Electronic Supplementary Information†

Eutectics as Improved Pharmaceutical Materials: Design, Properties and Characterization†

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The ESI contains details of a few bridge and additional experiments carried out on EDH eutectics stability to complete writing of this review article. References of the main paper are numbered as such. References added in ESI are numbered S1, S2.

Experimental Section

Materials: Ethambutol dihydrochloride (Lot#090M0189V) was purchased from Sigma-Aldrich (Hyderabad, India) and used without further purification. All other chemicals were of analytical or chromatographic grade. Water purified from a deionizer cum mixed bed purification system (AquaDM, Bhanu, Hyderabad, India) was used for experiments.

Ethambutol dihydrochloride ($C_{10}H_{26}Cl_2N_2O_2$):

^{1}H NMR (DMSO-d_6): δ 0.92 (3H, t, *J* 8), 1.68 (2H, m), 3.06 (1H, m), 3.71 (2H, m), 5.40 (1H, s), 9.29 (2H, d, *J* 80 (N–H coupling)). Protons of –CH_2 group (attached to –NH_2^+ group) merged with water peak of DMSO-d_6.

^{13}C NMR (DMSO-d_6): δ 10.24, 20.78, 41.27, 57.99, 60.74.

Preparation of Eutectics

Co-grinding: EDH and diacid were taken in an equimolar ratio to about 200 mg scale and subjected to neat grinding using a mortar-pestle for 15 min.

EDH–FA ($C_{14}H_{30}N_2O_6$):

^{1}H NMR (DMSO-d_6): δ 0.90 (3H, t, *J* 8), 1.65 (2H, m), 3.10 (1H, m), 3.64 (2H, m), 5.40 (1H, s), 6.61 (1H, s), 9.27 (2H, s, *br*). Protons of –CH_2 group (attached to –NH_2^+ group of EDH) merged with water peak of DMSO-d_6 and of carboxylic acid (FA) exchange in solvent.

^{13}C NMR (DMSO-d_6): δ 10.22, 20.76, 41.25, 57.95, 60.72, 134.43, 166.40.

EDH–SA ($C_{14}H_{32}N_2O_6$):

^{1}H NMR (DMSO-d_6): δ 0.90 (3H, t, *J* 8), 1.66 (2H, m), 2.39 (2H, s), 3.06 (1H, m), 3.65 (2H, m), 5.40 (1H, s), 9.28 (2H, s, *br*). Protons of –CH_2 group (attached to –NH_2^+ group of EDH) merged with water peak of DMSO-d_6 and of carboxylic acid (SA) exchange in solvent.

^{13}C NMR (DMSO-d_6): δ 10.22, 20.76, 29.23, 41.23, 57.93, 60.71, 174.05.

Powder X-ray Diffraction: PXRD were recorded on Bruker D8 Advance diffractometer using Cu-Kα X-radiation (λ = 1.5406 Å) at 40 kV and 30 mA. Diffraction patterns were collected over 2θ range of 5-50° at scan rate of 1° min^{-1}. Powder Cell 2.4 (ref. S1) was used to plot the diffraction patterns.

NMR Spectroscopy: Solution and solid state NMR spectra were recorded on a Bruker Avance spectrometer at 400 MHz. SS-NMR spectra were recorded on a Bruker 4 mm double resonance CP-MAS probe with zirconia rotors at 5.0 kHz with a cross-polarization contact time of 2.5 ms and a recycle delay of 8 s. ^{13}C CP-MAS spectra were recorded at 100 MHz and referenced to the methylene carbon of glycine, and then the chemical shifts were recalibrated to the TMS scale ($\delta_{glycine}$ = 43.3 ppm). The identity and stoichiometry of the components in the eutectics was established through solution ^{1}H NMR integration and ^{13}C NMR spectra.

Thermal analysis: DSC was performed on a Mettler Toledo DSC 1 module calibrated with indium (T_m = 156.60 °C; ΔH_f = 28.45 J g^{-1}) and zinc (T_m = 419.50 °C; ΔH_f = 107.50 J g^{-1}) as per the manufacturer's specifications. TGA was performed on a Mettler Toledo TGA/SDTA 851e module calibrated with indium (T_m = 156.60 °C) and aluminium (T_m = 660.30 °C). The typical sample size is 3–5 mg for DSC and 6–8 mg for TGA and the temperature range used is 30–250 °C at 5 °C min^{-1}. Samples were placed in crimped but vented aluminium pans for DSC and open alumina pans for TGA and were purged by a stream of dry nitrogen flowing at 50 mL min^{-1}.

Karl Fischer (KF) titration: Water content of the samples was determined using a Spectralab volumetric MA 101 C Karl Fischer titrator with KF reagent (single solution) as the titrant and anhydrous methanol as the solvent. About 50 mg of each sample was taken for analysis.

Hygroscopic/Accelerated stability testing: About 200 mg of each compound (EDH 200 mg and EDH-FA/SA 285 mg each) were placed in a glass petri dish and stored without a lid in a Thermolab T-908 stability chamber at 40 °C and 75% RH (as per the WHO/ICH guidelines)[84] for 2 months. Percentage water uptake of the samples was assessed periodically at 15, 30 and 60 days by KF titration and TGA. The integrity of the samples was established by NMR and PXRD (wherever possible) before and after the study.

Packing Diagrams: X-Seed (ref. S2) was used to prepare packing diagrams.

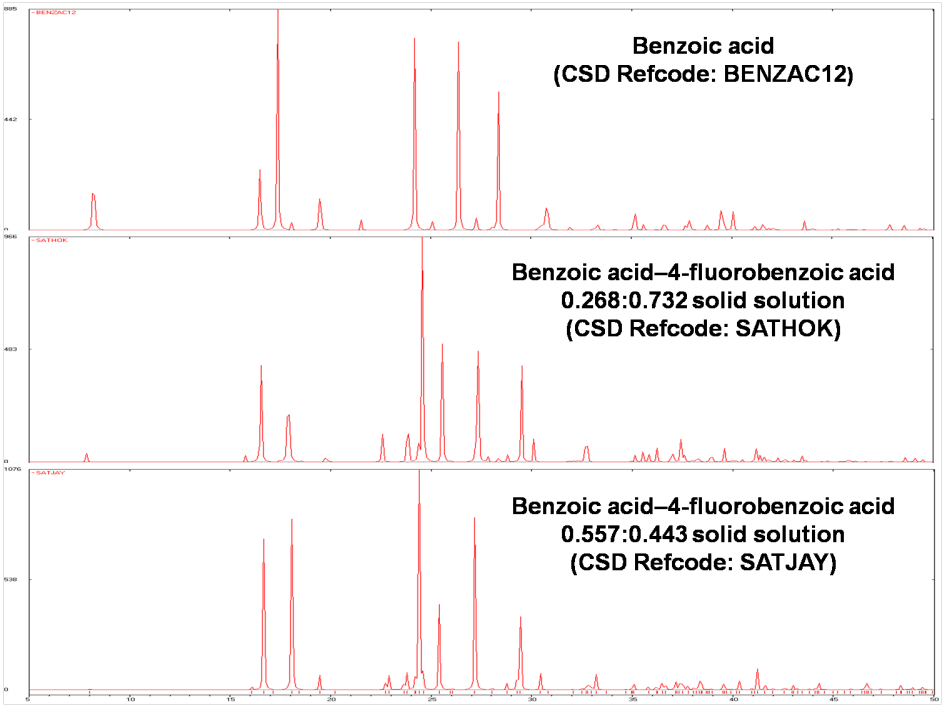

Figure S1 Benzoic acid−4-fluorobenzoic acid solid solutions exhibit diffraction peaks that are very close to those of the parent benzoic acids.

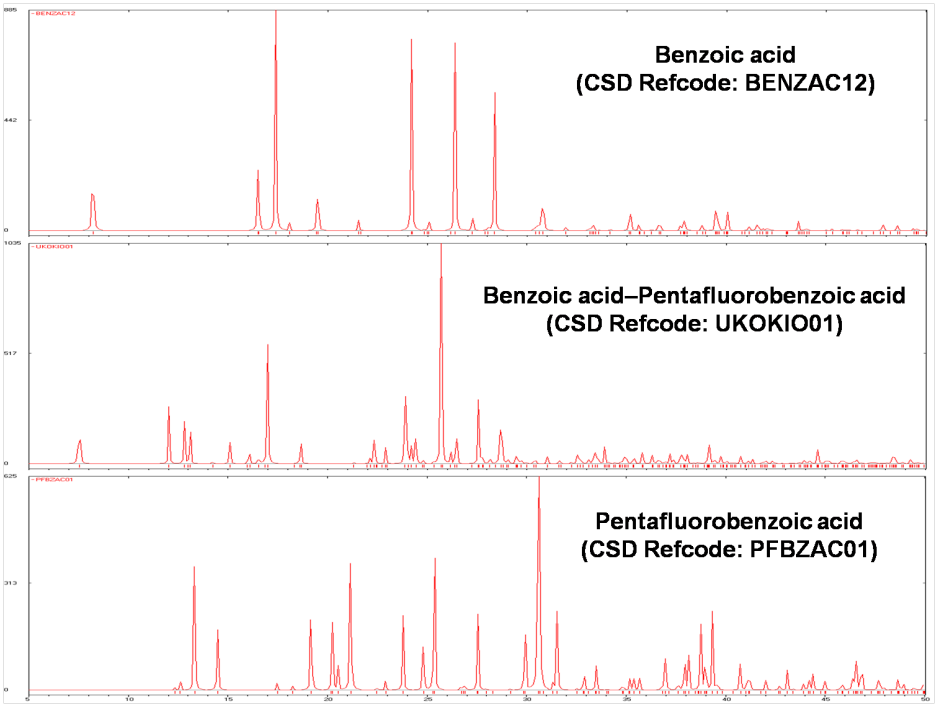

Figure S2 Benzoic acid–pentafluorobenzoic acid cocrystal exhibits distinct diffraction peaks compared to the parent acids.

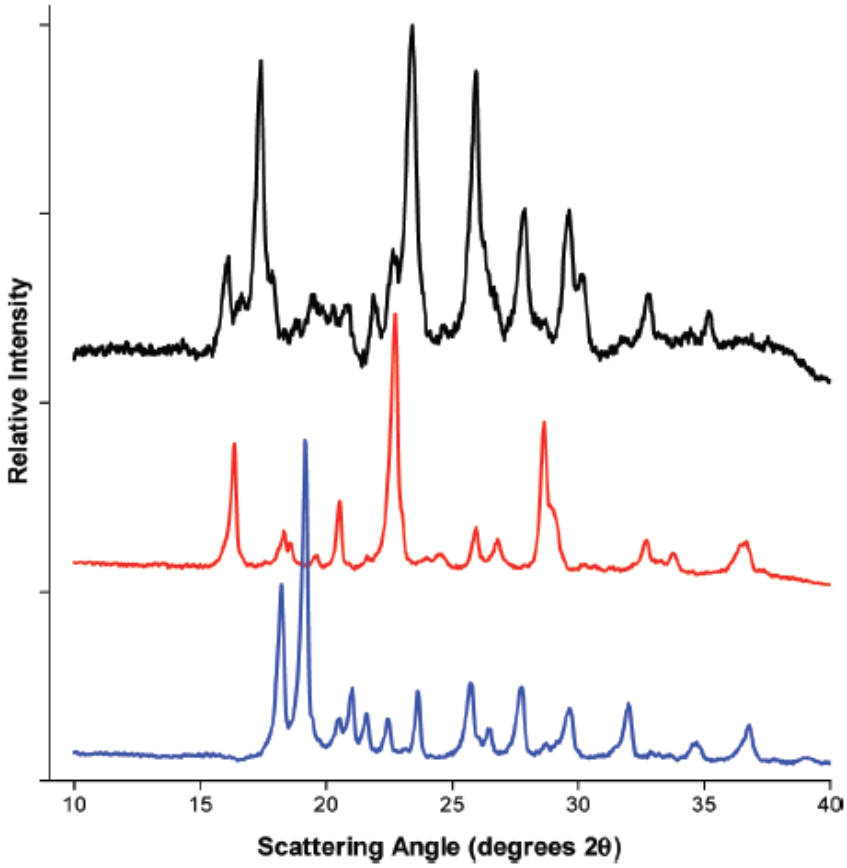

Figure S3 X-ray powder diffraction patterns of benzoic acid (blue trace), benzamide (red trace) and their 1:1 stoichiometry combination (black trace). Comparison of the line patterns shows that the combination does not exhibit any new signature peaks. Figure extracted from Ref. 36a.

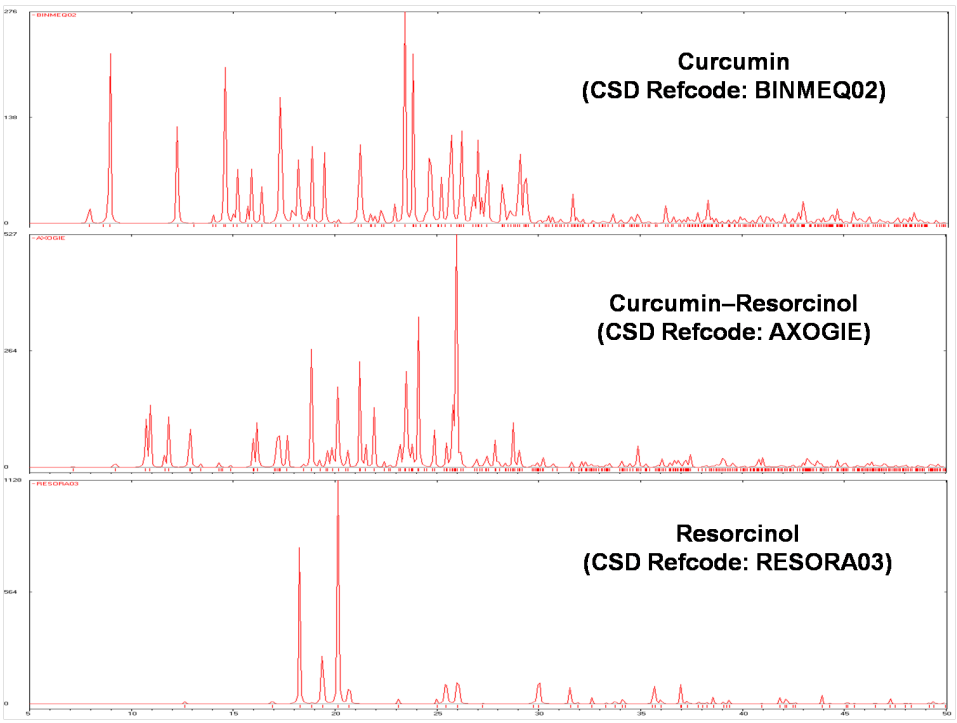

Figure S4 Curcumin–Resorcinol cocrystal exhibits distinct diffraction peaks compared to the parent components.

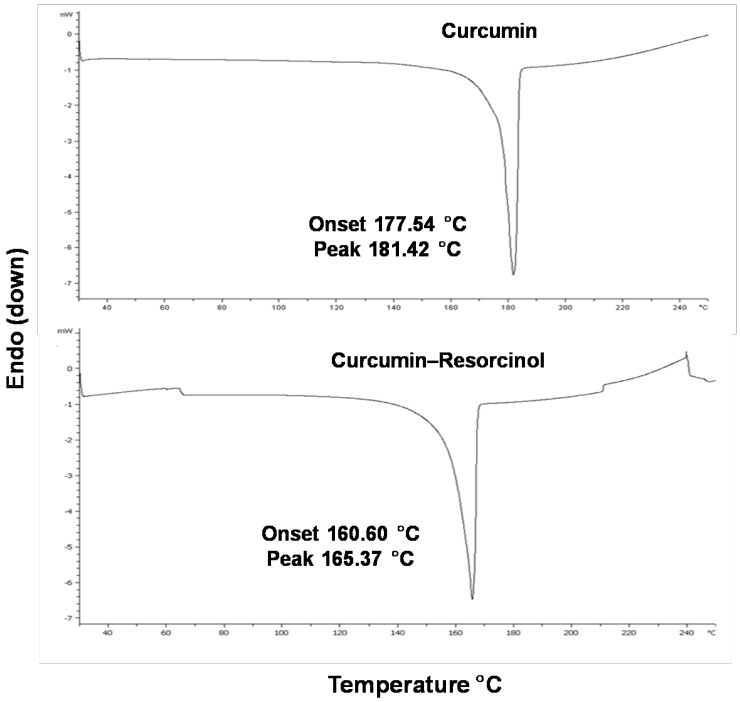

Figure S5 Curcumin–Resorcinol cocrystal exhibits intermediate melting point compared to the parent components (m.p. of Resorcinol 110 °C), Refs. 37 & 38.

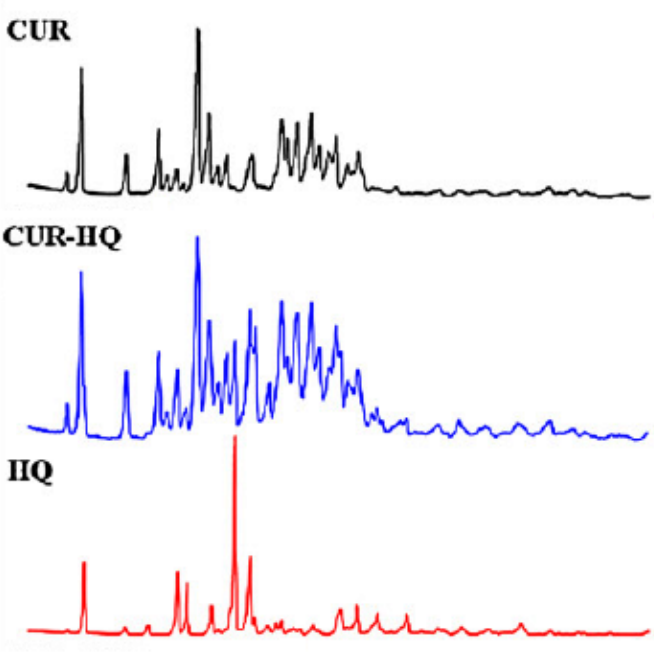

Figure S6 X-ray powder diffraction pattern of curcumin (black trace), hydroquinone (red trace) and their 1:1 stoichiometry combination (blue trace). Comparison of the line patterns shows that the product does not exhibit any new signature peaks. Extracted from Ref. 11.

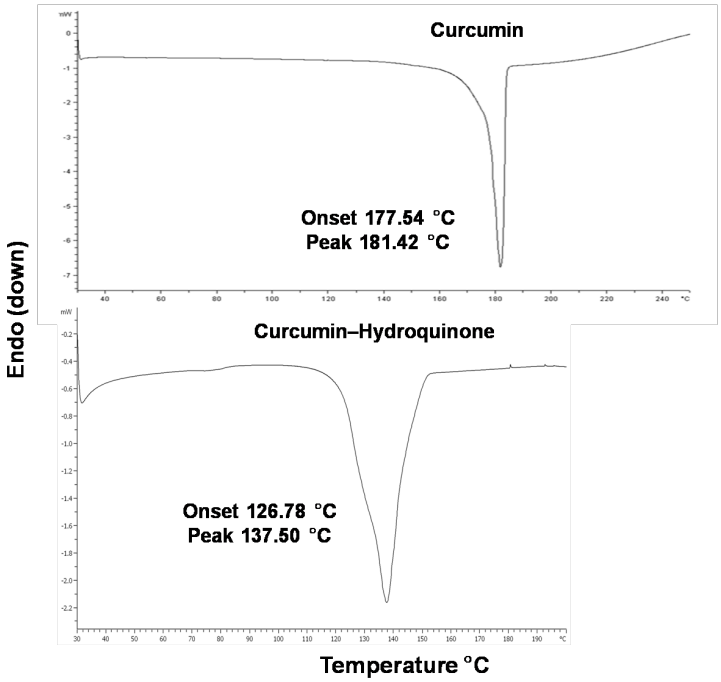

Figure S7 Curcumin–Hydroquinone eutectic exhibits lower melting point compared to the parent components (m.p. of Hydroquinone 172 °C), Ref. 11.

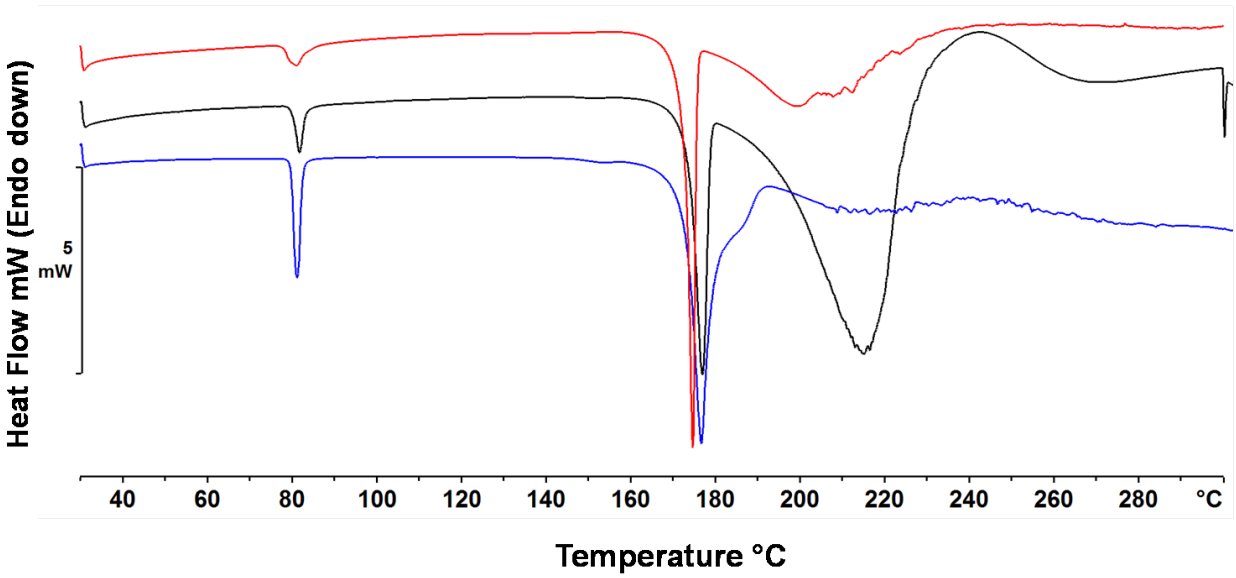

Figure S8 DSCs of 1:1 (red), 1:3 (black) and 3:1 (blue) EDH–FA molar compositions show an invariant eutectic solidus peak around 175 °C in common. The compositions are different with respect to onset temperature and shape of liquidus peak (above 175 °C) and polymorphic phase transition endotherm of EDH (form II → form I)[77] at 75 °C. The non-eutectic phases exhibit a broad to sharp liquidus peak for the excess component.

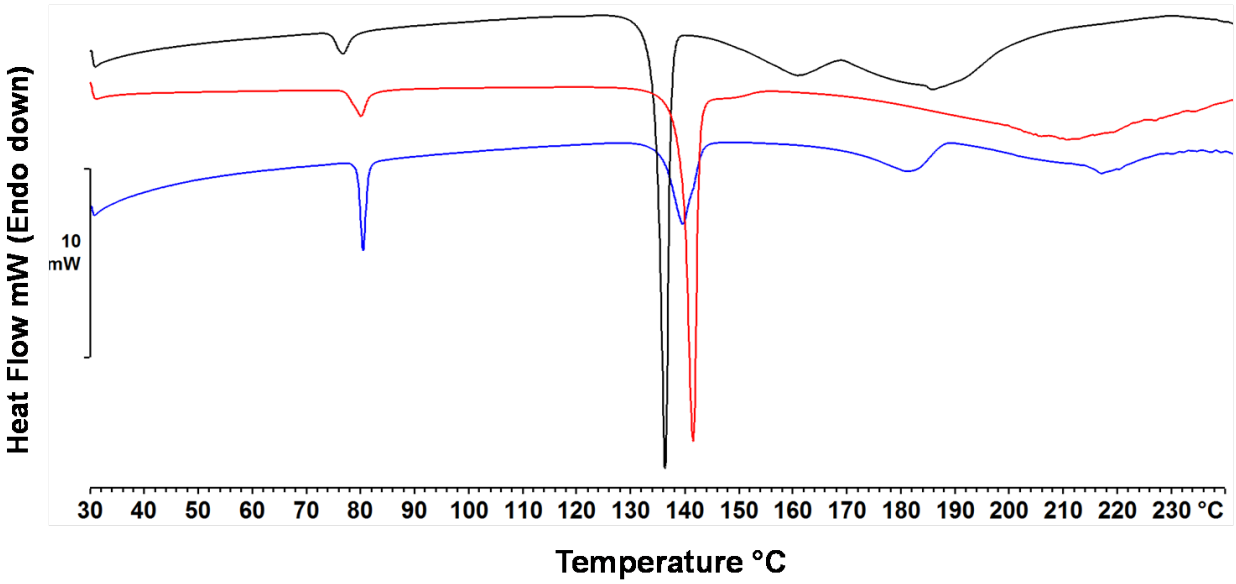

Figure S9 DSCs of 1:1 (red), 1:3 (black) and 3:1 (blue) EDH–SA molar compositions show an invariant eutectic solidus peak around 140 °C in common. The compositions are different with respect to onset temperature and shape of liquidus peak (above 140 °C) and polymorphic phase transition endotherm of EDH (form II → form I)[77] at 75 °C. The non-eutectic phases exhibit a broad to sharp liquidus peak for the excess component.

References

S1. PowderCell, *Program for Structure Visualization, Powder Pattern Calculation and Profile Fitting*, http://www.ccp14.ac.uk/index.html.

S2. L. J. Barbour, *X-Seed, Graphical Interface to SHELX-97 and POV-Ray*, *Program for Better Quality of Crystallographic Figures*; University of Missouri-Columbia: Missouri, USA, 1999.