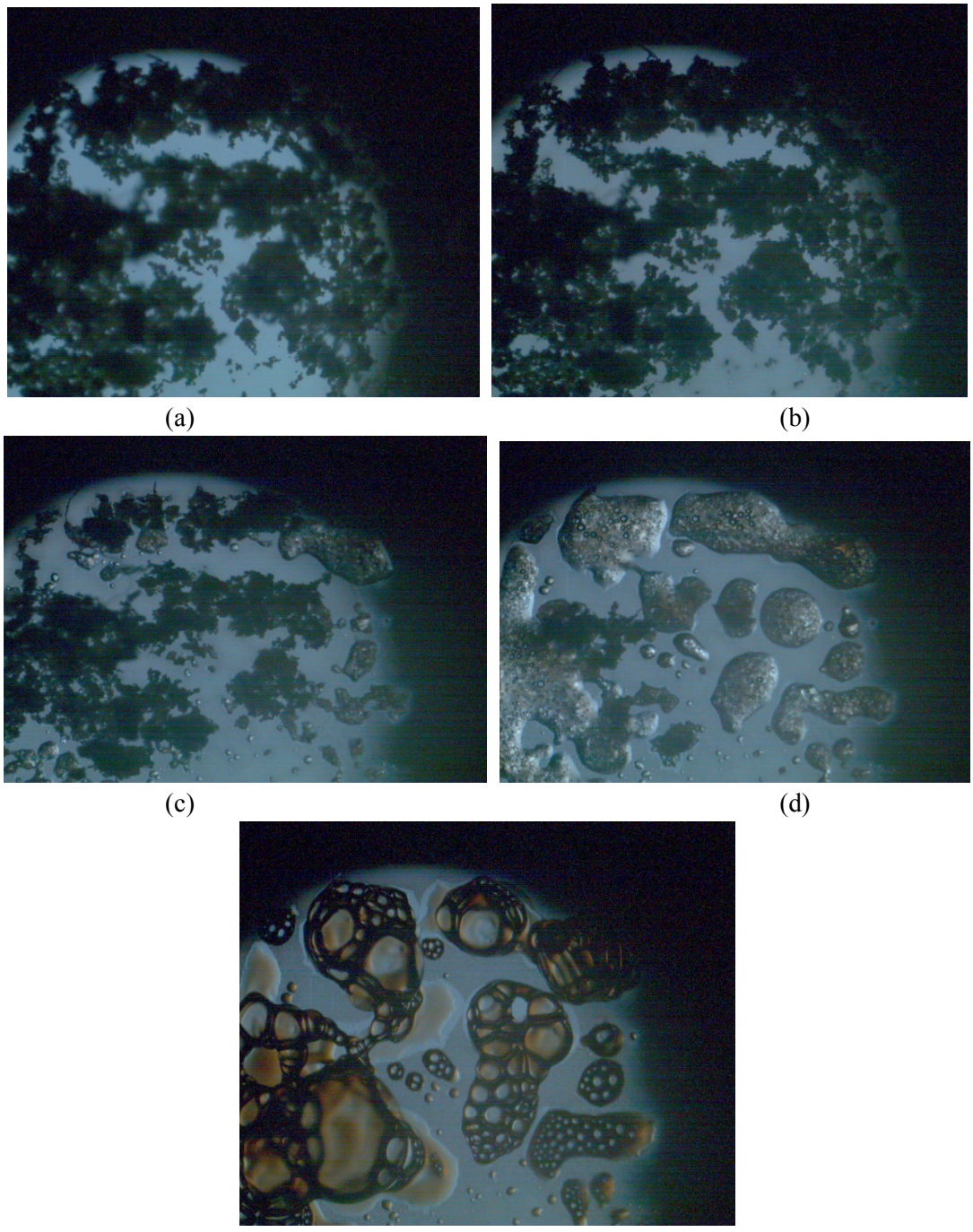


Figure S8. Hot stage microscopy images of 1:1 ascorbic acid:isonicotinic acid (ASC:INA) co-crystal. Images were captured at various temperatures (a) 170 (b) 175 (c) 178 (d) 180 and (e) 189 °C. Notice the melting of particles only in few areas in (c) taken at 178 °C. This suggests that the small endotherm in DSC (Fig. 4) at 178 °C was not due to a phase transition of the co-crystal. Hence this should correspond either to a new phase or an impurity effect by the presence of parent co-formers. Figure (e) shows the complete melting of sample at 189 °C which is in good agreement with the melting temperature observed in DSC.