Nonstoichiometric Carbamazepine Cocrystal Hydrates of 34/35 Dihydroxy benzoic acids: Coformer-Water Exchange

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1. Experimental Section

Materials

CBZ was purchased from Sigma Aldrich and used as received. All other coformers and solvents were purchased from local suppliers and used without further purification.

Single crystal preparation of CBZ cocrystal

CBZ (24 mg, 0.1 mmol) and all the corresponding coformers were taken in respective stoichiometries and ground in a mortar and pestle in absence (neat grinding, NG) as well as in presence (2-3 drops) of acetonitrile/ water as liquid (liquid assisted grinding, LAG) for 30 min, which resulted respective multicomponent solids. The powder materials obtained were characterised using powder X-ray diffraction (PXRD). In order to generate single crystals of the respective cocrystals for structure elucidation, powder materials obtained from milling (NG as well as LAG) were taken in 25 mL conical flask, dissolved in minimum volume of acetonitrile and kept for solution crystallisation at room temperature.

Powder X-ray diffraction (PXRD)

PXRD measurements were performed at room temperature on a Rigaku Ultima IV X-ray powder diffractometer operating with a Cu K α X-ray source, equipped with a Ni filter to suppress K β emission and a D/teX Ultra high-speed position sensitive detector, with a scan range $2\theta = 5-50^{\circ}$, step size of 0.02° and scan rate of 10° min⁻¹.

Single crystal X-ray diffraction

Single crystal X-ray diffraction (SCXRD) data of CBZ•VA•H₂O and CBZ•CA were collected on a Bruker SMART APEX II CCD diffractometer equipped with a graphite monochromator fine-focus (λ = 0.71073 and Mo Κα sealed tube Å); whereas, а CBZ•0.25(34DHBA)•0.5(H₂O) and 0.5(CBZ)•0.1(35DHBA)•0.4(H₂O) on an Oxford Xcalibur, Eos diffractometer with a graphite monochromator and a Cu Ka fine-focus sealed tube ($\lambda = 1.54184$ Å). Data integration was done using SAINT. Intensities for absorption were corrected using SADABS. Structure solution and refinement were carried out using Bruker SHELXTL. The hydrogen atoms were refined isotropically, and all the other atoms were refined anisotropically. Hydrogens on N-H and O-H groups were located from difference electron density maps, and C-H hydrogens were fixed using the HFIX command in SHELXTL. Molecular graphics were prepared using X-SEED and Mercury licensed version 3.9. Surprisingly in case of dihydroxybenzoic acid cocrystals (34DHBA and 35DHBA) the coformers appear to be highly disordered. Coformer molecule residing in symmetry position is the reason behind the observed static disorder. Incorporation of solvent molecule was established using thermal analysis. The phase purity of the cocrystals was further confirmed by comparing their PXRD patterns with their respective calculated powder patterns.

Thermal analysis

Thermogravimetric analysis (TGA) measurements were performed on a Mettler Toledo instrument with a temperature range 25–700 °C at a heating rate of 20 °C min⁻¹. Samples were placed in silica crucibles and purged by a stream of nitrogen flowing at 80 mL min⁻¹. Differential scanning calorimetry (DSC) measurements were performed on a Mettler Toledo DSC instrument with a temperature range 25–400 °C and heating rate of 10 °C min⁻¹ on sample on 40 μ L aluminium pan with pin-hole lid under an ultra high pure nitrogen environment purged at 40 mL min⁻¹.

2. Characterization of CBZ•VA•H₂O cocrystal

NG as well as LAG using acetonitrile as liquid shows formation of CBZ•VA•H₂O cocrystal based on PXRD analysis. Experimental powder patterns of the respective NG and LAG samples matches well with the calculated powder pattern as shown in Figure S1.



Figure S1. PXRD of the powder samples obtained using NG as well as LAG with ACN of resultant CBZ•VA•H₂O cocrystal compared with the calculated powder patterns obtained from SCXRD. Neat grinding showed presence of small amount of starting materials (CBZ and VA) along with the CBZ•VA•H₂O cocrystal.

TG analysis of the single crystals of CBZ•VA•H₂O cocrystal showed loss of solvent water correspond to 4.26% exactly matches with calculated value of 4.26% for one water molecule present in the asymmetric unit (Figure S2).



Figure S2. TGA of 1:1 CBZ-VA powder sample prepared using LAG. Thermal analysis showed presence of solvent water in the crystal lattice. The broad endotherm at ~90-100 °C in DTG is due to release of water prior to melting at ~190-200 °C. A weight loss of 4.26% (calc. for monohydrate 4.26%) in TGA matches one water molecule.

3. Characterization of CBZ•CA cocrystal

LAG using acetonitrile as liquid shows formation of CBZ•CA cocrystal based on PXRD analysis. Experimental powder patterns of the LAG sample matches well with the calculated powder pattern confirm its bulk purity (Figure S3).



Figure S3. PXRD of the powder sample obtained using LAG with ACN of CBZ•CA cocrystal compared with the calculated powder patterns obtained from SCXRD.

4. Characterization of (CBZ)•0.25(34DHBA)•0.5(H₂O) cocrystal

Solution crystallization of 1:1 stoichiometric mixture, LAG samples of 1:1 as well as 4:1 CBZ and 34DHBA showed identical powder pattern that matches well with the calculated

powder pattern obtained from SCXRD (Figure S4a). On further analysis of the powder samples obtained from LAG with acetonitrile in variable stoichiometry of the respective starting materials viz. CBZ and 34DHBA showed nearly identical powder pattern, confirms formation of continuous solid-solution or molecular alloy (Figure S4b).



Figure S4. (a) PXRD of the powder samples obtained using LAG with ACN of 1:1 mixture of CBZ-34DHBA (red) and 4:1 mixture of CBZ-34DHBA obtained from solution crystallization (grey) as well as LAG (green and blue) compared with the calculated powder pattern (brown) of (CBZ)•0.25(34DHBA)•0.5(H₂O) cocrystal obtained from SCXRD. Apart from intensity of a few peaks exact matching of the powder pattern suggests as if the cocrystal behaves like a molecular alloy. (b) On repeating the PXRD measurement of samples obtained from various stoichiometric ratios of CBZ and 34DHBA showed identical powder patterns to that of the calculated one. The intensity of the peak at 27.8 ° that is common for both the cocrystal as well as 34DHBA increases along with the increase in composition during grinding particularly for 1:1 and 1:4 LAG mixtures.

DSC thermogram of the single crystal obtained from solution crystallization showed solvent loss at 60.9 °C (onset) prior to melting at 119.7 °C (onset) followed by decomposition (Figure S5a). TG analysis of the powder samples of 1:1 as well as 4:1 CBZ•34DHBA prepared using LAG (ACN) showed variable weight loss (Figure S5b-c) suggesting coformer-water exchange under mechanochemical synthesis of the cocrystal.





(b)



(c)

Figure S5. (a) DSC thermogram of 4:1 CBZ•34DHBA powder prepared using LAG showed loss of solvent water at 60.9 °C followed by melting at 119.7 °C. Further heating of the cocrystal resulted decomposition of the material further supported by TGA (b) TGA of the powder sample of CBZ•34DHBA showed weight loss of ~3.59% (theoretical 3.17%), signifies presence of half water molecule in crystal lattice. (c) Repeat TGA of powder samples of 1:1 and 4:1 CBZ•34DHBA prepared using LAG (ACN) showed variable weight loss suggesting coformer-water exchange under mechanochemical synthesis.

5. Characterization of 0.5(CBZ)•0.1(35DHBA)•0.4(H2O) cocrystal

Similar to CBZ•0.25(34DHBA)•0.5(H₂O) cocrystal, 0.5(CBZ)•0.1(35DHBA)•0.4(H₂O) cocrystal also contains amide dimers connecting two CBZ molecules and 35DHBA is attached to the dimeric motif occupying the vacant space. 3D packing arrangement shows formation of a channel structure similar to CBZ dihydrate as well as various crystal structures listed in Table T1. Disordered 35DHBA and water molecule occupies the void space created by the CBZ host lattice (Figure S6).



Figure S6. (a-b) The centrosymmetric CBZ amide-dimer in $0.5(CBZ) \cdot 0.1(35DHBA) \cdot 0.4(H_2O)$ cocrystal. Disordered 35DHBA and water occupying the void space created by CBZ dimers. The isomorphous $0.5(CBZ) \cdot 0.1(35DHBA) \cdot 0.4(H_2O)$ cocrystal showing identical crystal packing arrangement similar to CBZ-34DHBA cocrystal.

Similar to CBZ-34DHBA cocrystal, CBZ-35DHBA cocrystal hydrate also forms molecular alloy over a wide range of wide range of stoichiometry (1:1, 2:1, 3:1, 4:1 and 5:1) with respect to CBZ and 35DHBA. On the other hand, 1:5 stoichiometric ratio contains a few additional peaks compared to the peaks correspond to CBZ-35DHBA cocrystal hydrate (Figure S7).



Figure S7. PXRD of the powder sample obtained using LAG with ACN of various stoichiometric mixture of CBZ and 35DHBA compared with the calculated powder pattern of $0.5(CBZ) \cdot 0.1(35DHBA) \cdot 0.4(H_2O)$ cocrystal obtained from SCXRD. Apart from 1:5 composition all other LAG samples exactly matches with the calculated powder pattern.

Similar to (CBZ)•0.25(34DHBA)•0.5(H₂O) cocrystal, powder samples of 2:1 as well as 5:1 CBZ•35DHBA prepared using LAG (ACN) showed variable weight loss (Figure S8b-c) under TG analysis suggesting coformer-water exchange under mechanochemical synthesis of the cocrystal.





(b)



Figure S8. (a) DSC and (b) TGA of 5:1 CBZ-35DHBA powder sample prepared using LAG. Thermal analysis showed presence of solvent water in the crystal lattice. The broad endotherm at 72.2 °C in DSC is due to release of water prior to melting at 143.9 °C. A weight loss of ~5.78% (theoretical 5.12%) in TGA signifies presence of 0.4 molecule of water in the asymmetric unit. (c) Repeat TGA of powder samples of 2:1 and 5:1 CBZ•35DHBA prepared using LAG (ACN) showed variable weight loss suggesting non-stoichiometric cocrystal hydrate formation under mechanochemical synthesis.

6. CSD search of reported isostructural CBZ channel structures

Crystallographic details viz. space group, reduce cell, volume as well as CSD refcode of the reported isostructural CBZ channel structures are summarized in Table T1 and compared with the respective CBZ-34/35DHBA cocrystal hydrate. The reason behind formation of molecular alloy for these two CBZ-DHBA cocrystals is due to structural similarity of the two cocrystal with CBZ dihydrate (CSD refcode **FEFNOT03**) highlighted with red colour in the table. Crystal structure with disordered guest molecules are highlighted in red and written in parenthesis.

Structure	Space Group Reduce cell		ell	volume	CSD refcode	
		a	b	c		
CBZ/benzoquinone (1:0.5)	$P2_1/c$	5.0	10.3	27.6	1393	UNEYOB
CBZ/hemikis(pyrazine-N,N'-	$P2_1/c$	5.1	10.2	27.2	1397	VIGGUO
dioxide) (1:0.5)						
CBZ/malonic acid (1:X) form B	$P2_{l}/c$	5.1	10.3	26.6	1357	MOXVUR
(disorder)						
CBZ/DL-tartaric acid (1:X)	$P2_{l}/c$	5.1	10.3	27.0	1366	MOXWIG
(disorder)						
CBZ/maleic acid (1:X)	$P2_{l}/c$	5.2	10.4	26.2	1376	MOXWOM
(disorder)						
CBZ/oxalic acid (1:X)	$P2_{l}/c$	5.1	10.3	26.2	1343	MOXWUS
(disorder)						
CBZ/water (1:2)	$P2_{l}/c$	4.8	10.1	28.8	1367	FEFNOT03
CBZ/ammonium chloride (1:1)	$P2_1/n$	5.3	10.9	25.2	1434	VUBCAW
(disorder)			_			
CBZ/ammonium bromide (1:1)	$P2_1/n$	5.5	11.1	24.9	1479	VUBCEA
CBZ/terephthalaldehyde (1:0.5)	C2/c	5.0	14.8	20.3	1470	UNEYUH
CBZ/4-hydroxybenzoic acid	C2/c	5.2	10.6	26.5	1396	MOXVIF02
(1:X) form B (disorder)						
CBZ/nitromethane (1:1)	$P2_1/n$	5.2	10.9	26.3	1460	KIWBOI
CBZ/formamide (1:1)	$P^{\overline{1}}$	5.1	16.1	17.8	1397	UNIBOI
CBZ/furfural (1:0.5)	$P2_{l}/n$	5.2	20.6	26.0	2776	FOMXAH
CBZ/PABA (4:1) (disorder)	C2/c	5.1	10.5	26.6	1376	INUZAU
hemikis(oxonium)	C2/c	4.9	14.9	19.5	1374	JORGEE
hemikis(chloride)						
carbamazepine monohydrate						
(disorder)						
CBZ/1,4-dioxane (2:1)	$P2_{l}/c$	4.9	20.5	28.1	2823	QABHOU01
(disorder)						
CBZ/thiourea (2:1) (disorder)	Сс	5.3	10.2	25.8	1343	UWAZID
CBZ/34DHBA/H ₂ O	12/a	5.2	21.0	26.3	2831	This work
(1:0.25:0.5) (disorder)						
CBZ/35DHBA/H ₂ O	12/a	5.1	21.3	26.7	2826	This work
(0.5:0.1:0.4) (disorder)						

Table T1. Comparison of the cell parameters of reported isostructural CBZ channel structures with CBZ-34/35DHBA cocrystal hydrates.

7. Crystallographic parameters of the synthesized CBZ cocrystals

	CBZ•CA	CBZ•VA•H ₂ O	CBZ•0.25(34DHBA)•0.5H ₂ O	0.5(CBZ)•0.1(35DHBA)•0.4(H ₂ O)
Chemical	$(C_{15}H_{12}N_2O)\bullet$	$(C_{15}H_{12}N_2O) \bullet (C_8H_8O_4) \bullet$	$(C_{15}H_{12}N_2O)\bullet 0.25(C_7H_5O_4)\bullet$	$0.5(C_{15}H_{12}N_2O)\bullet 0.1(C_7H_3O_4)\bullet$
formula	$(C_9H_8O_2)$	(H ₂ O)	0.5(H ₂ O)	0.4(H ₂ O)
$M_{ m r}$	384.42	422.42	283.55	140.45
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_{1}/c$	$P2_1/n$	<i>I2/a</i>	I2/a
Temperature (K)	296	296	293	293
(11) a (Å)	15.3512 (8)	8.4203 (4)	21.0388 (2)	21.29468 (18)
<i>b</i> (Å)	5.4506 (3)	21.4155 (8)	5.2261 (1)	5.12107 (5)
c (Å)	23.7358 (13)	11.6437 (5)	26.3430 (4)	26.6635 (2)
α (°)	90	90	90	90
β(°)	96.167 (3)	98.670 (2)	102.120 (1)	103.5459 (9)
γ(°)	90	90	90	90
$V(Å^3)$	1974.56 (18)	2075.66 (15)	2831.87 (7)	2826.81 (4)
Ζ	4	4	8	16
Radiation type	Μο Κα	Μο Κα	Cu Kα	Cu Ka
μ (mm ⁻¹)	0.09	0.10	0.74	0.74
D_{calcd} (g cm ⁻³)	1.293	1.352	1.330	1.320
Diffractometer	Bruker	Bruker APEX-II CCD	Xcalibur, Eos	Xcalibur, Eos
	APEX-II	diffractometer	diffractometer	diffractometer
	CCD			
	diffractometer			
No. of	28915	17655	13349	13629
measured				
reflections				
No. of	3418	3487	2384	2359
observed [<i>I</i> >				
2σ(<i>I</i>)]				
reflections				
R _{int}	0.034	0.024	0.016	0.015
$R[F^2 >$	0.054	0.041	0.045	0.047
$2\sigma(F^2)$],				
$wR(F^2)$	0.158	0.118	0.113	0.132
S	1.04	1.09	1.07	1.09
No. of	4035	4257	2582	2561
reflections	0.40	0.01	0.15	0.05
$\Delta \rho_{\text{max}}(e \text{ A}^{-3})$	0.49	0.21	0.15	0.25
CCDC No.	2225589	2225590	2225591	2225592

 Table T2. Crystallographic parameters of CBZ cocrystals



8. BFDH morphology of the synthesized CBZ cocrystals

Figure S9. BFDH morphology of (a) CBZ•VA•H₂O, (b) CBZ•CA, (c) CBZ•0.25(34DHBA)•0.5H₂O and (d) $0.5(CBZ)•0.1(35DHBA)•0.4(H_2O)$ showing the dominant crystal face used for nanoindentation study.



Figure S10: Histogram plots showing statistical data of Young's modulus (Ey) and hardness (H) of all indentations under 6 mN load obtained from several indentations from multiple crystals of CBZ-VA (a-b) and CBZ-CA (c-d).



Figure S11: Histogram plots showing statistical data of Young's modulus (Ey) and hardness (H) of all indentations under 6 mN load obtained from several indentations from multiple crystals of CBZ-34DHBA (a-b) and CBZ-35DHBA (c-d).