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Supporting Information for

Direct Co-crystal Assembly from Synthesis to Co-crystallization

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This PDF file includes:

Materials, Instrumentations, Experimental Section, Scheme S1, Figures S1 to S9, and Tables S1 and S2 are enclosed.

MATERIALS

Chemicals. *p*-aminophenol (C_6H_7NO, 98% purity, mp: 186-190°C, MW: 109.13, Lot: 10173539), naphthalene ($C_{10}H_8$, 99+% purity, mp: 80-82°C, MW: 128.17, Lot: 10156679), and acetamide (C_2H_5NO, 99% purity, mp: 76-81°C, MW: 59.07, Lot 10184880) were received from Alfa Aesar (England). Theophylline ($C_7H_8N_4O_2$, > 99% purity, mp: 271-273°C, MW: 180.17, Lot: SLBF2355V & 091M0214V), 3-acetamidophenol ($C_8H_9NO_2$, 97% purity, mp: 146-149°C, MW: 151.17, Lot: 06911LO), aspirin (acetylsalicylic acid) ($C_9H_8O_4$, mp: 134-136°C, MW: 180.16, Lot: SLBD8868V), carbamazepine ($C_{15}H_{12}N_2O$, mp: 191-192°C, MW: 236.27, Lot: SLBH2762B), benzoic acid ($C_7H_6O_2$, > 99.5% purity, mp: 121-125°C, MW: 122.12, Lot: 0001427310), and caffeine ($C_8H_{10}N_4O_2$, mp: 234-236.5°C, MW: 194.19, Lot: 099K1441) were purchased from Sigma Aldrich (St. Louis, MO). Salicylic acid ($C_7H_6O_3$, 99% purity, mp: 158-161°C, MW: 138.12, Lot: SR-2529F) and sodium hydroxide (NaOH, ≥ 96% purity, mp: 318°C, MW: 40, Lot: KU-3238P) were purchased from Showa Chemical Co. Ltd. (Tokyo, Japan). Meloxicam ($C_{14}H_{13}N_3O_4S_2$, > 96% purity, MW: 351.4, Lot: JQBJN-QS) was received from Tokyo Chemical Industry Co. Ltd. (Tokyo, Japan). Acetaminophen (paracetamol) ($C_8H_9NO_2$, 100% purity, mp: 168-172 °C (lit.), MW: 151.17, Batch: 0540385) was obtained from Lu'An (Anqiu, China).

Solvents. Acetic anhydride ($(CH_3CO)_2O$, ≥ 99% purity, mp: -73°C (lit.), MW: 102.09, Lot: SZBC1020V) was purchased from Sigma Aldrich (St. Louis, MO). Isopropyl alcohol (IPA) ($(CH_3)_2CHOH$, 99.8% HPLC grade, MW: 60.1, density: 0.785 g/cm^3, Lot: 14030108), acetonitrile (CH_3CN, 99.8% HPLC grade, MW: 41.05, Lot: AH3801-150), and ethyl acetate ($CH_3CO_2C_2H_5$, 99.9% purity, MW: 88.11, bp: 76.5-77.5°C, Lot: 711912) were received from TEDIA company (Fairfield, USA). Methanol (CH_3OH, 99.9% purity, bp: 64.7°C, MW: 32.04, Lot: 905309), ethanol (C_2H_5OH, 99.5% purity, bp: 78.37°C, MW: 46.07, Lot: 262611), chloroform (CH_3Cl, 99.99% purity, bp: 60.5-61.5°C, MW: 119.38, Lot: E554180) were purchased from Echo Chemical Co. Ltd. (Taipei, Taiwan). 1,4-dioxane ($C_4H_8O_2$, 98%

purity, MW: 88.11, Lot: SP-3432R) was obtained from Showa Chemical Co. Ltd. (Tokyo, Japan). Acetic acid glacial (CH_3COOH, 95+% (w/w) reagent grade, MW: 60.05, density: 1.05 g/cm^3, Lot: 10798903) obtained from Scharlab S. L., Sentmenat, Spain. Reversible osmosis (RO) water was clarified by a water purification system (model Milli-RO Plus) bought from Millipore (Billerica, MA).

INSTRUMENTATIONS

Polarized Optical Microscopy (POM). Polarized optical microscopy was performed on Olympus BX51 microscope which was equipped with a digital camera (Moticam 2000 2.0M Pixel USB2.0, Motic, Inc., Xiamen, China) to take images of crystal habits of the obtained co-crystals.

Fourier-Transform Infrared Spectroscopy (FTIR). Transmission Fourier-transform infrared (FTIR) spectroscopy was used to identify the obtained crystals by examining infrared absorption spectra. IR spectra were recorded on a Perkin Elmer Spectrum One spectrometer (Perkin Elmer Instruments LLC, Shelton, CT, USA). The KBr sample disk was scanned with a scan number of 8 from 4000 to 400 cm^{-1} having a resolution of 2 cm^{-1}.

Differential Scanning Calorimetry (DSC). Thermal analytical data of 3 to 5 mg of samples in perforated aluminum sample pans (60 μL) were collected on a Perkin Elmer DSC-7 calorimeter (Perkin Elmer Instruments LLC, Shelton, CT, USA) with a heating rate of 10℃/min from 40° to 200℃ under a constant nitrogen 99.99% purge. This instrument was calibrated with indium and zinc 99.999% having reference temperatures of 156.6° and 419.47℃, respectively (Perkin Elmer Instruments LLC, Shelton, CT, USA).

Powder X-ray Diffraction (PXRD). PXRD diffractogram provided another piece of information for the identification and crystallinity of the obtained co-crystals. PXRD diffractograms were detected by Bruker D8 Advance (Germany). The source of PXRD was CuKα (1.542 Å) and the diffractometer was operated at 40 kV and 40 mA. The X-ray was

passed through a 1 mm slit and the signal a 1 mm slit, a nickel filter, and another 0.1 mm slit. The detector type was a scintillation counter. The scanning rate was set at 1.2° 2θ/s ranging from 5° to 35°. The quantity of sample used was around 10 mg.

EXPERIMENTAL SECTION

Liquid-Assisted Grinding for Direct Assembly. The reactants and the co-former/API were weighted and added to a mortar with preset stoichiometric ratios, and ground continuously by a pestle with a few drop of solvent, which was able to partially dissolve the ingredients, until dryness. Solids obtained by liquid-assisted grinding were primarily characterized by FTIR.

Solvent Selection for Co-crystallization by Cooling. The gravimetric method had been used for the determination of drug solubility.[1-4] About 100 mg of solid samples were weighted in a 20 mL scintillation vial. Solvents were titrated carefully by a micropipette into the vial separately with an intermittent shaking until all solids were just dissolved as determined by eye. Solubility values of solids in a given solvent or solution at different temperatures were determined and listed in **Table S1** for cooling crystallization. Although the gravimetric method appeared to have an inherent inaccuracy of about ±10 to 20%, its advantages were its robustness, simplicity, without the need of performing any calibration and concerning for the formation of polymorph, hydrate or solvate during the early development stage. In addition, it could also be used to minimize the risk of producing byproducts at high temperature due to its rapidness. Since the similar solubility differences of co-crystal components during cooling were employed for solvent selection, the inherent ±10 to 20% inaccuracy of the gravimetric method was acceptable for this purpose. The selected solvents for co-crystal systems were listed in **Table S2**.

To verify the ±10 to 20% inaccuracy of the gravimetric method, the solubility values of acetaminophen measured by us were compared to the ones reported by Granberg and Rasmuson.[5] The solubility values of acetaminophen at 15°C were 97.38 and 69.29 g/kg of

solvent in IPA and *n*-butyl alcohol, respectively, which corresponded to 76.54 and 56.13 mg/mL. The inaccuracy could be calculated as:

$$Inaccuracy = \frac{S_{reported} - S_{measured}}{S_{reported}} \times 100\%$$

Therefore, in IPA: $Inaccuracy = \frac{76.54 - 62.30}{76.54} \times 100\% \cong 19\%$, and

in *n*-butyl alcohol: $Inaccuracy = \frac{56.13 - 48.90}{56.13} \times 100\% \cong 12.3\%$

Cooling Co-crystallization. The nearly saturated solutions of the co-crystal component were prepared as followed: (**1**) 454 mg (3 mmol) of acetaminophen and 540 mg (3 mmol) of theophylline in 1 mL of aqueous solution of acetic acid at 80°C, (**2**) 303 mg (2 mmol) of acetaminophen and 128 mg (1 mmol) of naphthalene in 2.4 mL of IPA at 60°C, (**3**) 276 mg (2 mmol) of salicylic acid (SA) and 472 mg (2 mmol) of carbamazepine (CBZ) in 6 mL of acetonitrile at 60°C,[6] (**4**) 360 mg (2 mmol) of aspirin and 472 mg (2 mmol) of carbamazepine in 1 mL of chloroform at 50°C, and (**5**) 540 mg of aspirin (3 mmol) and 354 mg of acetamide (6mmol) in 0.6 mL of ethyl acetate at 60°C. These solutions were slightly heated for ensuring total dissolution and then cooled to 15°C except for (**5**). Especially, 1:1 co-crystal of aspirin-acetamide was formed by rapid cooling in an ice bath. All of the produced co-crystals were obtained by filtration and 40°C oven drying.

Direct Assembly from Chemical Synthesis to Co-crystallization.

1:1 Co-crystal of Acetaminophen-Theophylline[7] (Scheme 2b). 1.5 g (13.7 mmol) of *p*-aminophenol, 2 mL of acetic anhydride, 2.2 g (12.2 mmol) of theophylline and 7.5 mL of water were added into a 20 mL vial in a 80°C water bath for 1 hr. After the completion of reaction, the reaction solution was cooled to 15°C for 8 hr.

2:1 Co-crystal of Acetaminophen-Naphthalene[6] (Scheme 2c). 1.5 g (13.7 mmol) of *p*-aminophenol, 2 mL of acetic anhydride, 0.8 g (6.2 mmol) of naphthalene and 6 mL of IPA

were added into a 20 mL vial in a 80°C water bath for 1 hr. After the completion of reaction, the reaction solution was cooled to 15°C for 8 hr.

1:1 Co-crystal of Acetaminophen-Theophylline with the Presence of 3-Acetamidophenol (Scheme 2d). 1.5 g (13.7 mmol) of *p*-aminophenol, 2 mL of acetic anhydride, 2.2 g (12.2 mmol) of theophylline and 7.5 mL of water were added into a 20 mL vial in a 80°C water bath for 1 hr. After the completion of reaction, 0.46 g (3.05 mmol), 0.73 g (4.88 mmol) and 0.92 g (6.1 mmol) of 3-acetamidophenol were individually introduced to the reaction solutions and kept at 80°C for 10 min. The resulting solutions were then cooled to 15°C for 8 hr.

1:1 Co-crystal of Aspirin-Carbamazepine[8] (Scheme 2e). 374 mg (1 mmol) of 1:1 co-crystal of SA-CBZ, 0.3 mL of acetic anhydride and 0.3 mL of chloroform were added into a 7 mL vial in a 70°C water bath for 10 min. After the completion of reaction, the reaction solution was cooled to 15°C for 8 hr.

1:2 Co-crystal of Sodium Benzoate-Benzoic Acid[9] (Scheme 2f). 0.2 g (5 mmol) of sodium hydroxide (NaOH), 1.22 g (10 mmol) of benzoic acid (HBz) and 4 mL of methanol/water (3:1 v/v) or ethanol/water (3:1 v/v) were added into a 20 mL vial at 60 °C water bath for 4 hr. As the resulting solution was totally dissolved, it was then cooled to 5°C for 1 day.

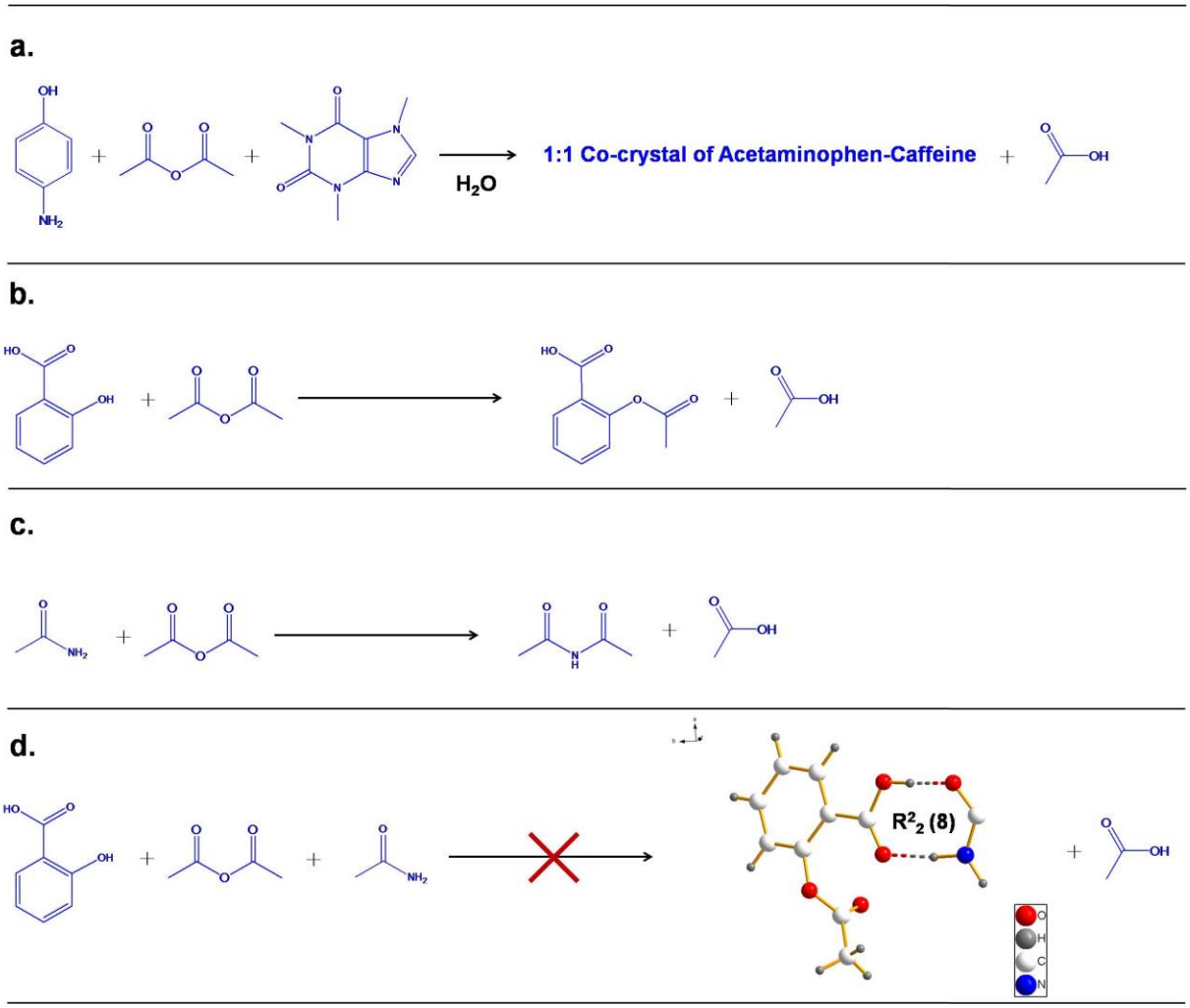
1:1 Co-crystal of Acetaminophen-Caffeine (Scheme S1). 1.5 g (13.7 mmol) of *p*-aminophenol, 2 mL of acetic anhydride, 2.4 g (12.4 mmol) of caffeine and 7.5 mL of water were added into a 20 mL vial in a 80°C water bath for 1 hr. After the completion of reaction, the reaction solution was cooled to 5°C for 1 day.

Those co-crystals were filtered, 40°C oven dried, and characterized by POM, FTIR, DSC and PXRD (Figures S1 to S8).

Establishment of Ternary Phase Diagram (TPD). The solubility of pure benzoic acid,

sodium hydroxide, sodium benzoate, and the 1:2 co-crystal of sodium benzoate-benzoic acid were measured at 25^{o}C by the gravimetric method. Points with different compositions of benzoic acid/sodium hydroxide/methanol/water (3:1 v/v) in TPD were prepared, and the resulting suspensions were stirred at 25^{o}C for 10 days to achieving thermodynamic equilibrium. The solid phase after equilibrium was characterized by FTIR spectroscopy.

SCHEME



Scheme S1. Schematic illustrations: (a) direct assembly of 1:1 co-crystal of acetaminophen-caffeine through the acetylation of *p*-aminophenol (no single crystal data available), (b) the synthesis of aspirin through the acetylation of salicylic acid with acetic anhydride, (c) the synthesis of *N*-acetylacetamide through *N*-acetylation of acetamide, and (d) the unsuccessful case for direct assembly of 1:1 co-crystal of aspirin-acetamide.

FIGURES

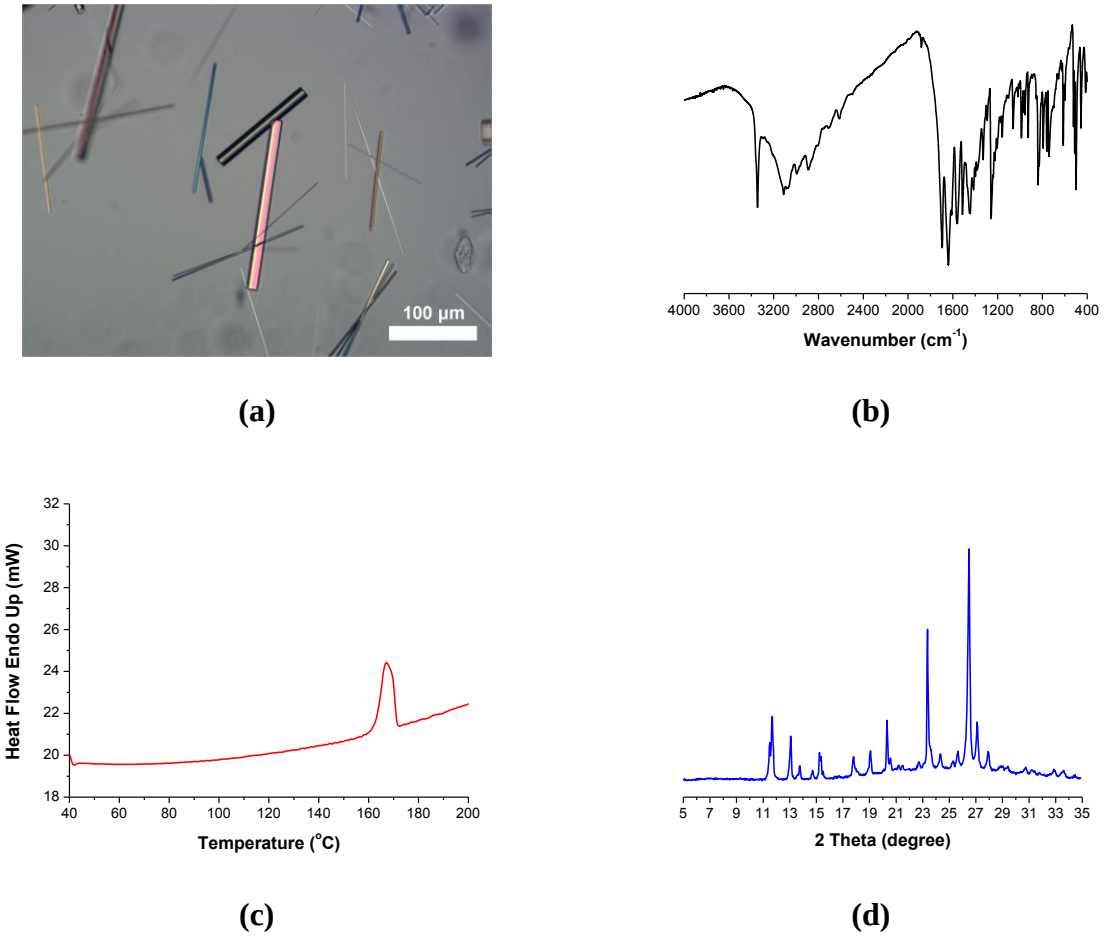
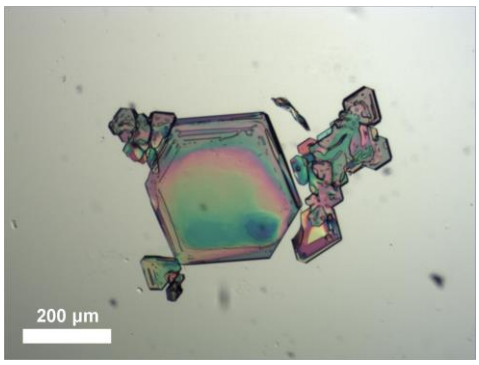


Figure S1. (a) POM image, (b) FTIR spectrum, (c) DSC scan and (d) PXRD pattern of 1:1 co-crystal of acetaminophen-theophylline.



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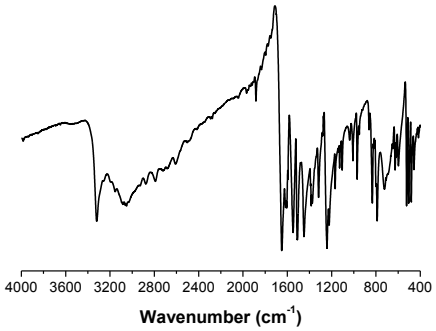

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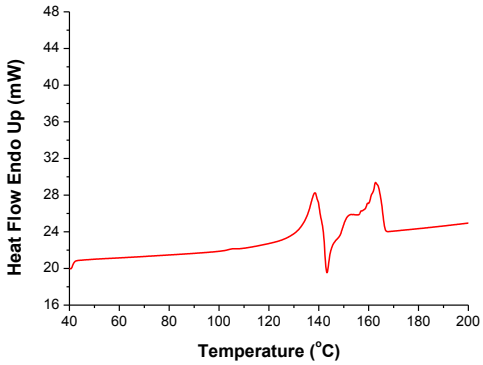

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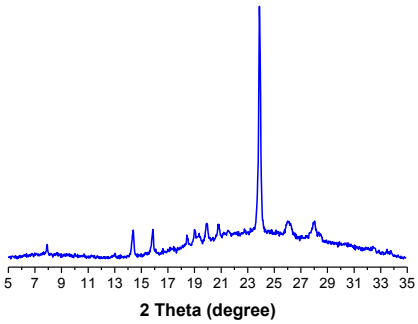


(d)

Figure S2. (a) POM image, (b) FTIR spectrum, (c) DSC scan and (d) PXRD pattern of 2:1 co-crystal of acetaminophen-naphthalene.

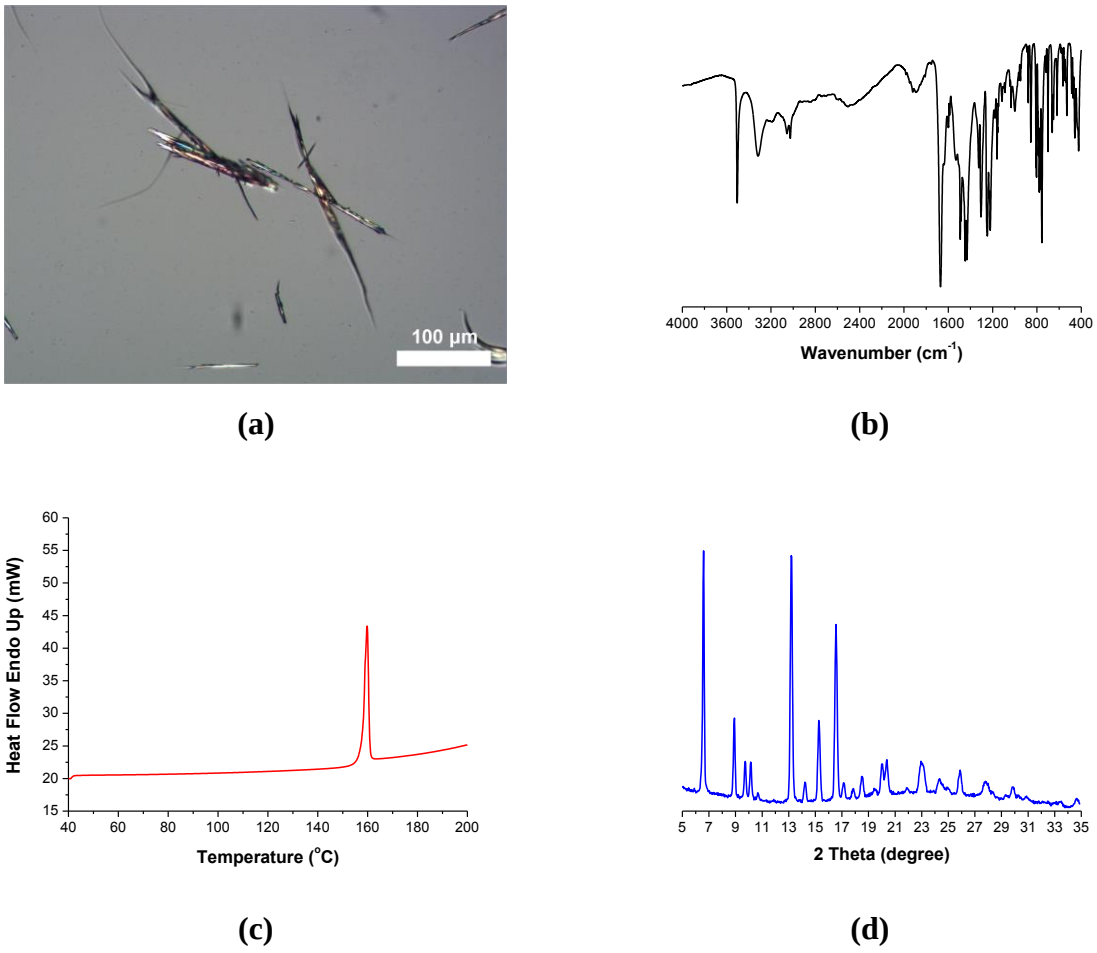


Figure S3. (a) POM image, (b) FTIR spectrum, (c) DSC scan and (d) PXRD pattern of 1:1 co-crystal of salicylic acid-carbamazepine.

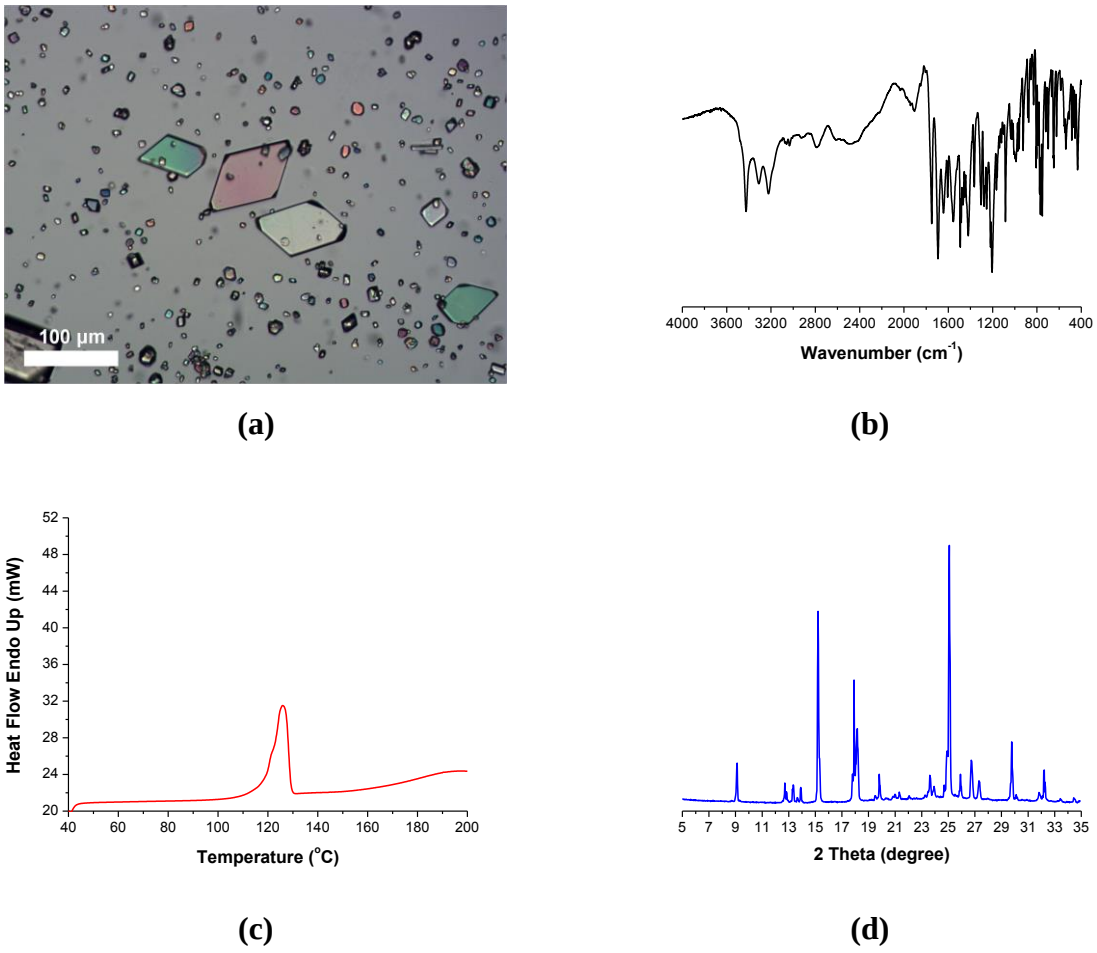


Figure S4. (a) POM image, (b) FTIR spectrum, (c) DSC scan and (d) PXRD pattern of 1:1 co-crystal of aspirin-carbamazepine.

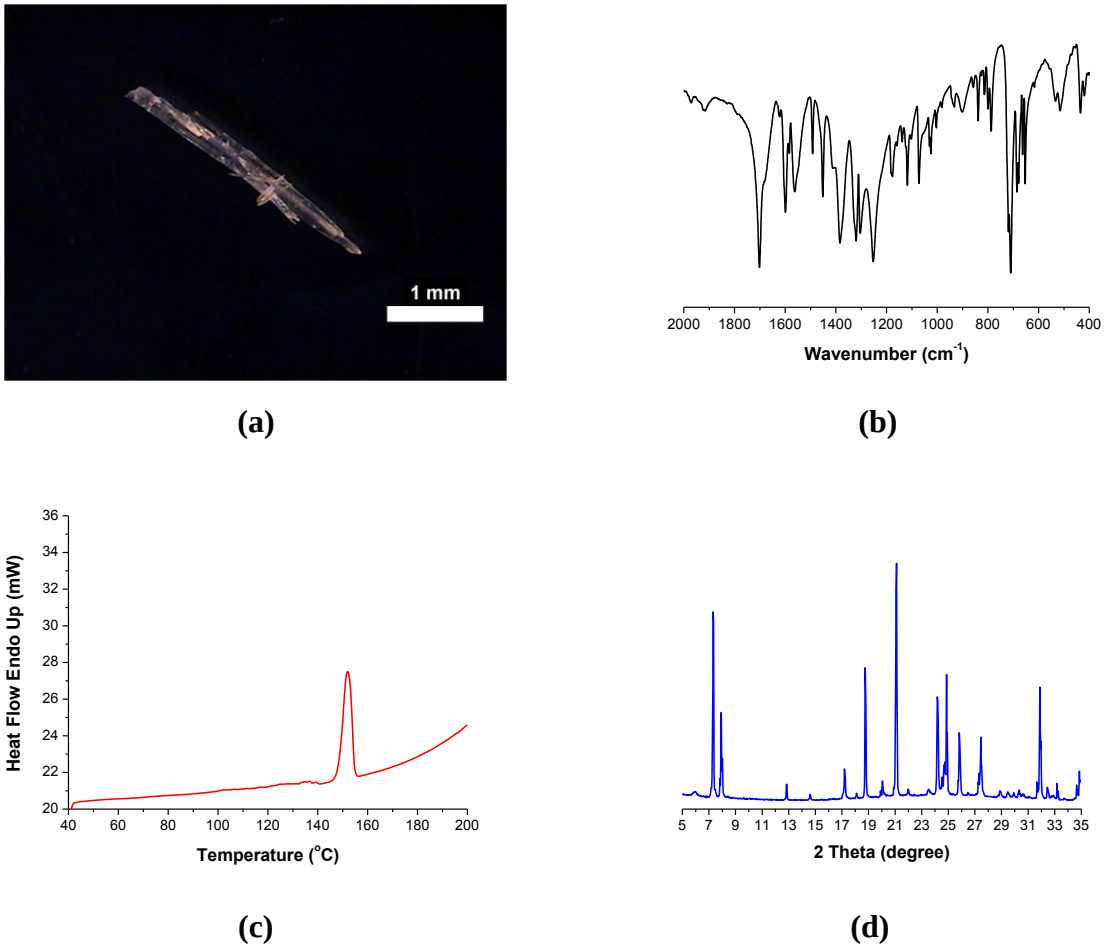


Figure S5. (a) POM image, (b) FTIR spectrum, (c) DSC scan and (d) PXRD pattern of 1:2 Form A co-crystal of sodium benzoate-benzoic acid.

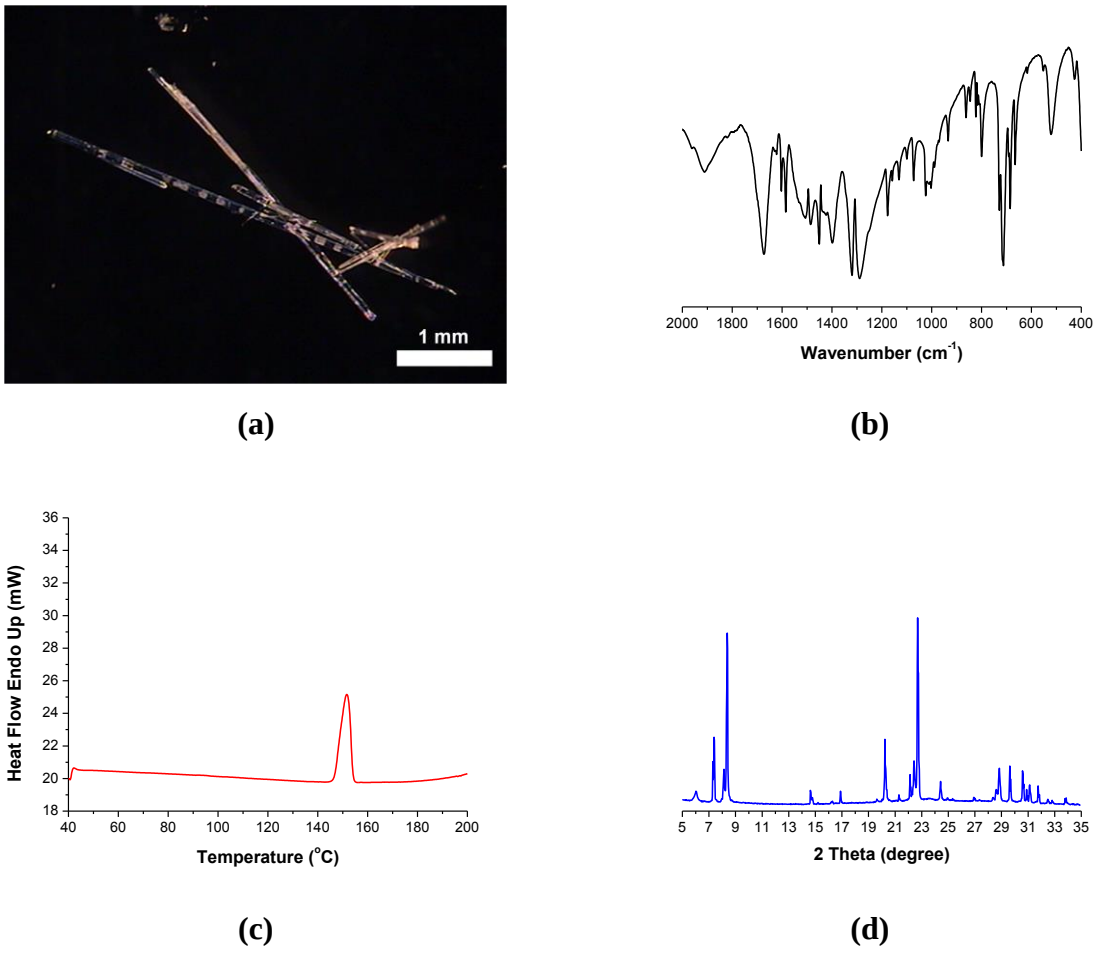
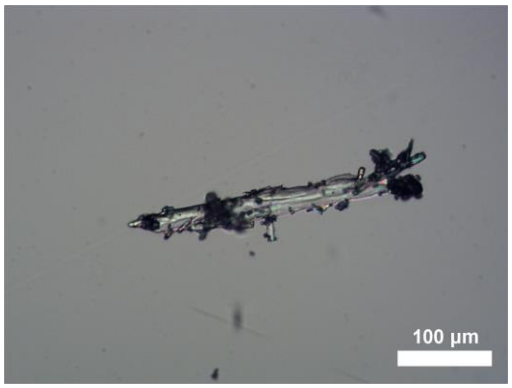
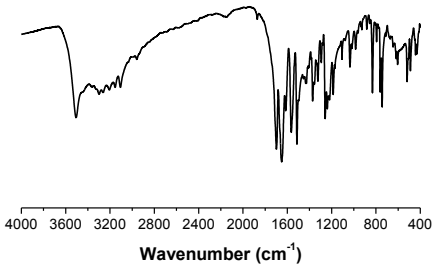


Figure S6. (a) POM image, (b) FTIR spectrum, (c) DSC scan and (d) PXRD pattern of 1:2 Form B co-crystal of sodium benzoate-benzoic acid.



(a)



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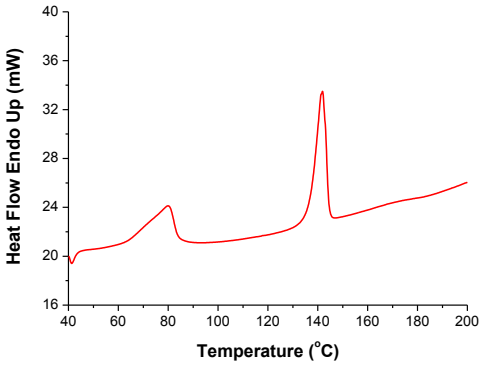

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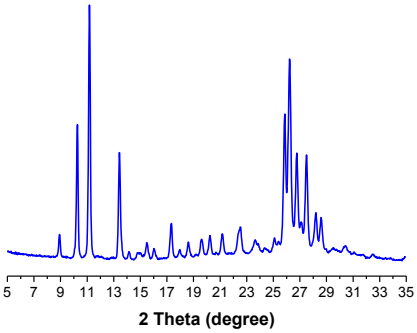
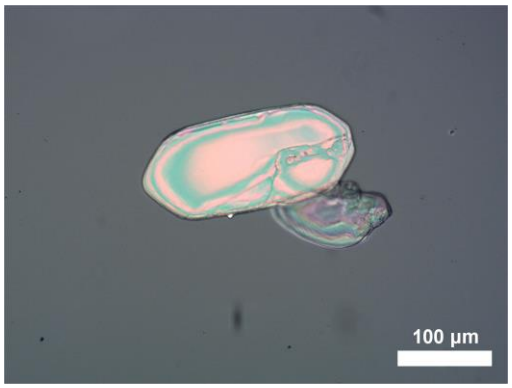
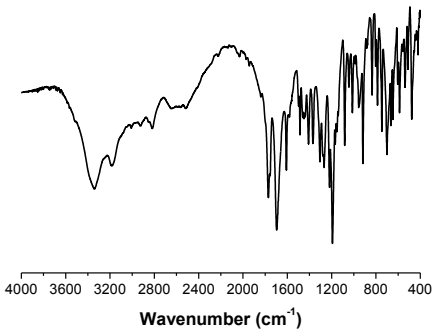


(d)

Figure S7. (a) POM image, (b) FTIR spectrum, (c) DSC scan and (d) PXRD pattern of 1:1 co-crystal of acetaminophen-caffeine.



(a)



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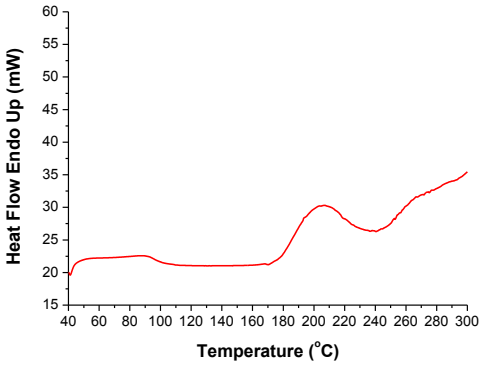

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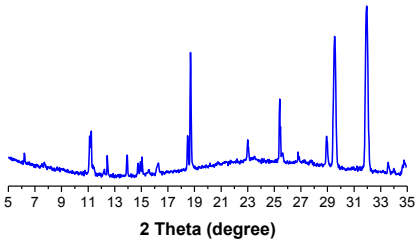

(d)

Figure S8. (a) POM image, (b) FTIR spectrum, (c) DSC scan and (d) PXRD pattern of 1:1 co-crystal of aspirin-acetamide.

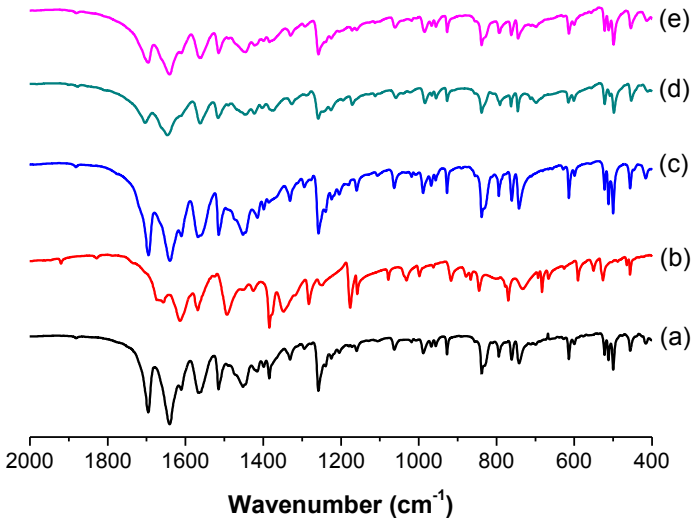

Figure S9. FTIR spectra of (a) 1:1 co-crystal of acetaminophen-theophylline, (b) 3-acetamidophenol, and 1:1 co-crystal of acetaminophen-theophylline produced in the presence of (c) 25 mol%, (d) 40 mol%, and (e) 50 mol% of the isomer of acetaminophen (i.e. 3-acetamidophenol).

TABLES

Table S1. Solubility values of co-crystal components in different solvents/solutions.

Co-crystal Components	Solvents/Solutions	Solubility Values (mg/mL)	
		at 15ºC	at 60ºC
Acetaminophen	Aqueous solution of acetic acid	25.9	144.5
	Isopropyl alcohol (IPA)	62.3	176.2
	n-Butyl alcohol	48.9	114.5
Theophylline	Aqueous solution of acetic acid	34.7	174.6
Salicylic acid	Acetonitrile	63.8	242.7
	Nitrobenzene	~ 2	93.4
Aspirin	Chloroform	22.2	88.6
	Benzyl alcohol	23.1	154.7
	Methanol	86.3	781.5
	Acetonitrile	31.8	157.5
	Ethyl acetate	27.4	182.7
	1,4-Dioxane	115.1	368.9
Carbamazepine	Acetonitrile	21.2	116.4
	Nitrobenzene	44.8	131.5
	Chloroform	126.0	351.8
	Benzyl alcohol	111.1	417.8
	Methanol	53.0	194.7
Acetamide	Acetonitrile	22.7	72.3
	Ethyl acetate	6.8	29.2
	1,4-Dioxane	13.4	57.8
Meloxicam	Chloroform	3.8	12.7
	Benzyl alcohol	X	X
	Methanol	X	X
	Acetonitrile	X	X
	Ethyl acetate	X	X
	1,4-Dioxane	X	X
Benzoic acid	MeOH/H_2O (3/1 v/v)	154.7	548.5

* The solubility in chloroform and methanol were measured in 15º and 50ºC due to the lower their boiling points.

Table S2. Solvents used in various co-crystal systems for cooling co-crystallization.

Co-crystal systems	Solvents/Solutions
Acetaminophen-Theophylline	Aqueous solution of acetic acid
Acetaminophen-Naphthalene	Isopropyl alcohol (IPA), *n*-butyl alcohol
Salicylic acid-Carbamazepine	Acetonitrile, nitrobenzene
Aspirin-Carbamazepine	Chloroform, benzyl alcohol, methanol
Sodium benzoate-Benzoic acid	Ethanol/water (3:1 v/v), methanol/water (3:1 v/v)
Acetaminophen-Caffeine	Aqueous solution of acetic acid
Aspirin-Acetamide	Acetonitrile, ethyl acetate, 1,4-dioxane, benzyl alcohol (seeding)

Notes and References

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