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Supporting Information

Solid Solution Polymorphs afford two High-Soluble Co-Drug Forms of Tolbutamide and Chlorpropamide

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Table S1. Summary of polymorphs of tolbutamide (TBA) and chlorpropamide (CPA) in the CSD.

TBA			CPA		
form	space group	CSD refcode	form	space group	CSD refcode
*I^L	*Pna*2_1	ZZZPUS02	α	$P2_12_12_1$	BEDMIG
I^H	*Pna*2_1	ZZZPUS17	α’	$P2_111$	BEDMIG17
II	*Pc*	ZZZPUS15	**β	*Pbcn*	BEDMIG01
III	$P2_1/n$	ZZZPUS13	β^{II}	*P2/c*	BEDMIG11
III^2	$P2_1/n$	ZZZPUS11	β^{III}	*P2/n*	BEDMIG12
IV	$P2_1/c$	ZZZPUS07	γ	$P2_1$	BEDMIG02
**V	*Pbcn*	ZZZPUS10	δ	*Pbca*	BEDMIG03
			*ε	*Pna*2_1	BEDMIG04
			ε’	*Pna*2_1	BEDMIG05

*Isomorphous pair of solid solution Form 1; ** isomorphous pair of solid solution Form 2.

Experimental Procedures

All reagents and solvents were purchased from Sigma Aldrich and used without further purifications.

Growth of single crystals from ethanol solution: 100 mg of the mixture of tolbutamide and chlorpropamide were prepared in the desired stoichiometric ratio (70:30, 50:50 and 30:70 respectively) and were dissolved in ≈ 2 mL of ethanol in a vial; single crystals formed after few days by solvent evaporation at room temperature and were analysed by SC-XRD. The crystals were also ground and analysed by XRPD and DSC.

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Crystallization from solution by fast evaporation: 100 mg of the mixture of tolbutamide and chlorpropamide were prepared in 50:50 stoichiometric ratio and were dissolved in ≈ 2 mL of ethanol in a vial and placed in the oven at 60 °C. The product obtained from the solvent evaporation was analysed by XRPD and DSC.

Slurry: 400 mg of the mixture of tolbutamide and chlorpropamide were prepared in 50:50 stoichiometric ratio and added to ≈ 1 mL of ethanol in a closed vial and left to stir for 48h at room temperature. The slurry was filtered, and product obtained was analysed by XRPD.

Solid-State synthesis: mechanochemical syntheses were performed by manual grinding of the reagents in the desired stoichiometric ratios with an agate mortar and pestle. Mechanochemical syntheses were also performed by kneading the reagents for 80 min in a Retsch MM400 ball miller, operated at a frequency of 25 Hz; 5 mL agate jar was used, with one agate ball 10 mm in diameter.
Tolbutamide: 100 mg of tolbutamide (0.37 mmol) were placed in an agate mortar and pestle, and ground for 20 minutes adding 4 drops of EtOH (1 drop every 5 minutes). The product was analysed by XRPD and DSC.
Chlorpropamide: 100 mg of chlorpropamide (0.36 mmol) were placed in an agate mortar and pestle, and ground for 20 minutes adding 4 drops of EtOH (1 drop every 5 minutes). The product was analysed by XRPD and DSC.
Tolbutamide/Chlorpropamide (85:15): 84.7 mg of tolbutamide (0.312 mmol) and 15.3 mg of chlorpropamide (0.055 mmol) were placed in an agate mortar and pestle; the mixture was ground for 20 minutes adding 4 drops of EtOH (1 drop every 5 minutes). The product was analysed by XRPD and DSC.
Tolbutamide/Chlorpropamide (70:30): 69.5 mg of tolbutamide (0.256 mmol) and 30.5 mg of chlorpropamide (0.110 mmol) were placed in an agate mortar and pestle; the mixture was ground for 20 minutes adding 4 drops of EtOH (1 drop every 5 minutes). The product was analysed by XRPD and DSC.
Tolbutamide/Chlorpropamide (50:50): 49.4 mg of tolbutamide (0.183 mmol) and 50.6 mg of chlorpropamide (0.183 mmol) were placed in an agate mortar and pestle; the mixture was ground for 20 minutes adding 4 drops of EtOH (1 drop every 5 minutes). The product was analysed by XRPD and DSC.
Tolbutamide/Chlorpropamide (30:70): 29.5 mg of tolbutamide (0.109 mmol) and 70.5 mg of chlorpropamide (0.254 mmol) were placed in an agate mortar and pestle; the mixture was ground for 20 minutes adding 4 drops of EtOH (1 drop every 5 minutes). The product was analysed by XRPD and DSC.
Tolbutamide/Chlorpropamide (15:85): 14.7 mg of tolbutamide (0.054 mmol) and 85.3 mg of chlorpropamide (0.306 mmol) were placed in an agate mortar and pestle; the mixture was ground for 20 minutes adding 4 drops of EtOH (1 drop every 5 minutes). The product was analysed by XRPD and DSC.
Tolbutamide/Chlorpropamide (50:50): 49.4 mg of tolbutamide (0.183 mmol) and 50.6 mg of chlorpropamide (0.183 mmol) were placed in an agate jar and the mixture was kneaded in the presence of one drop (50 µL) of ethanol, for 80 min in a Retsch MM400 ball miller, operated at a frequency of 25 Hz. The product was analysed by XRPD and DSC.
Tolbutamide/Chlorpropamide (30:70): 29.5 mg of tolbutamide (0.109 mmol) and 70.5 mg of chlorpropamide (0.254 mmol) were placed in an agate jar and the mixture was kneaded in the presence of one drop (50 µL) of ethanol, for 80 min in a Retsch MM400 ball miller, operated at a frequency of 25 Hz. The product was analysed by XRPD and DSC.

Crystallization from the melt: 100 mg of the mixture of tolbutamide and chlorpropamide were prepared in 50:50 stoichiometric ratio: 49.4 mg of tolbutamide (0.183 mmol) and 50.6 mg of chlorpropamide (0.183 mmol) were ground separately for few seconds and the obtained powders were mixed in a vial with a spatula. The vial was placed in a glass oven (Buchi B-585) set at 150 °C for 30 minutes; further 60 minutes were allowed for the cooling at room temperature. After cooling, the product was ground and analysed by XRPD and DSC.

X-Ray Powder Diffraction

All diffraction patterns were recorded on a PANalytical EMPYREAN diffractometer system using Bragg-Brentano geometry and an incident beam of Cu Kα radiation (λ = 1.5418 Å) in the 2θ range between 3° and 40° (step size: 0,013°; time/step: 30 s; soller slit: 0,04 rad; divergence slit: ⅛; anti-scatter slit: ¼; 45 mA X 40 kV). Room temperature scans were performed on a spinning silicon zero-background sample holder.

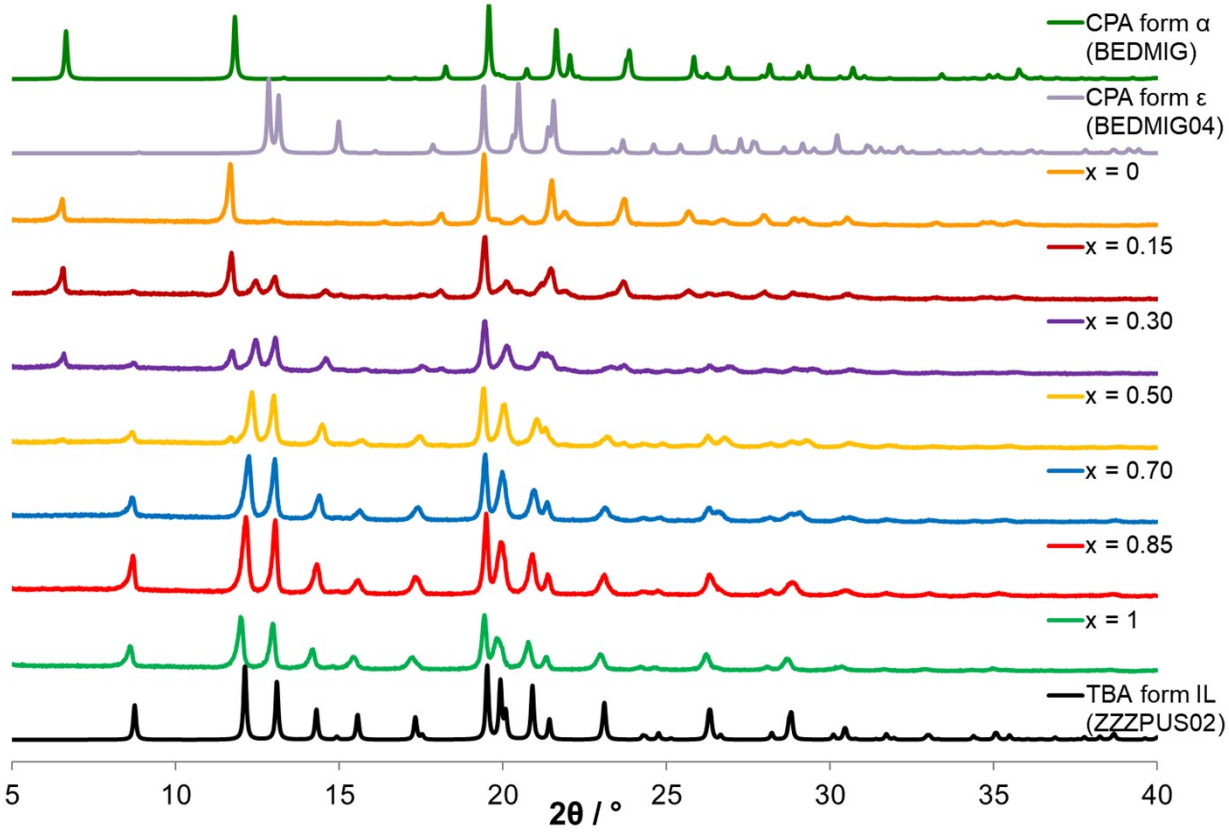

Figure S1. Comparison of experimental XRPD patterns for the product of the manual liquid assisted grinding of tolbutamide/chlorpropamide mixtures with different stoichiometric ratios; from top to bottom: calculated pattern of chlorpropamide form α (CSD refcode BEDMIG), calculated pattern of chlorpropamide form ε (CSD refcode BEDMIG04), experimental patterns for the product of the liquid assisted grinding of tolbutamide/chlorpropamide mixtures $(TBA)_x(CPA)_{1-x}$ with x = 0, 0.15, 0.30, 0.50, 0.70, 0.85 and 1 respectively, and the calculated pattern of tolbutamide form I^L (CSD refcode ZZZPUS02).

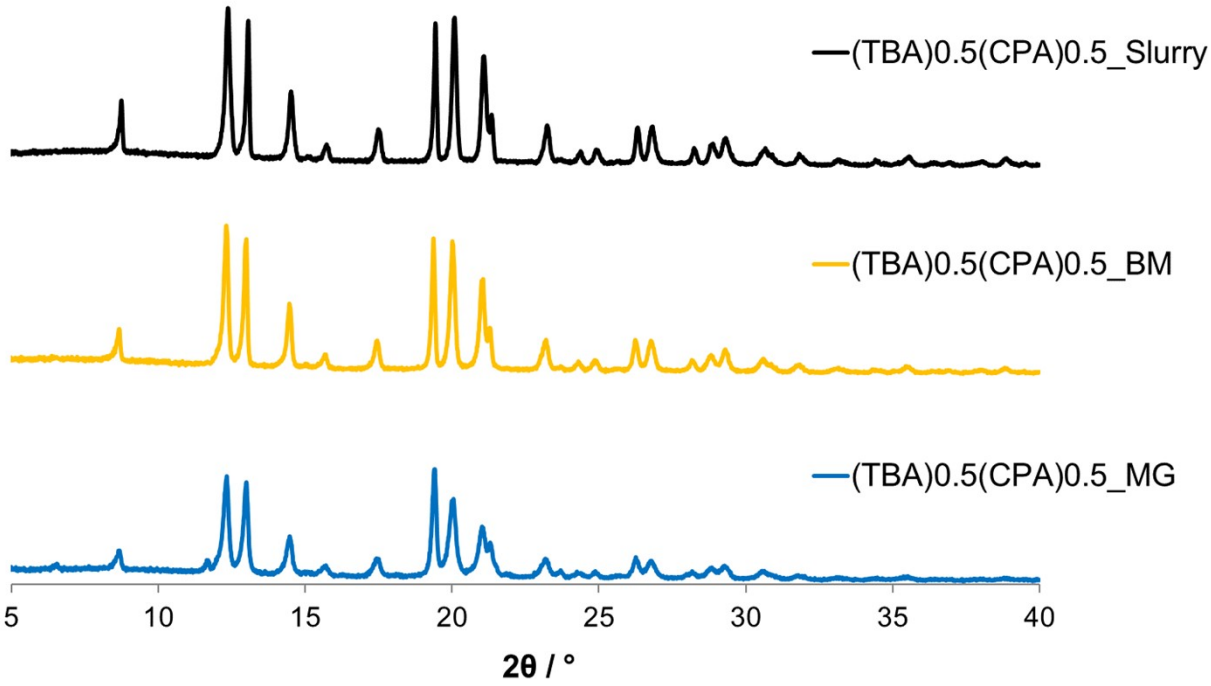

Figure S2. Comparison of experimental XRPD patterns for the product of the liquid assisted grinding performed by mortar and pestle (blue), ball mill (yellow) and the slurry (black) of the tolbutamide/chlorpropamide mixture $(TBA)_{0.5}(CPA)_{0.5}$.

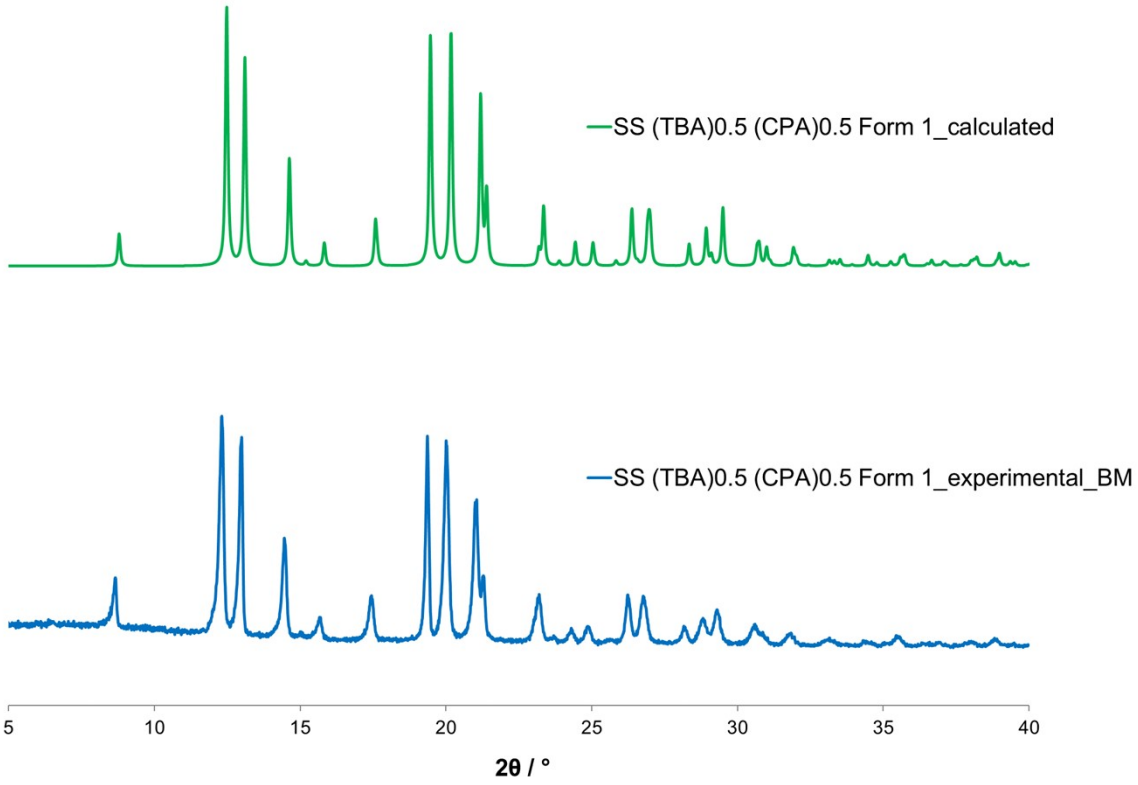

Figure S3. Comparison of the calculated (green) and experimental (blue) XRPD patterns for SS $(TBA)_{0.5}(CPA)_{0.5}$ Form 1.

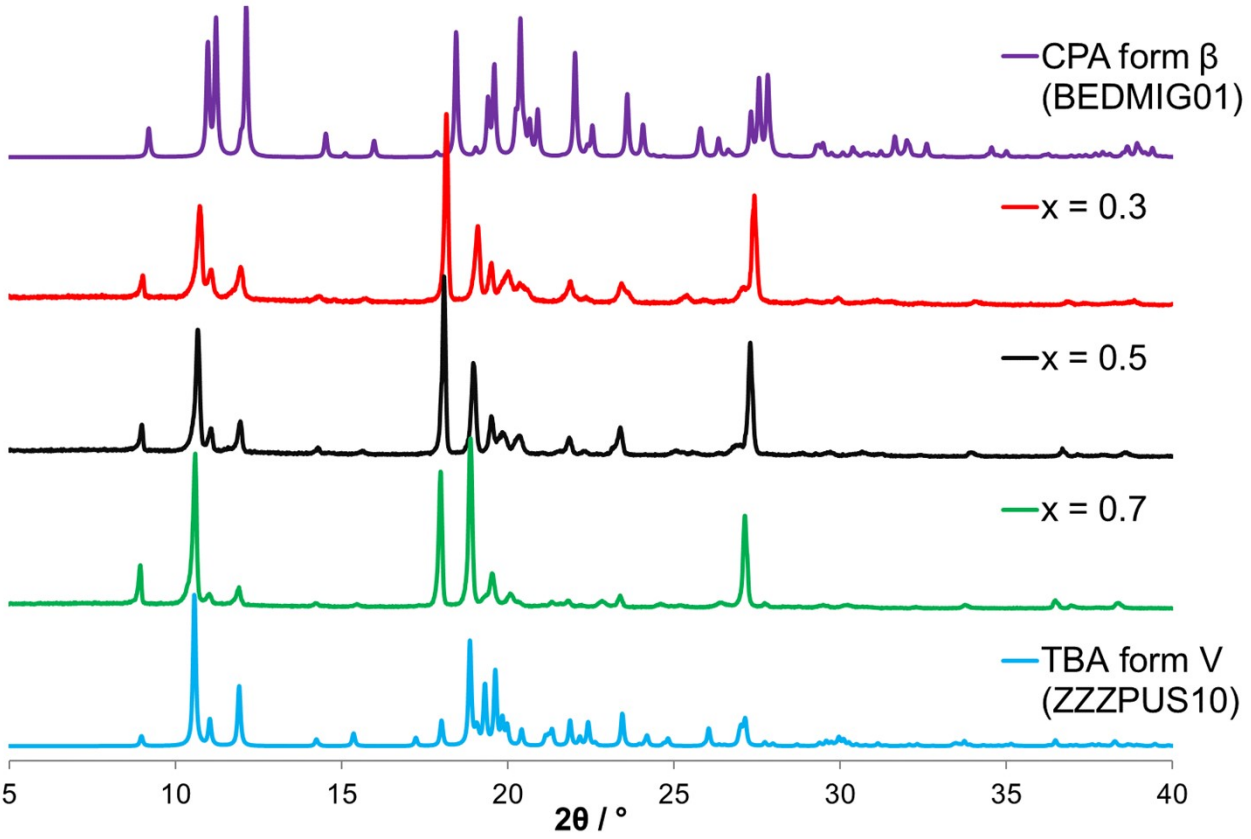

Figure S4. Comparison of experimental XRPD patterns for the product of the crystallizations by slow solvent evaporation at room temperature of the solutions of TBA/CPA mixtures with different stoichiometric ratios; from top to bottom: calculated pattern of chlorpropamide form β (CSD refcode BEDMIG01), experimental for the product obtained from the crystallizations of TBA/CPA mixtures $(TBA)_x(CPA)_{1-x}$ with x = 0.3, 0.5, 0.7 respectively, and the calculated pattern of tolbutamide form V (CSD refcode ZZZPUS10).

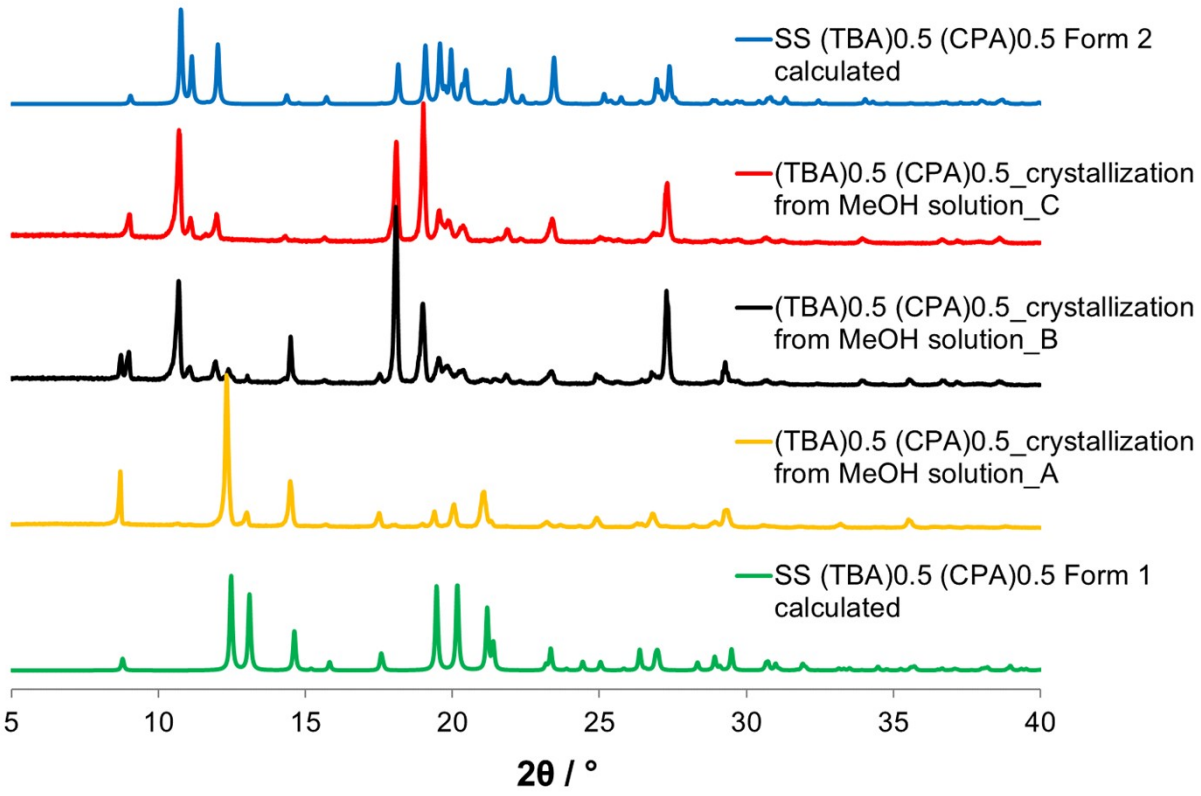

Figure S5. Comparison of experimental XRPD patterns for the product of three crystallizations by slow solvent evaporation at RT of MeOH solutions of the mixture $(TBA)_{0.5}(CPA)_{0.5}$ performed in the same experimental conditions (A, B and C), and the calculated pattern for SS $(TBA)_{0.5}(CPA)_{0.5}$ Form 1 and SS $(TBA)_{0.5}(CPA)_{0.5}$ Form 2.

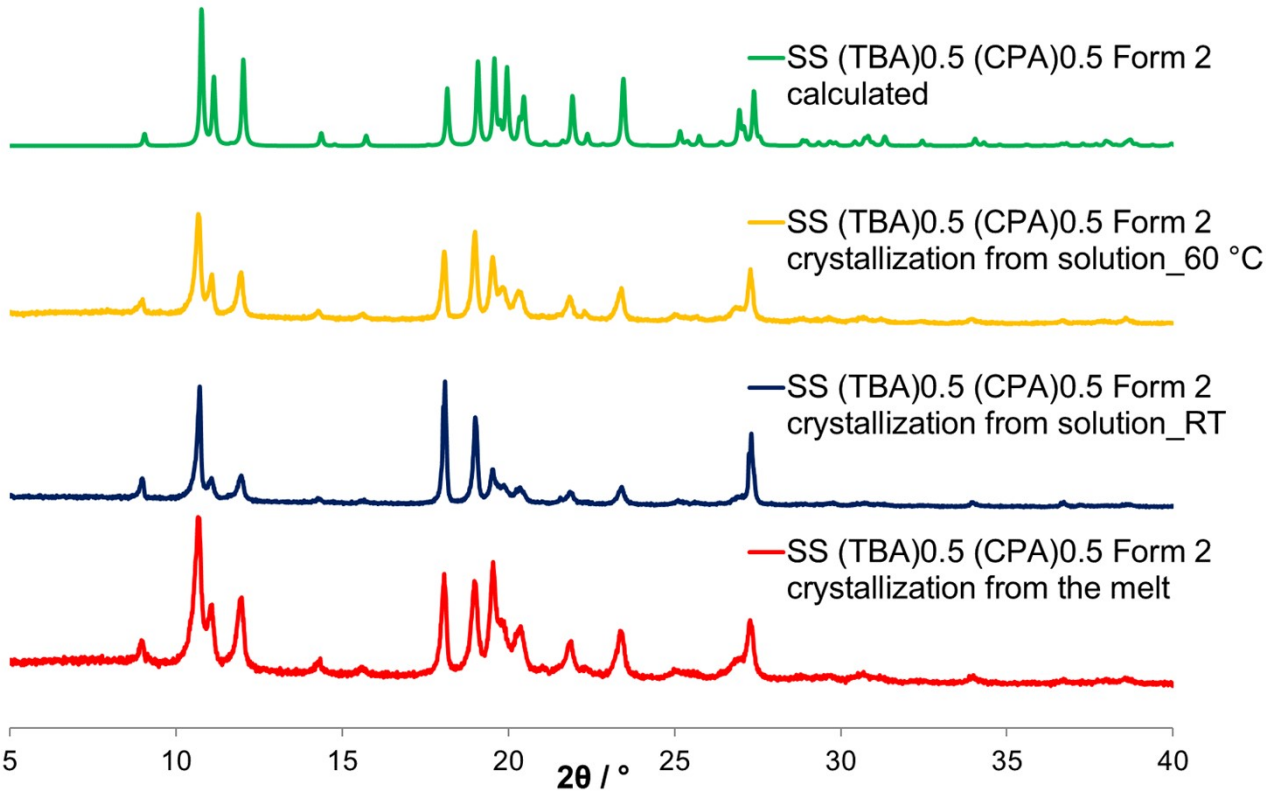

Figure S6. Comparison of experimental XRPD patterns for the product obtained from the crystallization from the melt of the mixture $(TBA)_{0.5}(CPA)_{0.5}$ (red), the product of the crystallization by slow solvent evaporation at RT (blue) and by fast solvent evaporation at 60 °C in the oven (yellow) of a EtOH solution of $(TBA)_{0.5}(CPA)_{0.5}$ and the calculated pattern for SS $(TBA)_{0.5}(CPA)_{0.5}$ Form 2 (green).

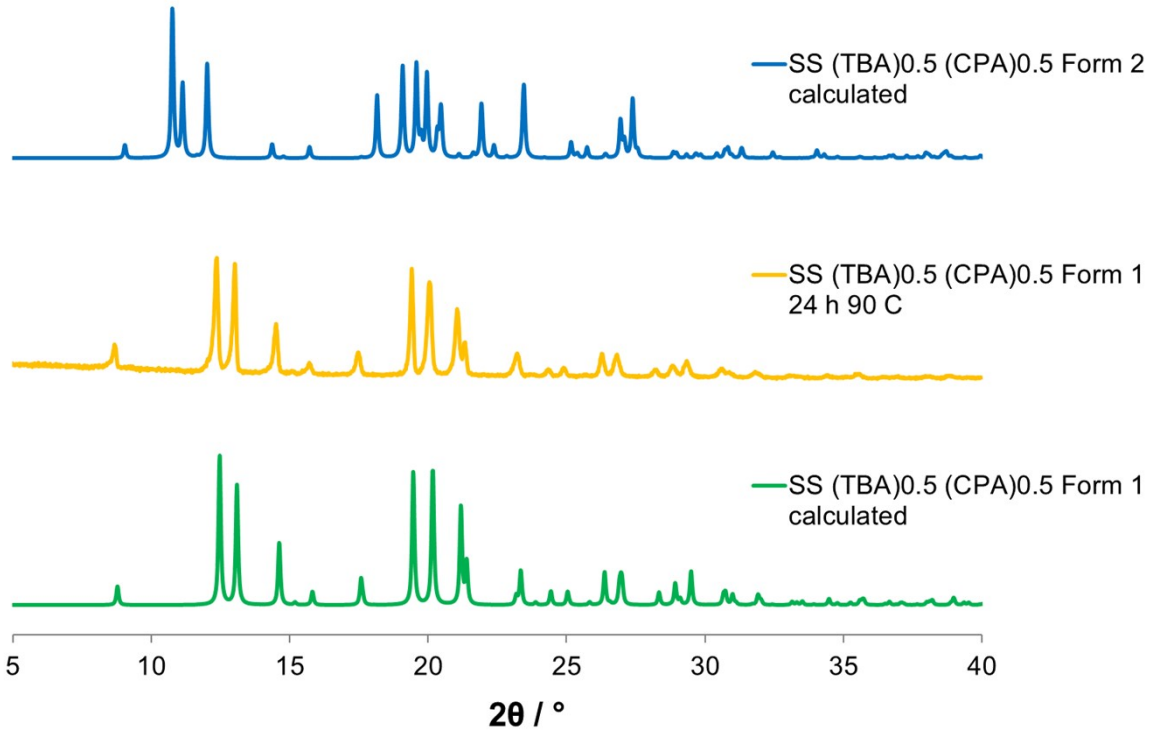

Figure S7: Comparison of the calculated XRPD patterns for SS $(TBA)_{0.5}(CPA)_{0.5}$ Form 1 (green), Form 2 (blue) and the experimental for the powder of SS $(TBA)_{0.5}(CPA)_{0.5}$ Form 1 incubated for 24 h at 90 °C (yellow).

Rietveld Refinement

The structures were refined by the Rietveld method against the structures deposited in the CSD (ZZZPUS02 and BEDMIG for tolbutamide form I^L and chlorpropamide form α respectively).

Table S2. Summary of the Rietveld refinement for the experimental XRPD patterns for the product of the manual liquid assisted grinding of tolbutamide/chlorpropamide mixtures with different stoichiometric ratios; at the bottom the refinement for the experimental XRPD patterns for the product of the grinding of tolbutamide/chlorpropamide mixtures carried out via ball milling (BM) and for the product of the slurry. Estimated standard deviation: on the cell axes is lower than 0.02 Å.

Reagents	Rietveld	Product phase analysis		Composition ZZZPUS02		ZZZPUS02 unit cell parameters			BEDMIG unit cell parameters			Melting Point (°C)
TBA:CPA ratio	R weighted	% ZZZPUS02	% BEDMIG	% TBA	% CPA	*a* (Å)	*b* (Å)	*c* (Å)	*a* (Å)	*b* (Å)	*c* (Å)	
100:0	10.5	100	0	100	0	20.22	7.82	9.07	-	-	-	127
85:15	13.0	99.2	0.8	85.7	14.3	20.22	7.76	9.07	5.32	8.95	26.26	120
70:30	14.3	98.5	1.5	71.1	28.9	20.21	7.70	9.09	5.25	9.08	26.78	114
50:50	16.0	94.7	5.3	52.8	47.2	20.19	7.63	9.11	5.22	9.09	26.65	111
30:70	14.4	78.7	21.3	38.1	61.9	20.11	7.55	9.10	5.24	9.08	26.63	112
15:85	13.0	42.6	57.4	35.2	64.8	20.09	7.53	9.10	5.23	9.08	26.66	117
0:100	14.0	0	100	-	-	-	-	-	5.22	9.08	26.65	129
50:50 (BM)	17.0	99.5	0.5	50.3	49.7	20.13	7.60	9.10	5.19	9.17	26.35	111
30:70 (BM)	14.6	74.2	25.8	40.4	59.6	20.10	7.55	9.11	5.23	9.09	26.66	110
50-50 (slurry)	18.0	99.8	0.2	50.1	49.9	20.15	7.62	9.11	5.29	8.89	27.35	108

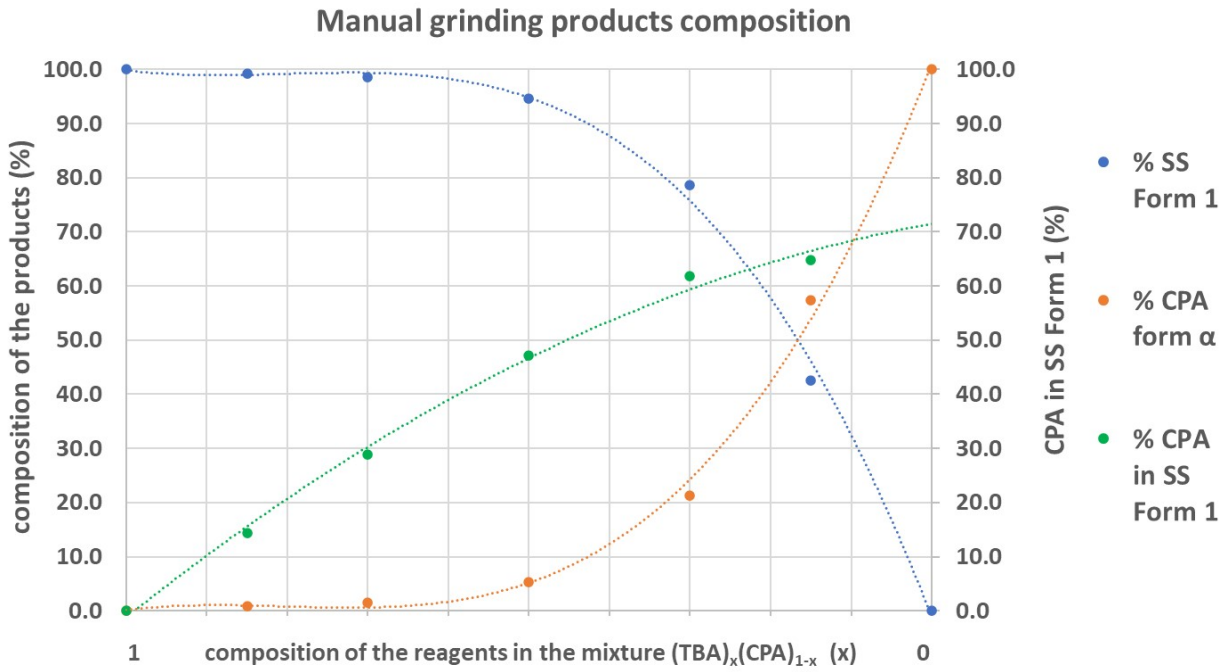

Figure S8. Phase composition for the product of the manual liquid assisted grinding of TBA/CPA mixtures as function of the reagents compositions: percentage of solid solution $(TBA)_x(CPA)_{1-x}$ Form 1 (blue dot line), percentage of BEDMIG (CPA form α, orange dot line) and the percentage of CPA presents in the SS Form 1 (green dot line).

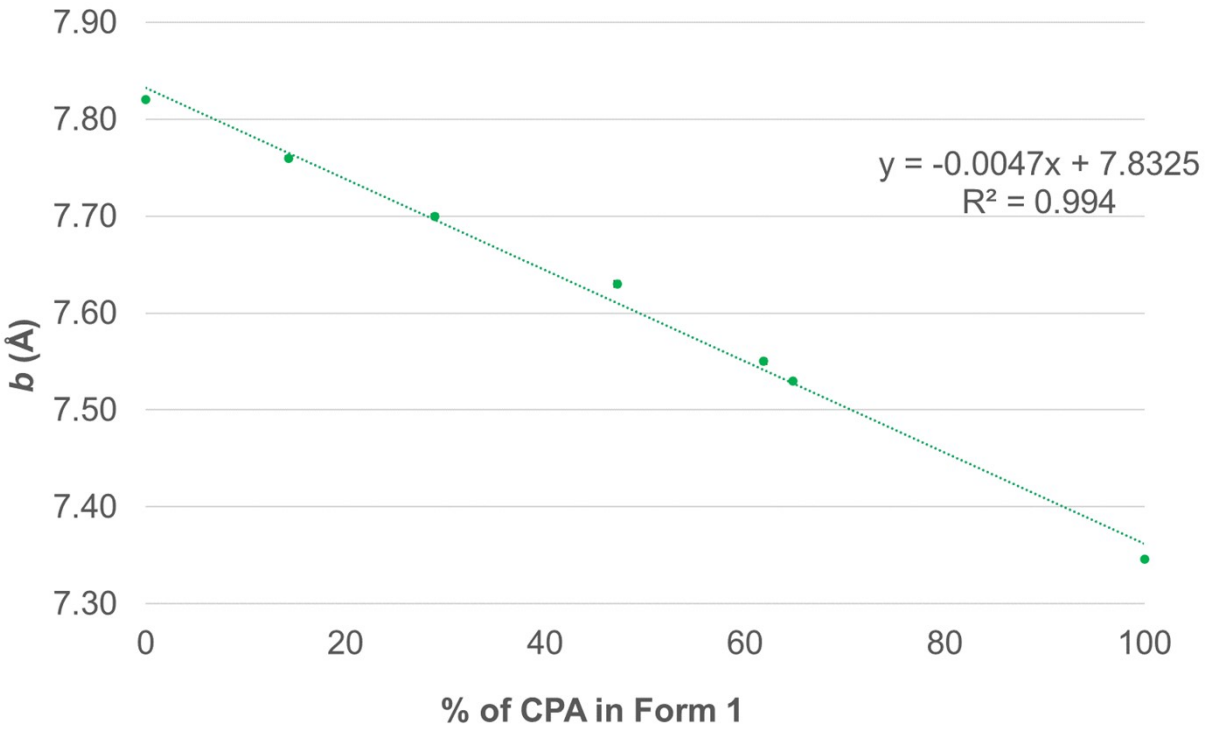

Figure S9. Linear dependence between the *b*-axis dimension and the percentage of CPA presents in the solid solution $(TBA)_x(CPA)_{1-x}$ Form 1.

Single Crystal X-Ray Diffraction

Single crystal X-ray diffraction data for SS $(TBA)_x(CPA)_{1-x}$ Form 1 and SS $(TBA)_x(CPA)_{1-x}$ Form 2 were collected at room temperature with a Bruker D8 Quest diffractometer equipped either with a Cu Kα (λ = 1.54178 Å) radiation or Mo Kα (λ = 0.71073 Å) radiation and Photon 100 detector. The data were integrated with Apex 4. Unit cell parameters for all compounds discussed herein are reported in Table S3, Table S4, Table S5. The structures were solved by the intrinsic phasing methods and refined by least-squares methods against F^2 using SHELXT[1] and SHELXL[2] through the X-SEED interface.[3] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions. The software X-Seed and Mercury were used for graphic representations.[4]

Table S3. Crystal data and details of measurement for SS $(TBA)_x(CPA)_{1-x}$ Form 2; analysis of different crystals taken from the same crystallization vial.

	SS $(TBA)_{0.66}(CPA)_{0.34}$ Form 2	SS $(TBA)_{0.53}(CPA)_{0.47}$ Form 2
Reagent Ratio TBA:CPA	50:50	50:50
C1 occupancy	0.661(15)	0.533(14)
Cl1 occupancy	0.339(15)	0.467(14)
Chemical formula	$C_{11.32}H_{16.31}Cl_{0.34}N_2O_3S$	$C_{11.07}H_{15.66}Cl_{0.47}N_2O_3S$
Mw, g mol^{-1}	272.52	273.35
T / K	296	294
Crystal system	orthorhombic	orthorhombic
Space group	*Pbcn*	*Pbcn*
a / Å	15.2556(11)	15.1745(11)
b / Å	9.3161(7)	9.3155(5)
c / Å	19.5590(15)	19.5240(12)
α / °	90	90
β / °	90	90
γ / °	90	90
V / Å^3	2779.8(4)	2759.9(3)
Z, Z'	8, 1	8, 1
d / g cm^{-3}	1.302	1.316
μ / mm^{-1}	0.299	0.325
Measd reflns	53341	33581
Indep reflns	2546	2530
Reflns with $I > 2\sigma(I)$	1296	1562
R_{int}	0.0951	0.0590
R [$F^2 > 2\sigma(F^2)$]	0.1098	0.0937
wR_2 (F^2)	0.3390	0.3051

Table S4. Crystal data and details of measurement for SS $(TBA)_x(CPA)_{1-x}$ Form 2.

	SS $(TBA)_{0.70}(CPA)_{0.30}$ Form 2	SS $(TBA)_{0.59}(CPA)_{0.41}$ Form 2	SS $(TBA)_{0.30}(CPA)_{0.70}$ Form 2
Reagent Ratio TBA:CPA	70:30	50:50	30:70
C1 occupancy	0.697(16)	0.591(15)	0.304(10)
Cl1 occupancy	0.303(16)	0.409(15)	0.696(10)
Chemical formula	$C_{11.39}H_{16.49}Cl_{0.30}N_2O_3S$	$C_{11.18}H_{15.96}Cl_{0.41}N_2O_3S$	$C_{10.61}H_{14.52}Cl_{0.70}N_2O_3S$
Mw, g mol^{-1}	272.26	272.97	274.79
T / K	297	298	298
Crystal system	orthorhombic	orthorhombic	orthorhombic
Space group	*Pbcn*	*Pbcn*	*Pbcn*
a / Å	15.5366(7)	15.2433(8)	14.9416(4)
b / Å	9.3050(3)	9.3138(5)	9.3109(3)
c / Å	19.6476(8)	19.5618(11)	19.3930(6)
α / °	90	90	90
β / °	90	90	90
γ / °	90	90	90
V / $Å^3$	2840.4(2)	2777.2(3)	2697.95(14)
Z, Z'	8, 1	8, 1	8, 1
d / g cm^{-3}	1.273	1.306	1.353
μ / mm^{-1}	2.577	0.312	3.421
Measd reflns	28137	63177	8156
Indep reflns	2775	2567	2560
Reflns with $I > 2\sigma(I)$	2211	1664	1832
R_{int}	0.0577	0.0640	0.0539
R [$F^2 > 2\sigma(F^2)$]	0.0862	0.1048	0.0763
wR_2 (F^2)	0.2777	0.3244	0.2525

Table S5. Crystal data and details of measurement for SS $(TBA)_x(CPA)_{1-x}$ Form 1.

	SS $(TBA)_{0.46}(CPA)_{0.54}$ Form 1
Reagent Ratio TBA:CPA	50:50
C1 occupancy	0.456 (10)
Cl1 occupancy	0.544 (10)
Chemical formula	$C_{10.91}H_{15.28}Cl_{0.54}N_2O_3S$
Mw, g mol^{-1}	273.86
T / K	298
Crystal system	orthorhombic
Space group	*Pna*2_1
a / Å	20.1171(17)
b / Å	7.5762(7)
c / Å	9.1129(7)
α / °	90
β / °	90
γ / °	90
V / $Å^3$	1388.9(2)
Z, Z'	4, 1
d / g cm^{-3}	1.310
μ / mm^{-1}	0.338
Measd reflns	32127
Indep reflns	2549
Reflns with $I > 2\sigma(I)$	2218
R_{int}	0.0515
R [$F^2 > 2\sigma(F^2)$]	0.0341
wR_2 (F^2)	0.0926

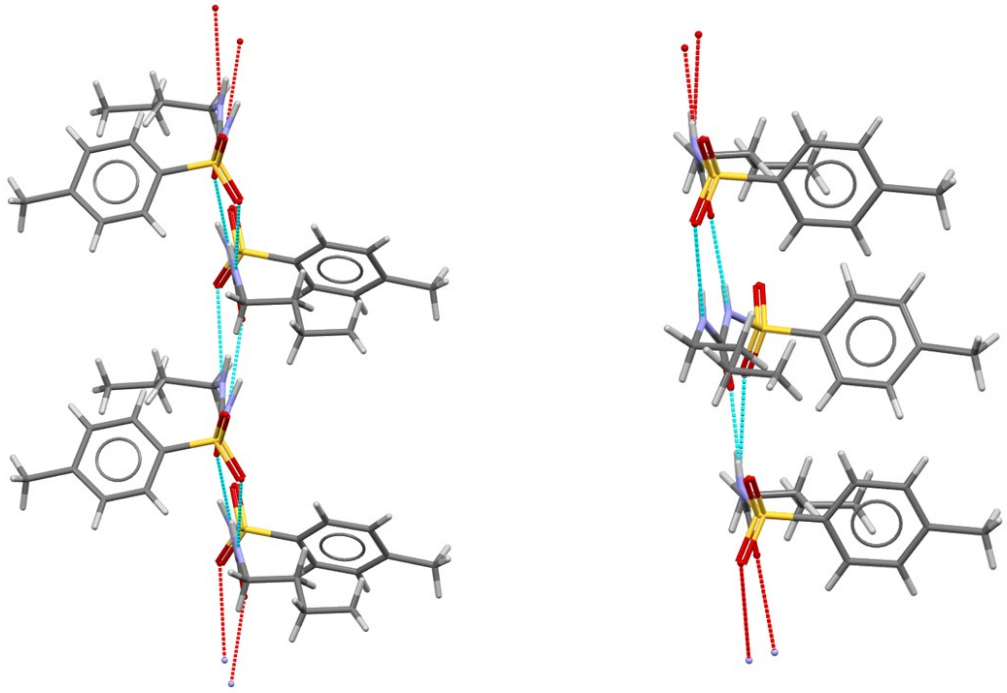

Figure S10. Representation of a fragment of the infinite hydrogen-bonded ribbons in the crystal structure of SS Form 1 (left) and Form 2 (right).

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) measurements were performed on TA DSC Q-2000 under nitrogen stream (50 mL/min) using hermetically closed pans, 4 to 6 mg of ground powder, between room temperature and 200 °C, at 5 °C/min heating rate.

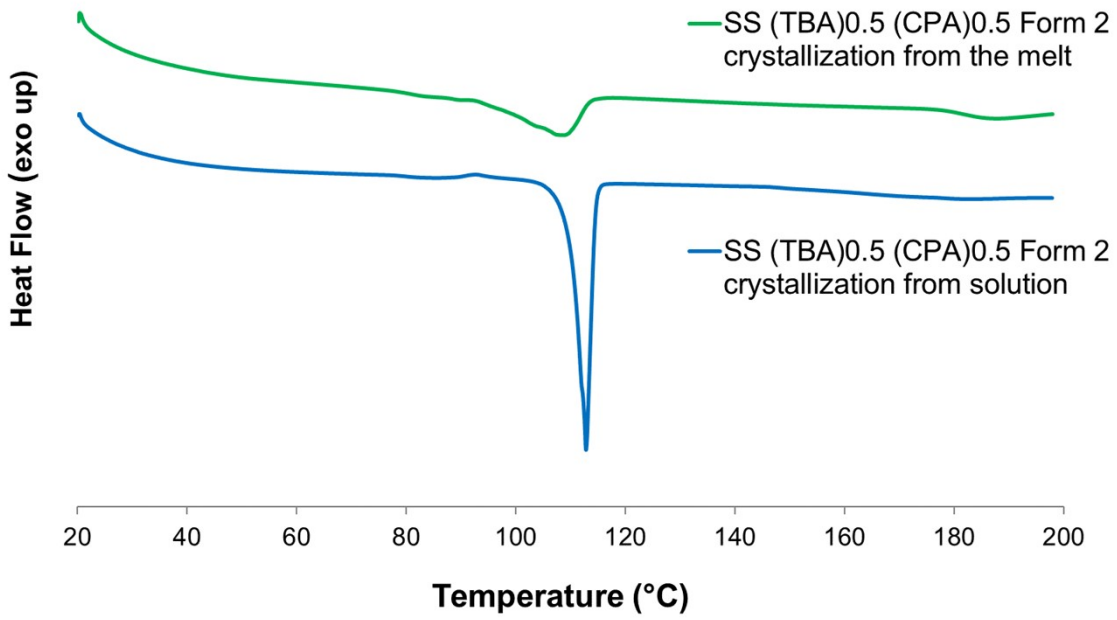

Figure S11. Superimposition of DSC thermograms of SS $(TBA)_{0.5}(CPA)_{0.5}$ Form 2 obtained from the crystallization by slow solvent evaporation (blue) and from the crystallization from the melt (green).

Powder dissolution test

Powder dissolution measurements were conducted in a Grant GD100 stirred water bath using stirring speed of 200 rpm at 37.5 °C. Accurately weighed powders of SS $(TBA)_{0.5}(CPA)_{0.5}$ Form 1, Form 2, TBA, CPA and the 1:1 physical mixture (40 mg) were added to 1000 mL of pH 1.2 hydrochloric acid buffer (n = 3). To minimize the size effect on the dissolution results, samples were sieved between 80-106 µm. Sampling was performed at intervals of 5, 10, 15, 20, 30, 40, 50, 60, 80, 100, 120, 180 minutes. Withdrawn suspensions were filtered with 0.45 µm syringe filters prior the injection into the HPLC spectrophotometer. The dissolution aliquots were analysed using Shimadzu (LC-20A) HPLC instrument with the Gemini® C18 (250 x 4.6 mm 5 µm) column. The wavelength was set to 229 nm; an injection volume was 5 µL with a flow rate of 0.5 mL/min; the oven was set at 40 °C. The isocratic mobile phase of 50:50 (0.1% orthophosphoric acid in acetonitrile: 0.1% orthophosphoric acid in H_2O).

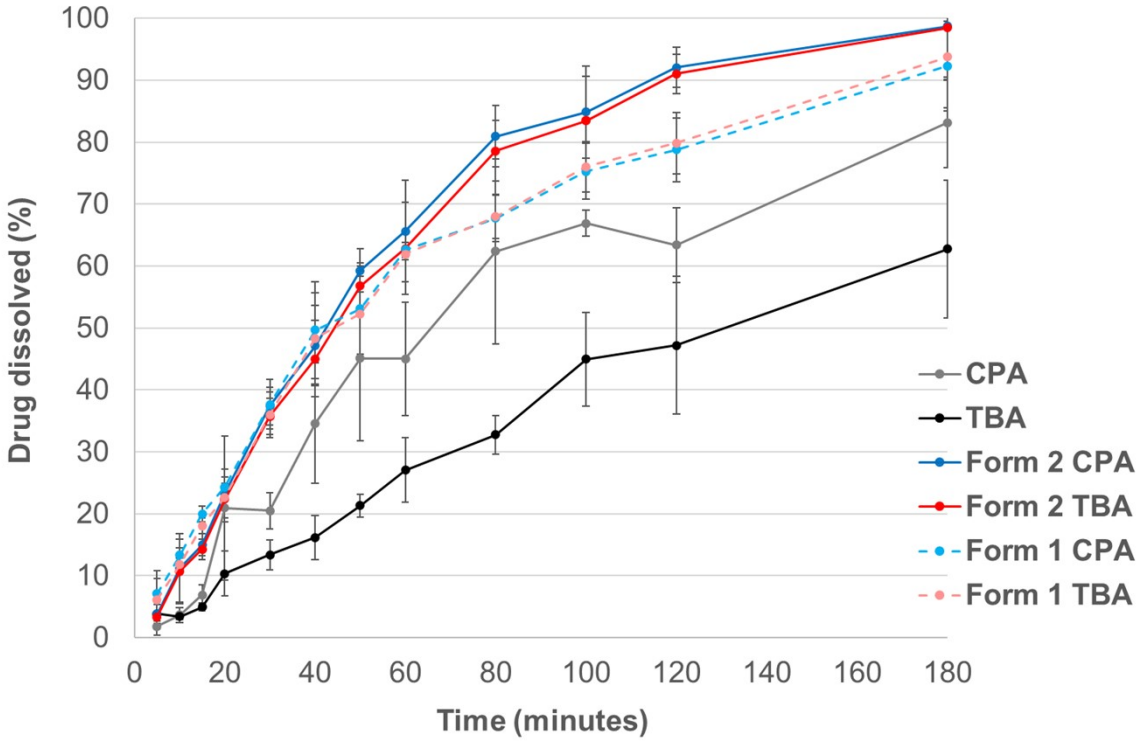

Figure S12. Powder dissolution experiments performed for SS ($TBA_{0.5}CPA_{0.5}$) Form 1 (TBA: pink dashed line, CPA: light blue dashed line), SS ($TBA_{0.5}CPA_{0.5}$) Form 2 (TBA: red line, CPA: blue line) and the pure molecules (TBA: black line, CPA: grey line). The powder dissolution experiment was conducted in 1000 ml of pH 1.2 hydrochloric acid buffer using stirring speed of 200 rpm at 37.5 °C.

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