Supporting Information

Spherical crystallization of carbamazepine/saccharin co-crystals: selective agglomeration and purification through surface interactions

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SI.1 Calculated PXRD patterns of carbamazepine Form III, carbamazepine dihydrate, saccharin, carbamazepine/saccharin co-crystal Form I and Form II.

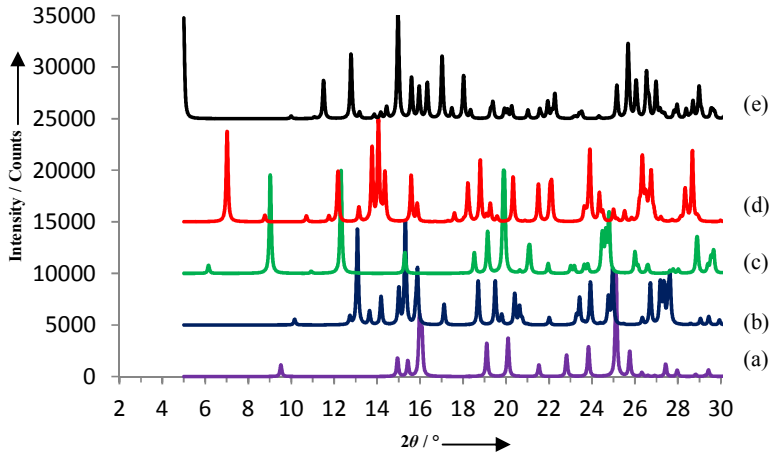


Fig. 1 Calculated PXRD pattern of a) saccharin, b) carbamazepine Form III, c) carbamazepine dihydrate, carbamazepine/saccharin co-crystal d) Form I and e) Form II.

PXRD Method:

XRPD pattern of all samples were recorded using Bruker D8 diffractometer, X-ray wavelength - 0.154 nm, source – Cu, Voltage – 40kV and filament emission 40 mA. All samples were scanned from 2 to 30° 2θ with scanning speed of 0.01° step width

SI.2 PXRD patterns of crystal forms obtained during crystallization experiment performed without addition of bridging liquids.

1) Crystal forms obtained when methanol used as a good solvent in reverse anti-solvent addition experiments

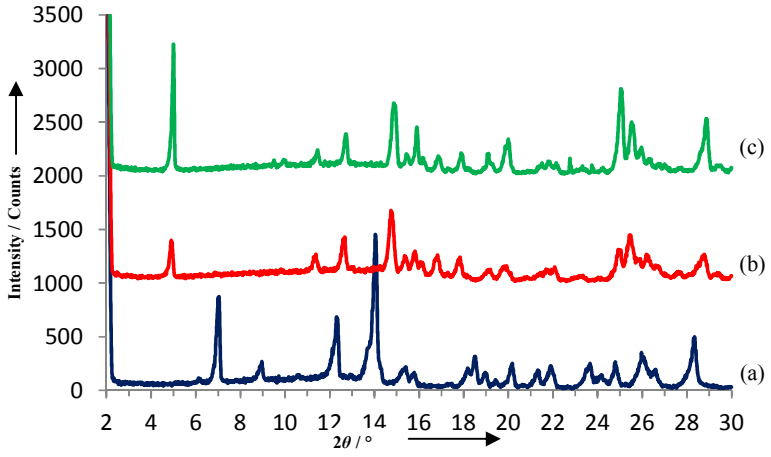


Fig. 1 PXRD pattern of precipitate obtained from methanol solution containing CBZ and SAC in (a) 1:1, (b) 1:1.5 and (c) 1:2 molar ratio

(a) --- CBZ/SAC 1:1 Form I co-crystal with CBZ dihydrate
(b) --- CBZ/SAC 1:1 Form II co-crystal
(c) --- CBZ/SAC 1:1 Form II co-crystal

2) Crystal forms obtained when ethanol used as a good solvent in reverse ant-solvent addition experiments

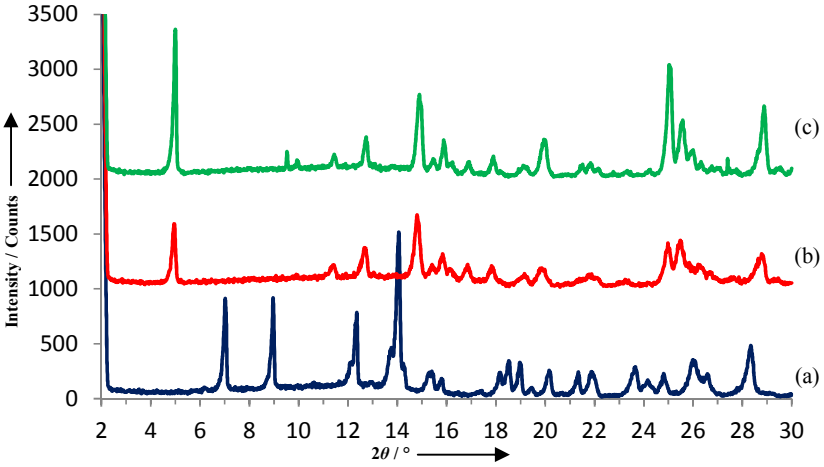


Fig. 2 PXRD patterns of crystal forms obtained from ethanol solution containing CBZ and SAC in (a) 1:1, (b) 1:1.5 and (c) 1:2 molar ratio

(a) --- CBZ/SAC 1:1 co-crystal Form I with CBZ dihydrate
(b) --- CBZ/SAC 1:1 co-crystal Form II
(c) --- CBZ/SAC 1:1 co-crystal Form II

SI.3 PXRD summary table used for developing phase diagram.

CBZ/SAC ratio	Good Solvents	Good solvent : Bad solvent			
		1:9	2:9	3:9	4:9
1:1	DMSO	FI + CBZ-D	F I + CBZ-D	FI + CBZ-D	CBZ-D
	Methanol	NA	F I	FI + CBZ-D	FI + CBZ-D
	Ethanol	NA	F I	FI + CBZ-D	CBZ-D + FI
1:1.5	DMSO	FII	F I	FI	CBZ-D
	Methanol	NA	F II	FI	FI
	Ethanol	NA	F II	FI	FI
1:2	DMSO	FII	F II	F I	F I + CBZ-D
	Methanol	NA	F II	F II	F II
	Ethanol	NA	F II	FII + FI	FII + FI

SI.4 HPLC analysis method and data for the determination of solubility of CBZ and SAC in different solvent systems and quantification of unreacted SAC present in the final product (crystallisation batches both with and without addition of bridging liquid)

1) HPLC method details

HPLC analysis of all samples was performed on Waters e-2695 separation module integrated with degasser and photodiode array detector (PDA-2998). The obtained chromatograms were analysed using Empower 3 software. The details of column and composition of mobile phase used for analysis of carbamazepine and saccharin are mentioned in the Table 1 along with process parameters.

Table 1 Details of HPLC method

Drug	Column	Mobile phase	Flow rate (ml/min)	Injection volume (µL)	λ_{max} (nm)	Calibration curve range (µg/ml)	Retention time (min.)
Saccharin	Waters symmetry C18 column, 5 µm, and 4.6 × 250 mm	70:30 (Water + 0.1 % TFAA: Acetonitrile + 0.1% TFAA) TFAA: Trifluroacetic acid	1	10	280	1-10	6
Carbamazepine	Hypersil Shandon C18 column, 5µm, and 4.6 × 100mm	70:30 (Water + 0.1 % TFAA: Acetonitrile + 0.1% TFAA)	1	10	280	1-10	3.5

2) Solubility study

The solubility of carbamazepine and saccharin in all good solvents (DMSO, methanol and ethanol), bad solvent (water) and bridging liquids (benzene, DCM and ethyl acetate) was performed at room temperature. Also the solubility of CBZ/SAC co-crystal Form I and Form II were measured in bridging liquids. The amount of each solvent used for solubility study was kept constant to 5 ml. The solvent was stirred at 600 rpm and components were added separately and slowly to the solvent. Addition was stopped upon the observation of precipitate in the solvent and stirring was continued for further 30 min. Then these mixtures were filtered through 0.45µ nylon syringe filter. Filtrate was diluted and used for HPLC analysis to estimate the solubility of carbamazepine and saccharin in the mentioned solvents. The solubility data was provided in the main manuscript.

3) Solubility study of CBZ/SAC co-crystal Form I and Form II in presence of saccharin

The solubility of carbamazepine, CBZ/SAC co-crystal Form I and Form II was measured in good solvents as well as in the mixture of good (2 parts) and bad solvent (9 parts). Three different levels of saccharin concentrations were used depending on its solubility in the solvent system see below table.

Solvent system	Saccharin levels (M)		
Methanol	0.12	0.18	0.22
Methanol + water	0.006	0.010	0.015
Ethanol	0.11	0.13	0.15
Ethanol + water	0.006	0.010	0.015
DMSO	1.5	2.5	3.5
DMSO + water	0.006	0.010	0.015

The amount of each solvent used for solubility study was kept constant to 5 ml. The solvent was stirred at 600 rpm and carbamazepine and saccharin was added separately and slowly to the solvent. Addition was stopped upon the observation of precipitate in the solvent and stirring was continued for further 6 hrs. Then these mixtures were filtered through 0.45µ nylon syringe filter. Filtrate was diluted and used for HPLC analysis to estimate the solubility of carbamazepine and saccharin in the mentioned solvents.

Below figures represents the drop in solubility of co-crystals FI and FII during anti-solvent co-crystallization experiments.

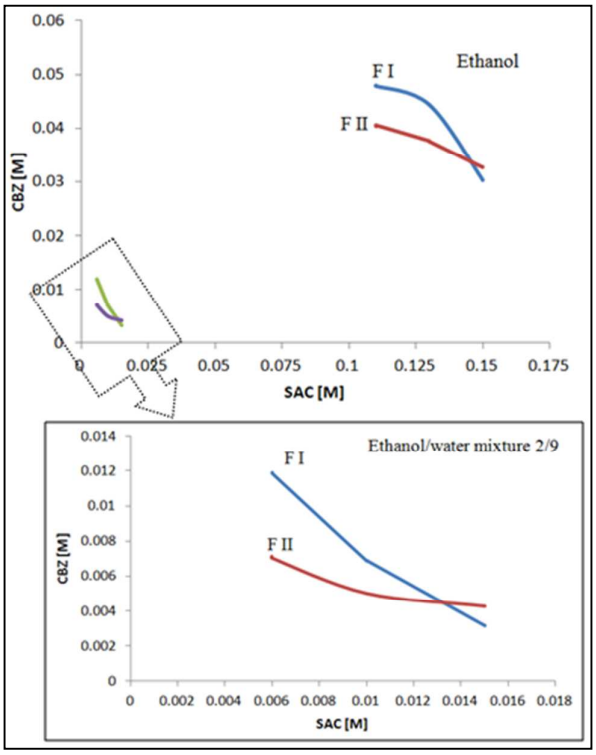


Figure 1. Phase solubility shift of FI and FII during anti-solvent crystallization in ethanol/water (2/9) system.

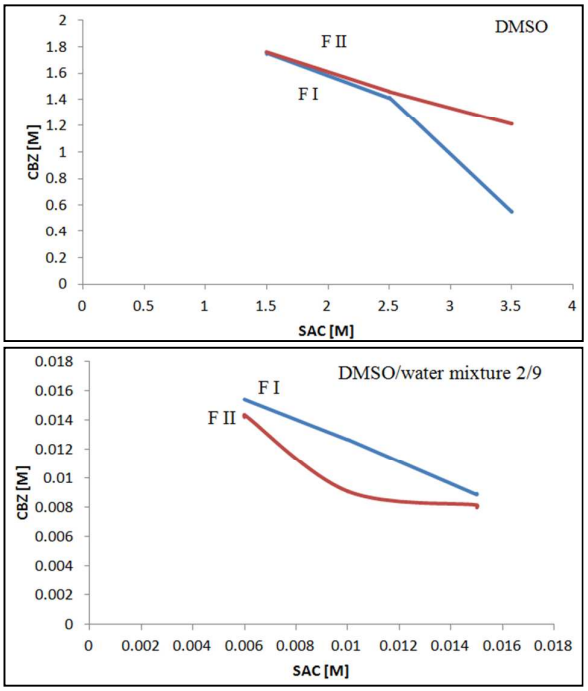


Figure 1. Phase solubility shift of FI and FII during anti-solvent crystallization in DMSO/water (2/9) system.

4) Quantification of unreacted saccharin in the final product (i.e. crystallization batches both with and without addition of bridging liquid)

20 mg of the final product obtained from crystallization batches taken without addition of bridging liquid and with the addition of bridging liquid (spherical crystallization batches) was dissolved in 2 ml of methanol. This solution was filtered through 0.45µ nylon syringe filter and used for HPLC analysis with suitable dilution. Table 2 represent the moles of carbamazepine and saccharin present in the final product.

Table 2 Amount of carbamazepine and saccharin present in the final product

Good solvent	Bridging liquid	Carbamazepine (Mole)	Saccharin (Mole)
DMSO	*No bridging liquid*	0.106319	0.122271
	Benzene	0.08569	0.08908
	Ethyl acetate	0.08895	0.10327
	DCM	0.09115	0.10441
Methanol	*No bridging liquid*	0.097323	0.151856
	Benzene	0.09637	0.09675
	Ethyl acetate	0.09134	0.12272
	DCM	0.09558	0.09153
Ethanol	*No bridging liquid*	0.098603	0.136356
	Benzene	0.09244	0.09221
	Ethyl acetate	0.09233	0.09964
	DCM	0.0944	0.09758

SI.5 PXRD patterns of crystal forms obtained during spherical crystallization experiment performed with addition of bridging liquids.

1) **Spherical crystallization experiments of CBZ/SAC co-crystals performed using ethanol as good solvent with three bridging liquids.**

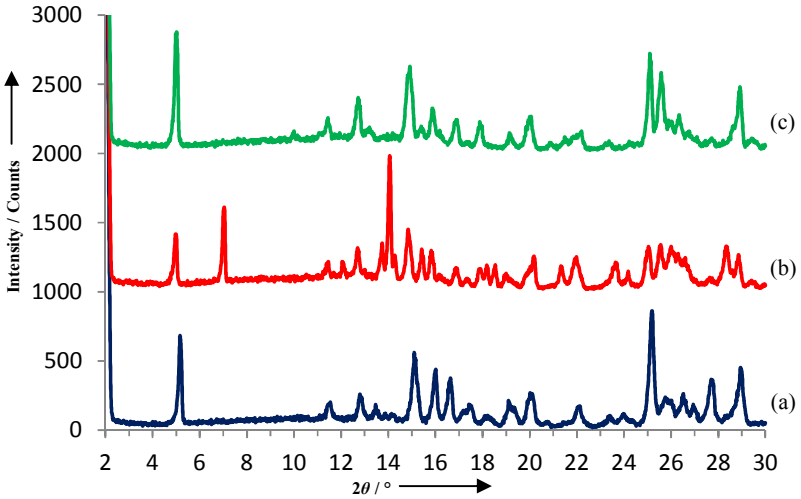


Figure 1 PXRD patterns of crystal forms of spherical agglomerates of CBZ/SAC co-crystals obtained from ethanol solution containing CBZ and SAC in 1:2 ratio in water and agglomeration with (a) BEN, (b) DCM and (c) EA

(a) --- CBZ/SAC 1:1 co-crystal Form II
(b) --- CBZ/SAC 1:1 co-crystal Form I major and Form II minor
(c) --- CBZ/SAC 1:1 co-crystal Form II

2) **Spherical crystallization experiments of CBZ/SAC co-crystals performed using ethanol as good solvent with three bridging liquids.**

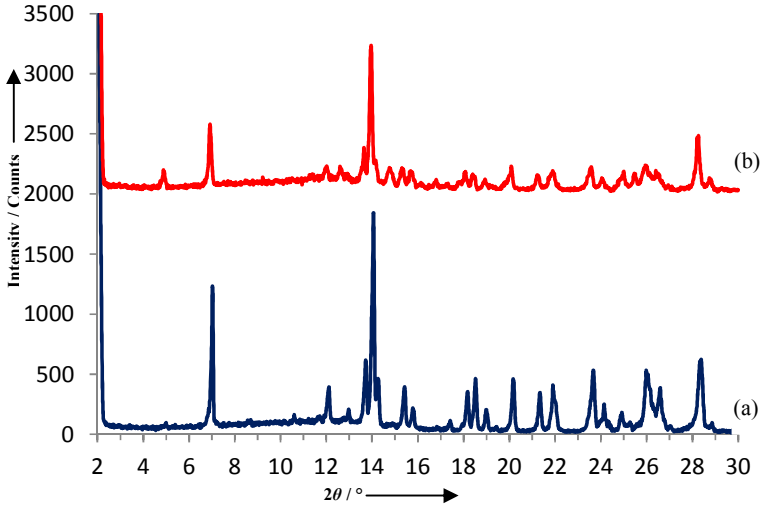


Figure 2 PXRD patterns of crystal forms of spherical agglomerates of CBZ/SAC co-crystals obtained from DMSO solution containing CBZ and SAC in 1:2 ratio in water and agglomeration with (a) DCM and (b) EA

(a) --- CBZ/SAC 1:1 co-crystal Form I
(b) --- CBZ/SAC 1:1 co-crystal Form I major and Form II minor

3) Spherical crystallization experiments of CBZ/SAC co-crystals performed using DMSO as good solvent and addition of bridging liquids after 10 min.

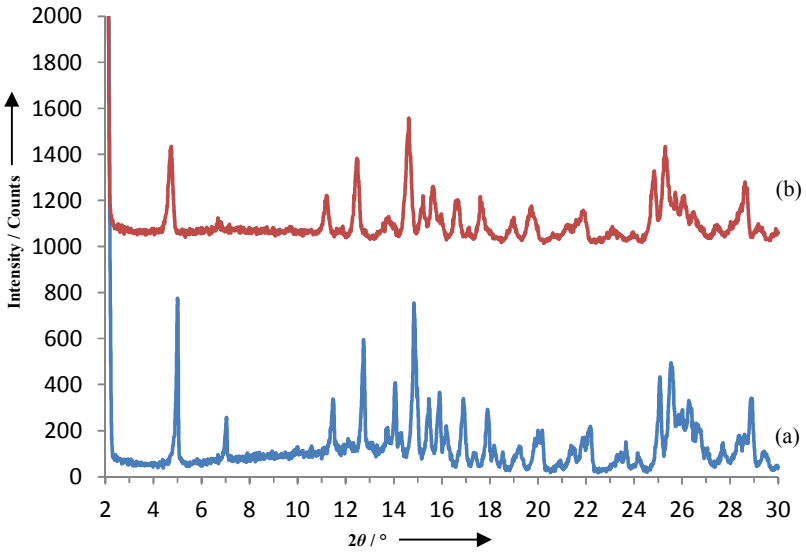


Figure 3 PXRD patterns of crystal forms of spherical agglomerates of CBZ/SAC co-crystals obtained from DMSO solution containing CBZ and SAC in 1:2 ratio in water and agglomeration after 10 minutes with (a) DCM and (b) EA

(a) --- CBZ/SAC 1:1 co-crystal Form II major and Form I minor
(b) --- CBZ/SAC 1:1 co-crystal Form II

SI. 5 Calculations on the Carbamazepine Saccharin Co-crystal

Crystal Structure Data

Crystal structures of carbamazepine, saccharin and the carbamazepine-saccharin co-crystal were obtained from the Cambridge Crystallographic Database [1]. Carbamazepine has 4 polymorphs with crystal structures in the database. Calculations were performed on the *P*-monoclinic, Form III polymorph [2] with CSD identifier CBMZPN10 [3]. The experimental crystal structure for saccharin used as the starting point for calculations has the CSD identifier SCCHRN and belongs to the $P2_1/n$ space group [4]. Calculations were also performed starting from the experimental triclinic P-1 Form I [5] and the monoclinic $C2/c$ Form II [6] carbamazepine-saccharin co-crystals with CSD codes UNEZAO and UNEZAO01 respectively.

Methods

Materials Studio 4.1[7] was used to perform calculations of the optimised unit cells using a variety of force fields and atomic charge models. The force field and charge model which gave the least deviation between the experimental starting crystal structure and the final optimised structure was used to perform the other calculations reported here. Using the Morphology module, calculations of the growth morphology for all three crystals were performed by calculating the attachment energies of all the low index surfaces of each crystal. The surfaces with the lowest energies were used to explore their interaction with a variety of sorbent molecules including; benzene, dimethylsulphoxide (DMSO), dichloromethane (DCM), ethanol, methanol, ethylacetate and water. The Sorption module was used to introduce sorbent into a slit whose top and bottom surfaces were composed of the surface of interest. The width of the slit between the surfaces was chosen to be 15 Å and the thickness of the slab of crystal was chosen between 15 and 20 Å depending on the crystal. Several sorption calculations were carried out for each sorbent; a constant loading of 10 molecules in the slit and a constant partial pressure of 10 kPa of sorbent molecules.

Results

Tables 1, 2, 3 and 4 shows a comparison of unit cells calculated with a variety force fields and charge models with experiment for the three crystal structures CBMZPN10, SCCHRN, UNEZAO and UNEZAO01 respectively.

Table 3: Percentage fractional deviation of the optimised unit cells of carbamazepine from experiment

Carbamazepine	a	b	c	β
Experiment (Å and °)	7.537	11.156	13.912	92.86
Universal FF, Gasteiger charges (%)	10.1	0.9	-8.1	-0.6
Universal FF, QEQ charges (%)	1.8	0.8	0.6	1.3
Dreiding FF, QEQ charges (%)	2.8	-2.0	-2.3	1.3
Dreiding FF, Gasteiger charges (%)	3.7	-1.3	-1.9	1.1
CVFF, FF assigned (%)	4.3	1.0	-4.4	2.5
CVFF, Gasteiger charges (%)	4.4	1.5	-4.2	2.8
CVFF, QEQ charges (%)	4.1	0.2	-4.5	1.3
PCFF, FF assigned charges (%)	5.9	-4.4	-3.7	2.3
PCFF, QEQ charges (%)	5.3	-4.5	-3.7	1.9
PCFF, Gasteiger charges (%)	7.2	-3.1	-4.1	1.8

Table 4: Percentage fractional deviation of the optimised unit cells of saccharin from experiment

Saccharin	a	b	c	β
Experiment (Å and °)	9.563	6.913	11.822	103.85
Universal FF, Gasteiger charges (%)	19.1	0.6	-15.7	0.3
Universal FF, QEQ charges (%)	5.4	-0.1	-6.5	0.0
Dreiding FF, QEQ charges (%)	-4.2	-2.0	3.0	2.7
Dreiding FF, Gasteiger charges (%)	1.7	-0.4	3.2	3.7
CVFF, FF assigned (%)	17.8	-4.2	-9.5	2.4
CVFF, Gasteiger charges (%)	21.0	-4.5	-12.4	2.5
CVFF, QEQ charges (%)	10.0	-4.3	-5.8	1.5
PCFF, FF assigned charges (%)	4.0	-1.1	-4.2	-1.0
PCFF, QEQ charges (%)	5.2	-3.7	-8.0	-0.7
PCFF, Gasteiger charges (%)	18.5	-2.7	-15.6	-0.4

Table 5: Percentage fractional deviation of the optimised unit cells of carbamazepine-saccharin co-crystal Form I from experiment

Carbamazepine Saccharin Form I	a	b	c	α	β	γ
Experiment (Å and °)	7.514	10.4538	12.6826	83.642	85.697	75.411
Universal FF, Gasteiger charges (%)	0.2	4.1	-0.6	-2.6	3.8	3.3
Universal FF, QEQ charges (%)	-3.2	4.9	0.0	-2.1	-1.5	1.8
Dreiding FF, QEQ charges (%)	-3.1	3.5	1.1	-1.1	-0.5	-0.7
Dreiding FF, Gasteiger charges (%)	0.7	-0.4	2.9	0.4	1.3	0.6
CVFF, FF assigned (%)	-0.4	-0.4	3.4	-2.6	-2.9	-1.9
CVFF, Gasteiger charges (%)	0.3	-0.9	3.4	-2.8	-3.1	-1.4
CVFF, QEQ charges (%)	-2.1	2.0	1.4	-4.3	-2.9	-1.9
PCFF, FF assigned charges (%)	-2.4	-1.7	2.9	-3.7	-1.8	3.6
PCFF, QEQ charges (%)	-6.1	1.4	2.1	-4.4	-2.3	2.0
PCFF, Gasteiger charges (%)	-2.7	-1.6	3.9	-1.3	-0.8	1.9

Table 6: Percentage fractional deviation of the optimised unit cells of carbamazepine-saccharin co-crystal Form II from experiment

Carbamazepine Saccharin Form II	a	b	c	β
Experiment (Å and °)	35.7188	6.8367	16.1114	98.026
Universal FF, Gasteiger charges (%)	1.3	5.1	-0.4	-2.3
Universal FF, QEQ charges (%)	4.7	0.8	-2.2	0.2
Dreiding FF, QEQ charges (%)	1.6	0.8	-1.4	0.3
Dreiding FF, Gasteiger charges (%)	2.6	1.9	-0.6	1.1
CVFF, FF assigned (%)	-6.1	5.2	5.1	0.5
CVFF, Gasteiger charges (%)	-5.6	4.9	5.0	-0.2
CVFF, QEQ charges (%)	0.9	2.9	-1.5	0.0
PCFF, FF assigned charges (%)	-6.0	6.9	2.2	-3.9
PCFF, QEQ charges (%)	0.5	3.9	-3.9	1.0
PCFF, Gasteiger charges (%)	-2.3	5.8	0.7	-0.7

Table 7: The square root of the mean sum of fractional deviations squared for each crystal and their average, expressed as a percentage

	Carbamazepine	Saccharin	Co-crystal I	Co-crystal II	Average
Universal FF with Gasteiger charges	6.50	12.36	2.88	2.87	6.15
Universal FF with QEQ charges	1.23	4.21	2.72	2.63	2.70
Dreiding FF with QEQ charges	2.18	3.11	2.05	1.13	2.12
Dreiding FF with Gasteiger charges	2.25	2.62	1.39	1.71	1.99
CVFF with FF assigned	3.37	10.38	2.26	4.74	5.19
CVFF with Gasteiger charges	3.45	12.48	2.31	4.48	5.68
CVFF with QEQ charges	3.10	6.19	2.61	1.68	3.40
PCFF with FF assigned charges	4.26	3.00	2.83	5.09	3.80
PCFF with QEQ charges	4.08	5.14	3.45	2.83	3.88
PCFF with Gasteiger charges	4.54	12.21	2.27	3.15	5.54

Table 5 summarises the deviations from experiment found for each crystal, force field and charge model. The Dreiding force field with Gasteiger charges shows the lowest average deviation from experiment. This force field also shows the smallest deviation from experiment for the crystals of saccharin and the cocrystal and the second smallest for the crystal of carbamazepine. All further calculations were performed with the Dreiding force field with Gasteiger charges.

The crystal morphology was for each crystal was calculated using the Morphology module of Materials Studio. Attachment energies were calculated using the Dreiding force field with Gasteiger charges and the resulting energies were used to determine the likely growth morphologies of the crystal, which are shown in Figures 1, 2 and 3 show the predicted growth morphologies of the

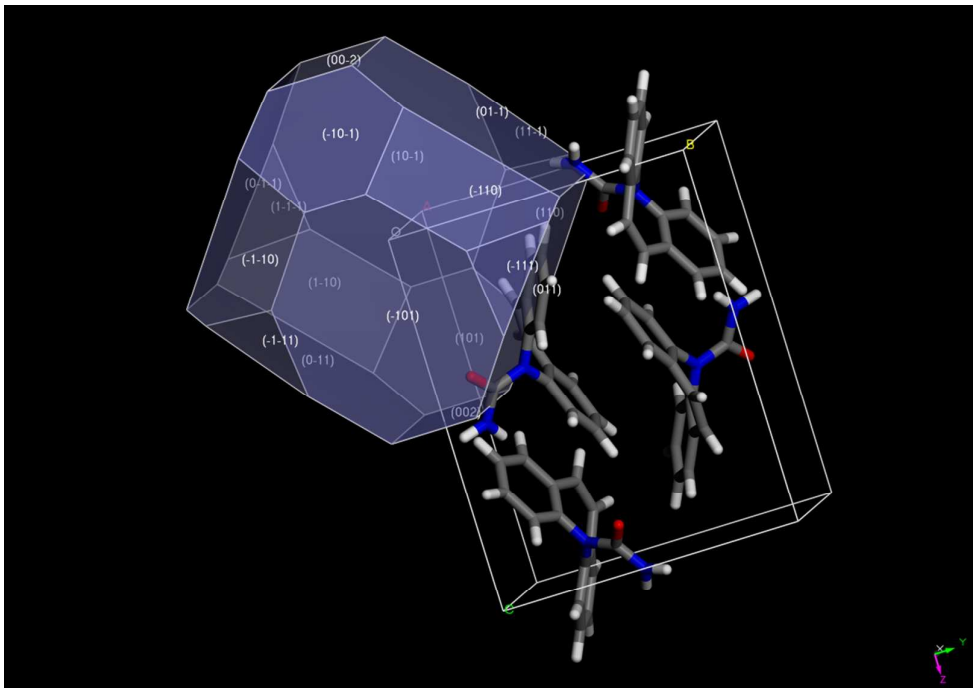


Figure 1: Calculated growth morphology of Form III of carbamazepine

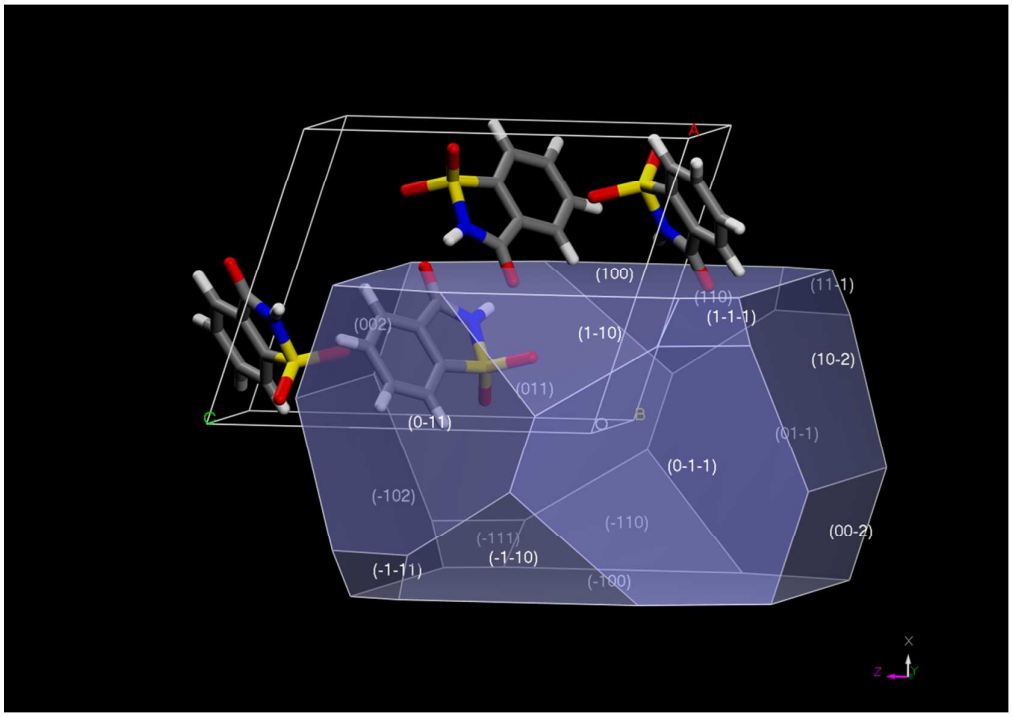


Figure 2: Calculated growth morphology of saccharin

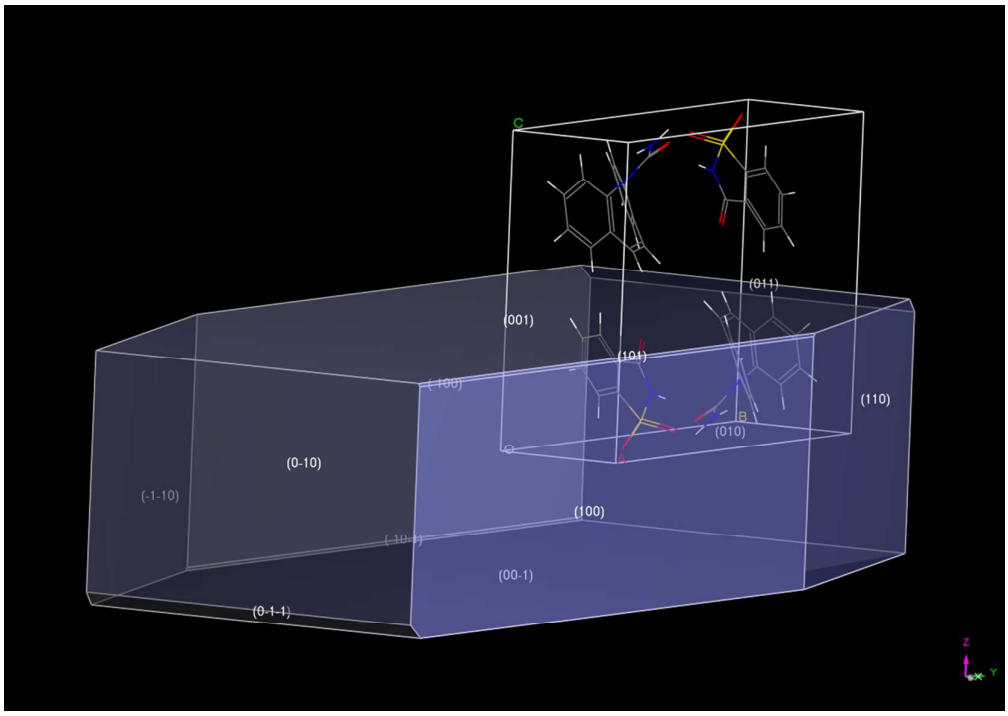


Figure 3: Calculated growth morphology of Form I of the carbamazepine-saccharin co-crystal

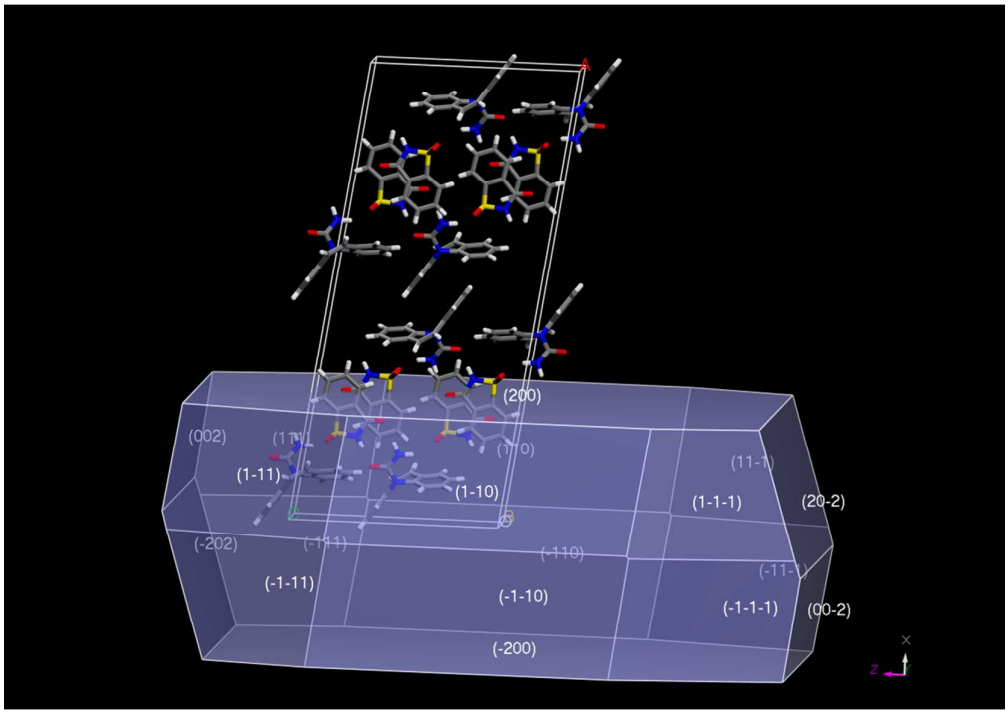


Figure 4: Calculated growth morphology of Form II of the carbamazepine-saccharin co-crystal

Based on the calculated growth morphologies the dominant surface was determined for each crystal. For carbamazepine, saccharin and the Forms I and II co-crystals the {011}, {100}, {001} and {200} families of surfaces were calculated to provide 49%, 41%, 56% and 53% of the surface area of the crystal respectively and were therefore subjected to further study. The make-up of each surface can be seen in Figure 5.

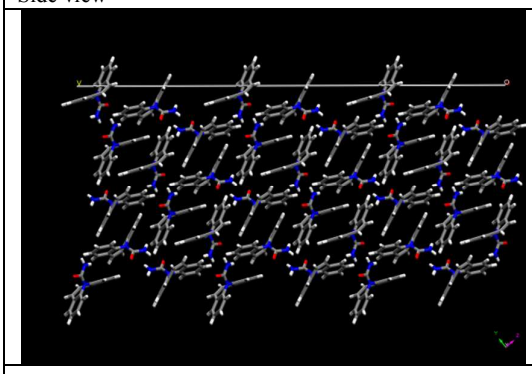
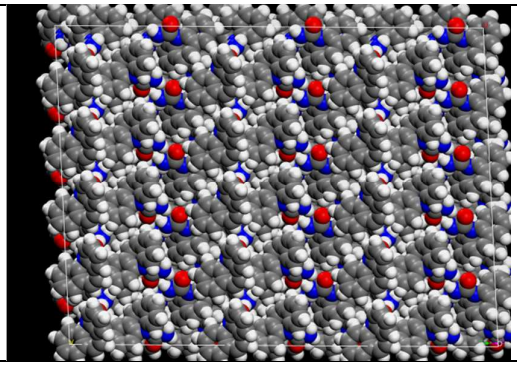
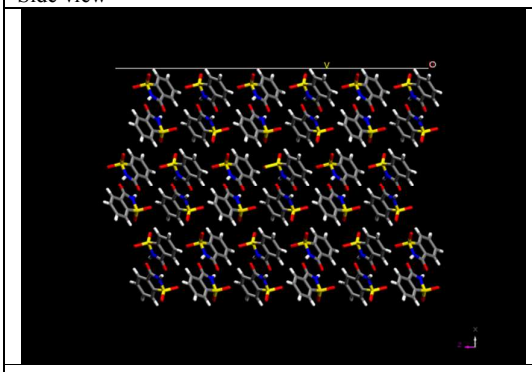
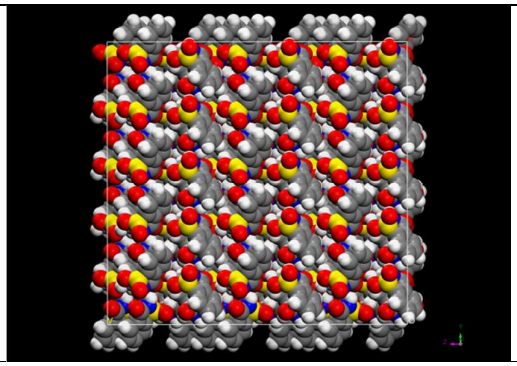
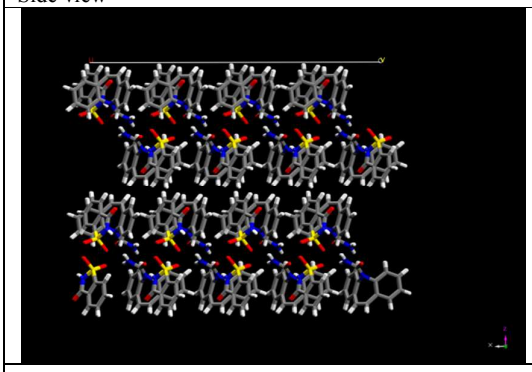
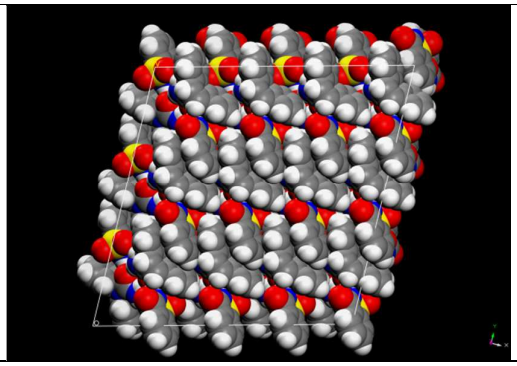
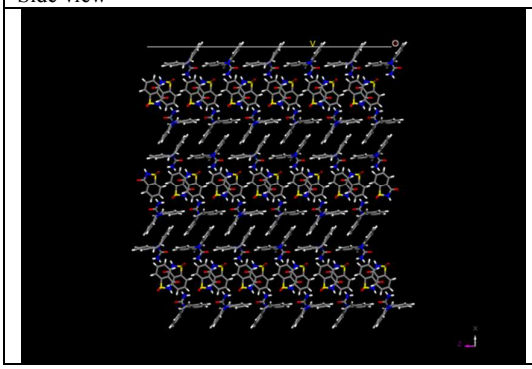
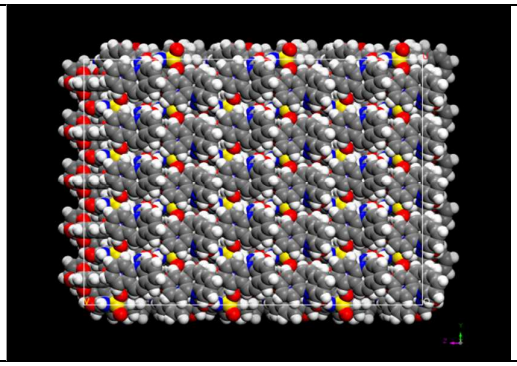
Carbamazepine (011) surface Side view		Overview
		
Saccharin (100) surface Side view		Overview
		
Co-crystal Form I (001) surface Side view		Overview
		
Co-crystal Form II (200) surface Side view		Overview
		

Figure 5: The important surfaces of carbamazepine, saccharin and the co-crystal

Both the (100) and (001) surfaces of saccharin and the co-crystal have a low energy because there is a cleaving place than can be chosen which does not break any hydrogen bonding between the sheets of molecules which lie parallel with the surface. In the case of the co-crystal the surface is dominated by the ring CH groups of molecules. Saccharin also has some CH groups on the surface, but there is also oxygens on the surface which come from the sulphone group in the molecule. The (011) surface of carbamazepine is more complex with aromatic units on the surface, along with amide groups.

The crystal surface of the Form II co-crystal is quite different to that of Form I, being similar to that found in carbamazepine. The cleaving plane in the Form II co-crystal and in carbamazepine breaks the alternating face to face and edge to face interactions between the phenyl groups

Constant load sorption calculations were carried out by introducing 10 gas phase sorbent molecules into a vacuum slit between slab whose surfaces represented those of interest and the resulting isosteric heats of adsorption are shown in Table 6.

Table 8: Isosteric heats of adsorption for constant loading (kcal/mol)

Sorbent	Carbamazepine (011)	Saccharin (100)	Co-crystal I (001)	Co-crystal II (200)
DCM	7.1	5.1	4.6	7.5
Water	1.6	1.5	1.1	1.3
Benzene	12.7	7.4	6.8	11.4
DMSO	9.3	12.2	9.8	12.4
Ethanol	5.2	4.4	3.5	5.8
Methanol	4.6	3.3	2.4	4.0
Ethyl Acetate	11.9	7.3	6.6	9.9

DMSO has the strongest adsorption energy for saccharin and the co-crystal but in the case of carbamazepine the strongest adsorption energy comes from benzene. Water has the weakest interactions with all surfaces and DCM shows stronger adsorption than water but less than benzene and DMSO. As suggested by the structural similarities of the surfaces, the energies of adsorption for the carbamazepine (011) surface and the co-crystal Form II (200) surface are very similar. Only DMSO seems to have a strong interaction with the co-crystal Form II (200) surface. The strengths of adsorption are both high for benzene as suggested by the structure of the surface.

Constant pressure adsorption calculations were also performed using mixtures of sorbent molecules at 10 kPa partial pressure each. The results are broadly consistent with those from the constant loading calculations. The spread of adsorption energies for each molecule was found to vary considerably. Water showed a relative narrow range of adsorption energies varying from 0.2 to 6.6 kcal/mol. DMSO on the other showed a much wider range of adsorption energies, varying from 0.6 to 28.8 kcal/mol. A histogram show the distribution of adsorption energies for a mixture of water and DCM adsorbing onto the 001 surface of the co-crystal is shown in Figure 6. The broad distribution of adsorption energies for DCM is clearly seen, which contrasts with the narrow distribution of water adsorption energies.

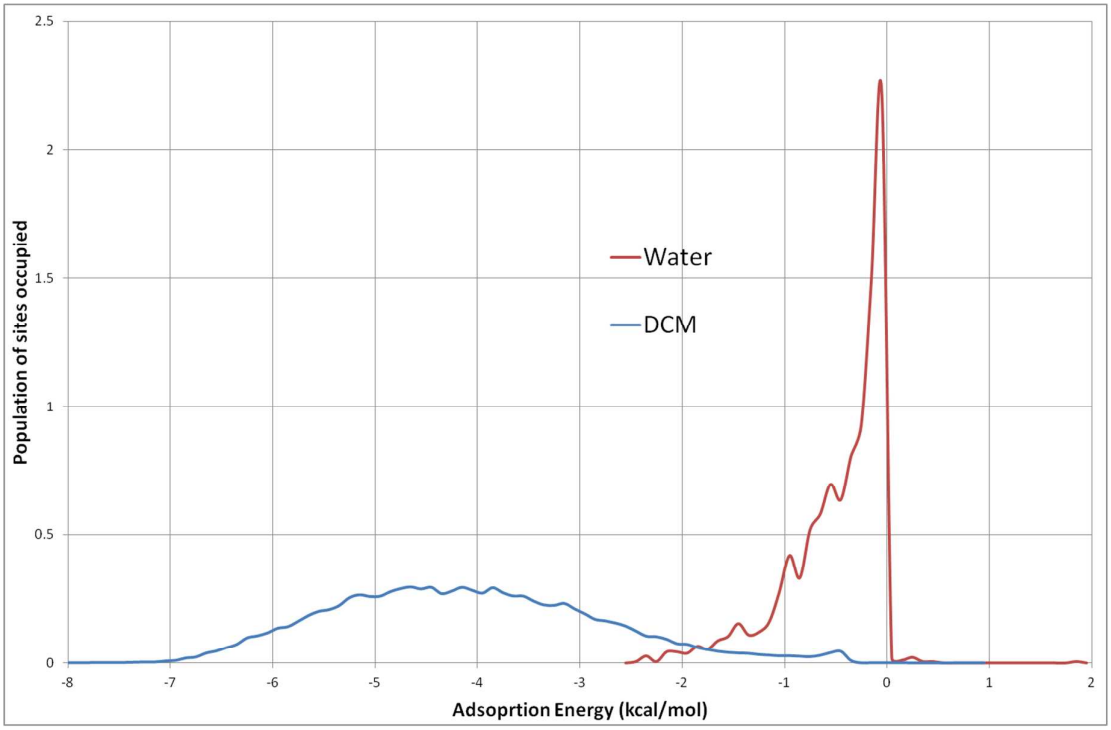


Figure 6: Population of adsorption energies for a mixture of water and DCM adsorbing onto the (001) surface of the co-crystal

References

[1] F. H. Allen, "The Cambridge Structural Database: a quarter of a million crystal structures and rising," *Acta Crystallographica Section B-Structural Science*, vol. 58, pp. 380–388, 2002.

[2] A. L. Grzesiak, M. Lang, K. Kim, and A. J. Matzger, "Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I.," *Journal of Pharmaceutical Sciences*, vol. 92, no. 11, pp. 2260–71, Nov. 2003.

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[6] W. W. Porter, S. C. Elie, and A. J. Matzger, "Polymorphism in Carbamazepine Cocrystals.," *Cryst Growth Des*, vol. 8, no. 1, pp. 14–16, Jan. 2008.

[7] "Materials Studio 4.1," *Materials Studio 4.1, Accelrys Inc, San Diego*, 2007.

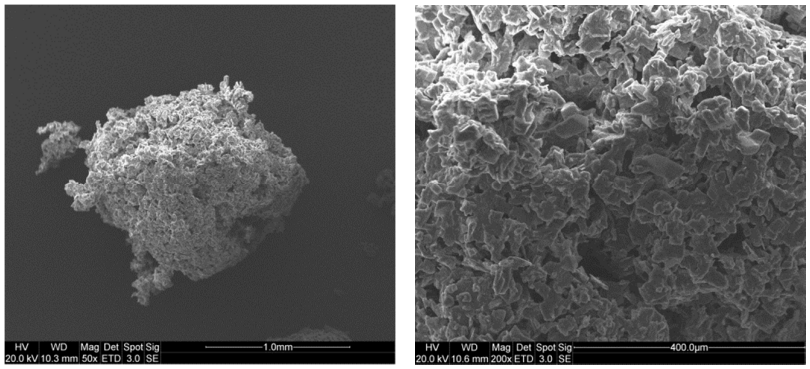
SI.7 Scanning electron microscopic images of spherical agglomerates of CBZ/SAC co-crystal

Method:

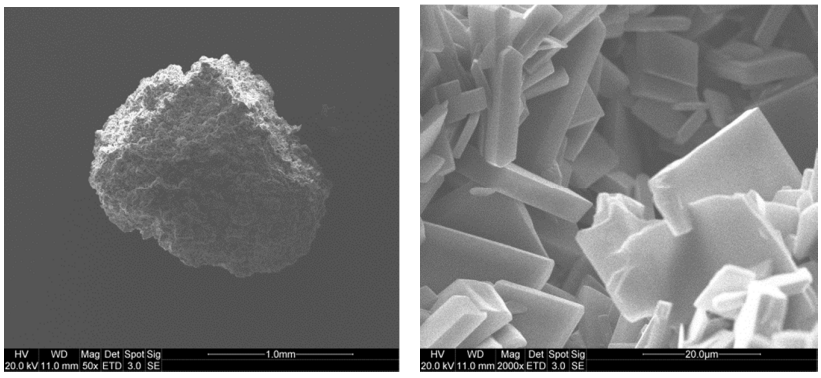
The morphological study of spherical agglomerates were performed by using SEM. Samples were mounted on aluminium pin-stubs (Agar Scientific, Stansted, U.K.) for SEM using self-adhesive carbon mounts (Agar Scientific). The mounted samples were examined using an FEI Quanta 400 Scanning Electron Microscope (Cambridge, U.K.) in high vacuum operated at an acceleration voltage of 20 kV. XTM Microscope control software version 2.3 was used for imaging.

1) Spherical agglomerates of CBZ/SAC obtained using DMSO as a good solvent with three bridging liquids

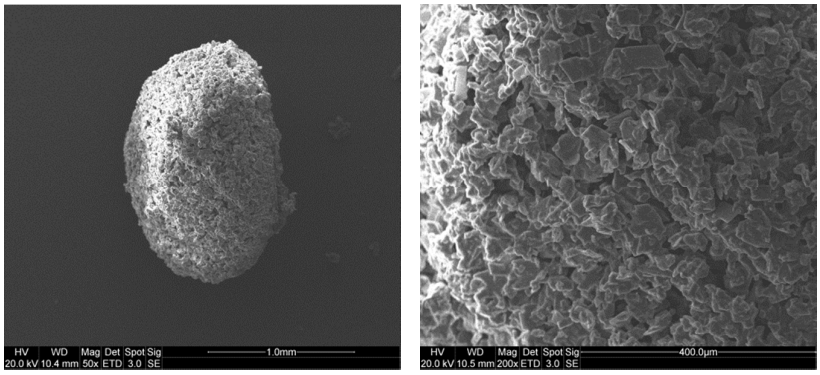
1a) Benzene as a bridging liquid



1b) DCM as a bridging liquid

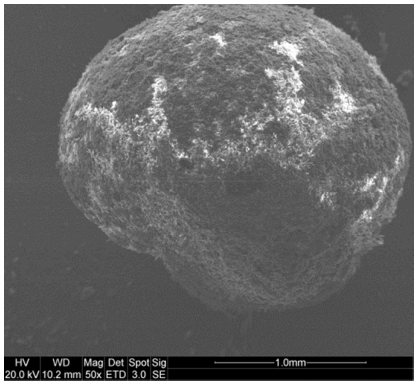


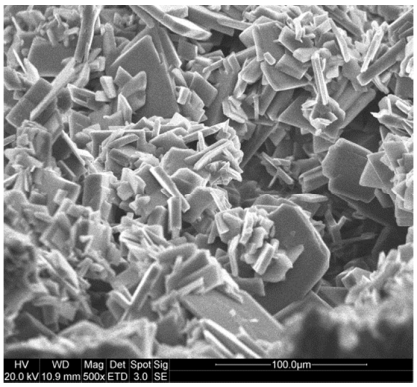
1c) Ethyl acetate as a bridging liquid



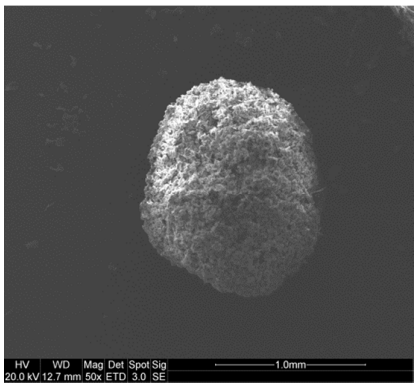
2) Spherical agglomerates of CBZ/SAC obtained using ethanol as a good solvent with three bridging liquids

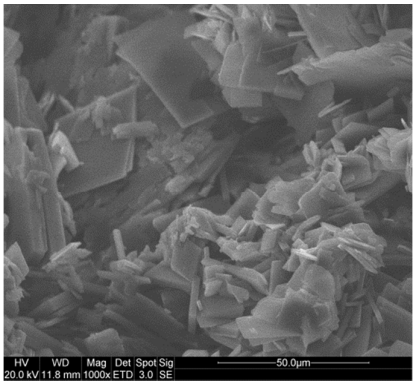
2a) Benzene as a bridging liquid



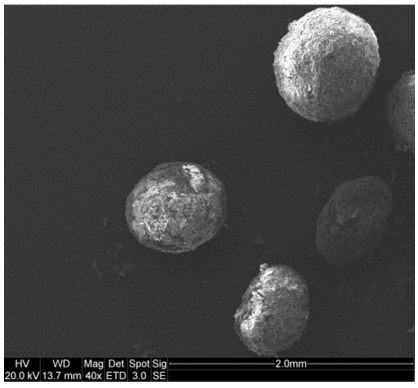


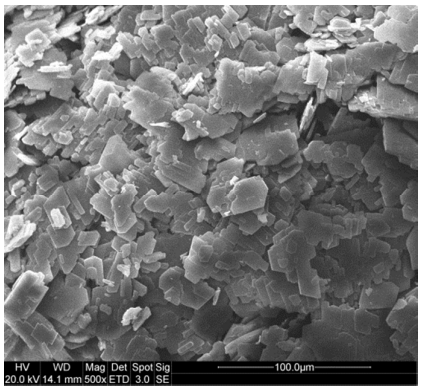
2b) DCM as a bridging liquid





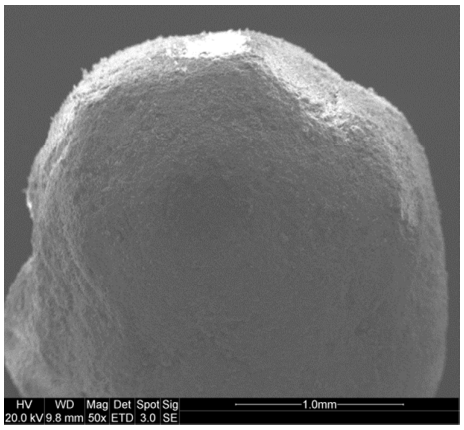
2c) Ethyl acetate as a bridging liquid

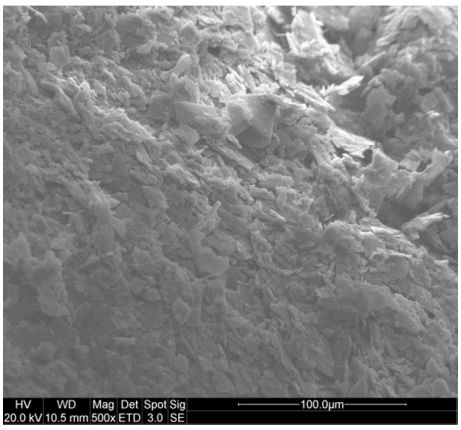




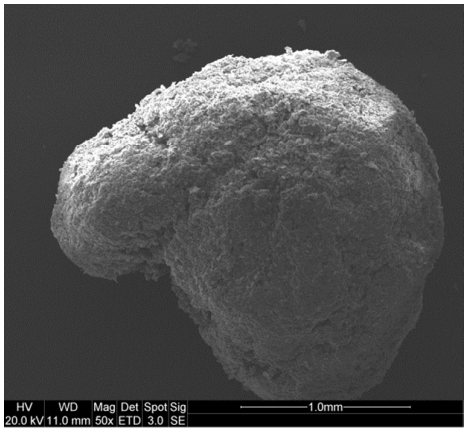
3) Spherical agglomerates of CBZ/SAC obtained using methanol as a good solvent with three bridging liquids

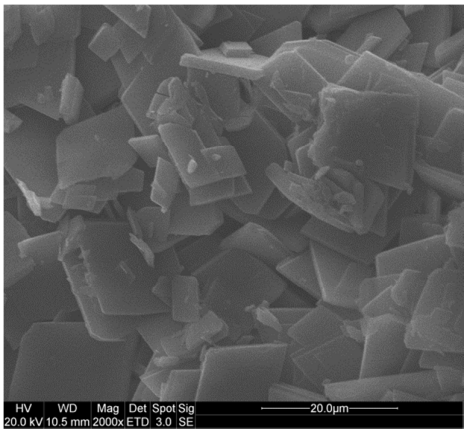
3 a) Benzene as a bridging liquid



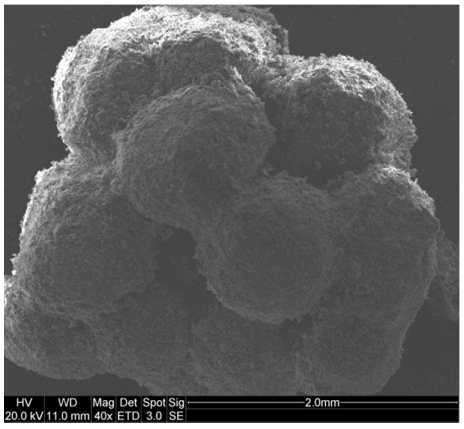


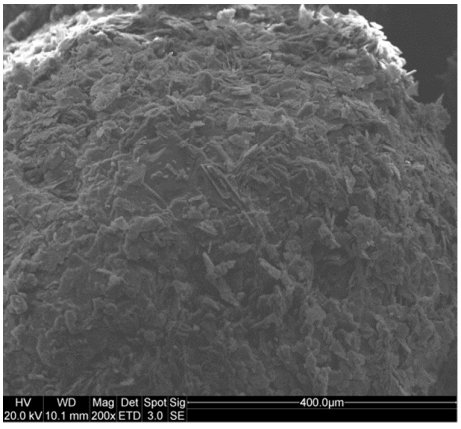
3 b) DCM as a bridging liquid





3 c) Ethyl acetate as a bridging liquid





SI.8 Physicochemical properties of the solvents

Solvent	Vapour pressure in mmHg [a]	logP [a]
Water	19	---
DMSO	0.7	---
Methanol	103	-0.82
Ethanol	45.7	-0.32
DCM	376	1.25
EA	78	0.73
BEN	78	2.13

Reference:

A) Smallwood, I. M. *Handbook of Organic Solvent Properties*, 2nd ed.; London: New York: Arnold; Halsted Press, 1996, pp. 35 – 301.