Intriguing High Z" Cocrystals of Emtricitabine

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ABSTRACT: Emtricitabine (ECB) afforded dimorphic cocrystals (Forms I, II) of benzoic acid (BA), whereas with p-hydroxybenzoic acid (PHBA), p-aminobenzoic acid (PABA) are resulted in as high Z" cocrystals. Intriguingly, the Z" of cocrystals are trends from two to fourteen based on the manipulation of functional groups on the para position of BA (where H atom is replaced with that of OH or NH_2 group). ECB–PABA cocrystal consists of six molecules each and two

water molecules in the asymmetric unit (Z"=14) with 2D planar sheets represents the rare pharmaceutical cocrystal. The findings suggest that the increment of H bond donor(s) systematically via a suitable coformer are in correspondence with attaining high Z" cocrystals. Further, solid state NMR spectroscopy in conjunction with single crystal X-ray diffraction are demonstrated as significant tools to enhance the understanding of the number of symmetry independent molecules in the crystalline lattice and provide insights to the mechanistic pathways of crystallization.

Crystallization of organic compounds with more than one molecule in the asymmetric unit garners an immense curiosity among the scientific community.[1-16] For single component crystals, number of symmetry independent molecules in the asymmetric unit is designated with Z' value whereas for multicomponent crystals, Z" is generally considered as the total number of symmetry independent molecules in the asymmetric unit.[17-21] In some reports, the researchers used Z' for multicomponent crystals as well.[20,21,24] However, majority of studies thus far focused on single component crystals and less attention is paid toward high Z" multicomponent crystals. In this contribution, multicomponent crystals viz. cocrystals have been investigated and referred to as Z" in the study.

The high Z' crystal structures are often considered as metastable solid forms or fossil relics on the way of transforming to the thermodynamically stable form.[2,4,12] There are several debates as to why an organic compound crystallizes with more than one symmetry independent molecule.[3,4] Efforts in this direction may uncover insights to the mechanistic pathways of crystallization.[4] High Z' crystals may display improved physical properties, for instance,

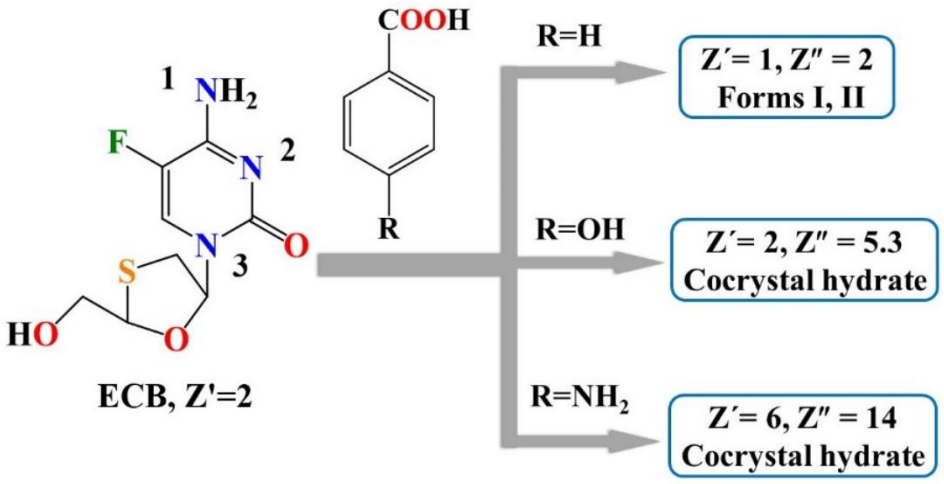
compressibility of pharmaceuticals.[5] A survey of the Cambridge Structural database (CSD) suggests that ~12% of the organic compounds crystallize with Z'>1 and that probability decreases exponentially with increasing Z' value.[6,7] Most often than not, high Z' crystals are located by serendipity. It is extremely difficult to design a molecule with more symmetry independent molecules in its crystalline lattice. The following literature findings suggest promising tendencies about Z' crystals. A substantial number of compounds with Z'>1 have pseudosymmetry elements and are generally crystallized in low symmetry crystal lattices, with preferable space groups including but not limited to *P*1, *P*-1 and $P2_1$. In general, high Z' crystal structures are correlated with their irregular molecular shape, chiral geometry, strong directional hydrogen/halogen bonds, crystallization variables and supersaturation.[8-9] High Z' structure arises owing to the competition between strong directional hydrogen bonds and close packing during nucleation processes.[4,6,7] Notably, small and rigid organic molecules may have difficulty in close packing compared to flexible molecules. Hence, the former are compensated by either constituting unsymmetrical interactions or increasing the number of symmetry independent molecules in their crystalline lattices.[10,11] In addition, molecular chirality with centrosymmetric dimer motifs may also lead to high Z′ crystal structures as two homochiral molecules cannot be correlated by center of inversion.[11,14] Interestingly, it is observed that high Z′ crystals conceive planar sheet-like solid-state packing in which the stacking between the layers suppress the overall symmetry.[5,16]

Single component crystals exhibit a higher tendency toward Z′>1 crystals compared to multicomponent crystals (Z''), which is similar to polymorphism of single and multicomponent crystals.[17] It is because of the presence of a second component, which may improve the crystal packing with an enhanced synthon complementarity or optimized geometry.[18] It should be

mentioned that a fewer systems being studied so far.[19-24] Accordingly, the design of high Z" cocrystal is challenging in the context of crystallization phenomenon, which needs molecular level of understanding and mechanism thereof. In this contribution, we aim to investigate the high Z" cocrystals and rationally advance the understanding of high Z" crystallizations.

Emtricitabine (ECB, chemical name: 2',3'-dideoxy-5-fluoro-3'-thiacytidine, Scheme 1) is marketed either for monotherapy (brand name: Emtriva®) or a fixed dose triple combination with efavirenz and tenofovir disoproxil fumarate (brand name Atripla) for the prevention and treatment of HIV infection.[25]

ECB, is considered as one of the essential medicines in the model list of World Health Organization. ECB is an (–) enantiomer of a thio analogue of cytidine and chemically very similar to lamivudine, except for fluorine substituent at C5-position. Lamivudine is reported to exist in two polymorphic forms, a hemihydrate form, and cocrystals with zidovudine, and several dicarboxylic acids, a few salts and interestingly, a solid solution with ECB.[26-28] Isostructural ECB, thus far is known to have four polymorphic forms[29,30] and one unstable sesquihydrate. Of which, only one crystal structure (Refcode-HAKJIM) is reported in the CSD. However, no pure cocrystals of ECB are reported in the prior art. Herein, we demonstrate ECB cocrystals with systematically selected three coformers, namely, benzoic acid (BA), p-hydroxybenzoic acid (PHBA) and p-aminobenzoic acid (PABA). ECB–BA (Z"=2) crystallized as dimorphic cocrystals, whereas both ECB–PABA and ECB–PHBA unraveled as high Z" cocrystal hydrates, see Scheme 1.



Scheme 1. High Z" ECB cocrystals with increasing H bond donor(s) at *p*ara position of a coformer.

The cocrystals were synthesized using mechanical grinding and the resulting materials were subjected to evaporative crystallizations. ECB–BA (1:1) cocrystal polymorphs were concomitantly crystallized as Form I (hexagonal plates, >95%) and Form II (long fibers, minor quantity) from ethanol, see Figure. S1 in the Supporting Information (SI). Suitable single crystals of ECB–PHBA hydrate were harvested as colorless long thin plates from either water or methanol. Similarly, ECB–PABA hydrate as orange plates (hexagonal morphology) were produced from acetone or 1:1 mixture of ethanol-ethyl acetate. A full characterization of cocrystals were performed using powder/single crystal X-ray diffraction (PXRD/SCXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and ^{15}N solid-state nuclear magnetic resonance (SSNMR) spectroscopy. A brief crystallography data of the high Z" cocrystals are summarized in Table 1.

Table 1. Crystallography data of ECB cocrystals.

	ECB–BA (Form I)	ECB–BA (Form II)	ECB–PHBA hydrate	ECB–PABA hydrate
Chemical formula	$C_8H_{10}FN_3O_3S$, $C_7H_6O_2$	$C_8H_{10}FN_3O_3S$, $C_7H_6O_2$	$2(C_8H_{10}FN_3O_3S)$, $2(C_7H_6O_3)$, $1.3(H_2O)$	$3(C_8H_{10}FN_3O_3S)$, $3(C_7H_7N_2)$, (H_2O)
M_r	369.38	369.38	795.44	1171.17
Crystal system, space group	Monoclinic, $P2_1$	Orthorhombic, $P2_12_12_1$	Monoclinic, $P2_1$	Monoclinic, $P2_1$
T(K)	298 (2)	298 (2)	100(2)	107(11)
a (Å)	6.7863(6)	5.255(3)	9.0950(5)	8.7980(2)
b (Å)	16.9680(14)	13.741(8)	5.3045(3)	31.5096(6)
c (Å)	7.4773(6)	23.141(12)	34.750(2)	18.0924(3)
α, β, γ (°)	90, 101.114(1), 90	90, 90, 90	90, 90.697(3), 90	90, 90.335(2), 90
V (Å^3)	844.86(12)	1671.0(16)	1676.39(16)	5015.52(17)
Z, Z', Z''	2, 1, 2	4, 1, 2	4, 2, 5.3	12, 6, 14
ρ_{calc} (g cm^{-3})	1.452	1.468	1.576	1.551
R factor	0.0509,	0.0468,	0.0817,	0.0468,
WR_2	0.1008,	0.1365,	0.1704,	0.0944,
GOF	1.147	1.125	1.186	1.025

Crystallization of ECB-BA and their crystal structure analysis are quite interesting as it confirms two concomitant cocrystal polymorphs of this binary system. The crystal structures of ECB–BA polymorphs (Forms I, II) are determined in monoclinic ($P2_1$) and orthorhombic

($P2_12_12_1$) lattices, respectively (Figure 1). ECB–BA Form I (Z″=2) is primarily stabilized by 2-aminopyridine···acid heterosynthon and hydroxyl···carbonyl interactions between two ECB molecules via O–H···O hydrogen bonds. Aside, four ECB molecules form a tetramer ring of $\boldsymbol{R_4^4}(30)$ using hydroxy···carbonyl and amine···hydroxy hydrogen bonds. In addition, ECB tetramer ring $\boldsymbol{R_2^4}(28)$ also formed via hydroxy···carbonyl and S···O chalcogen bonds.[31] The overall crystal packing is somewhat similar to a host-guest complex,[32] where each BA molecule is embedded under the cavity of ECB tetramer ring (Figure 1a). In ECB–BA Form II (Z"=2), the principal 2-aminopyridine···acid heterosynthon between ECB and BA is retained. Unlike that ECB tetramer seen in Form I, herein two ECB trimers are bound by hydroxyl···carbonyl interactions and form hexamolecular ring motif of $\boldsymbol{R_8^8}(56)$ through drug-coformer heterosynthons. It does not have S···O chalcogen bonds instead auxiliary C–H···S contacts are observed. The 3D packing reveals that two BA molecules are trapped in the hexamolecular assembly of ECB (Figure 1b). As ECB–BA dimorphs differ by conformation and packing due to flexible 5-membered oxathiolan ring (Figure S2, SI), hence the dimorphic system is referred to as conformational and as well as packing polymorphs.[33] Thermal analysis indicated that melting point of Form I (T_{onset}=129.9 ±0.1 ^{O}C, T_{peak}=130.7 ±0.2 ^{O}C, ΔH_f = –121.3 J/g) is 2 ^{O}C greater than that of Form II (T_{onset}=126.0 ±0.2 ^{O}C, T_{peak}=128.3 ±0.2 ^{O}C, ΔH_f = –82.1 J/g) and they are monotropically related as there is no phase transformation until their melting points, see Figure. S4a, SI.

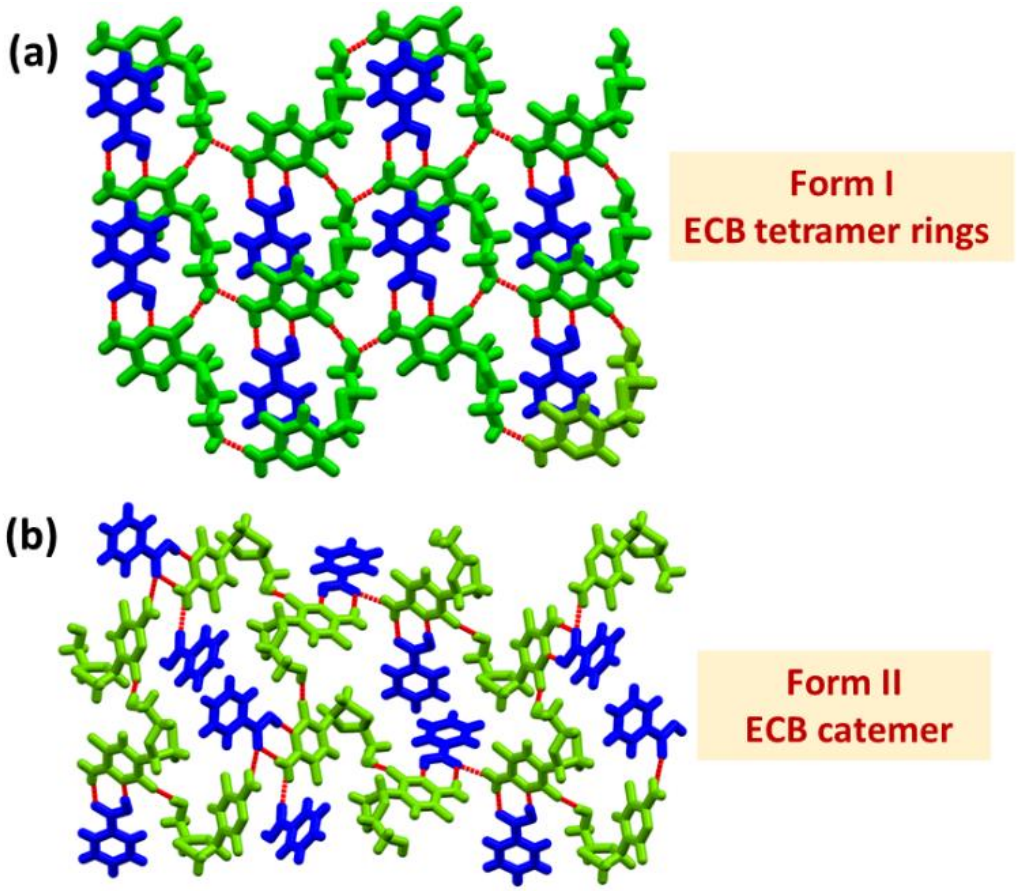


Figure 1. Packing differences among (a) Form I, and (b) Form II of ECB–BA cocrystal system.

Next, ECB was cocrystallized with PHBA, where with a OH group at *p*-position, adding a H bond donor and acceptor. It resulted in a serendipitous, but interesting outcome i.e. high Z" cocrystal hydrate (Z"=5.3). Addition of an extra H bond donor (and also two H bond acceptors, which apparently not involved in crucial interactions) via OH group may have disproportionated the overall number of donors/acceptors. The crystal structure of ECB–PHBA reveals that it has crystallized in monoclinic system with $P2_1$ space group [2(ECB·PHBA)·1.3H_2O]. ECB–PHBA has two molecules of ECB in asymmetric unit i.e. similar to that of pure drug, but here one of

ECB molecules is disordered at the 2-hydroxymethyl group (s.o.f. of O11/O11A; 0.49, 0.51). The remainder of the asymmetric cell comprises two molecules each of PHBA and water (s.o.f. of O01F/O1; s.o.f. 1.0, 0.36). Crystal packing reveals the presence of a key heterosynthon of 2-aminopyridine···acid. Further, the hydroxyl group of PHBA forms O–H···O interaction with carbonyl group of ECB, a tetramer ring motif with $\boldsymbol{R_4^4}(24)$ graph set, which makes the 2D sheet arrangement (Figure 2a). Two water molecules propagate via O–H···O interactions and form 1D column, viewed down the *b* axis, see Figure 2b. Water molecules act as connector between the 2-aminopyridine···acid heterosynthon of two different conformers. This is a typical example of a non-stoichiometric channel hydrate, which is not uncommon among high Z" cocrystal hydrates.[34] The loosely bound water molecule (O1) may elude during storage at ambient conditions. The deviations in experimental PXRD (at 298K) vs simulated PXRD (obtained from SCXRD at 100K) patterns suggest not only temperature differences between them, but also indicate the unstable nature of non-stoichiometric channel hydrates (Figure S3, SI). Thermal profiles of ECB–PHBA suggests that water loss occurs at 40–60 ^{O}C (Figure S4, SI) suggests the possibility of losing of nonstoichiometric channel water (O1), which is weaklly bound to just ECB molecules expected to leave without altering the crystal packing. It is followed by the loss of second water molecule during 120-140 ^{O}C, which is strongly bound to both ECB and PHBA molecules.

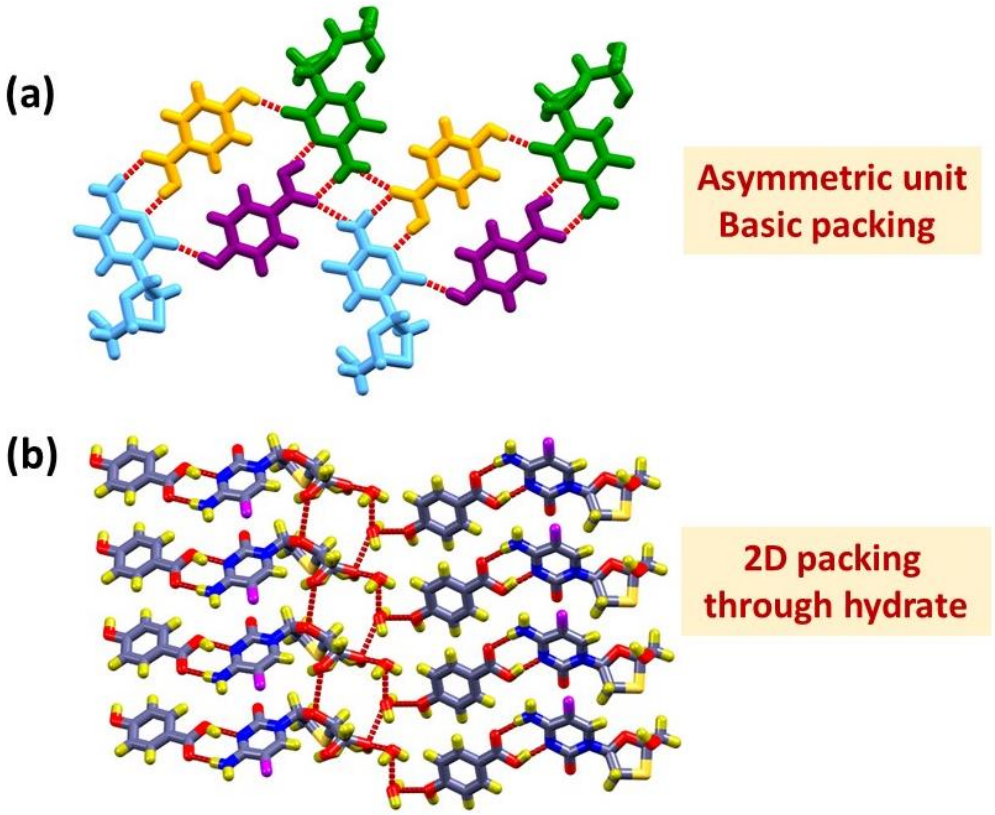


Figure 2. (a) 2D sheet of ECB–PHBA cocrystal hydrate (2:2:1.3) in which one ECB conformer is disordered over hydroxymethyl group (top). (b) Two non-stoichiometric water molecules alternatively arrange to form 1D chain, viewed down the b axis. Note, non-stoichiometric water molecule (O1) is only hydrogen bonded with ECB, not PHBA.

In order to increase the number of symmetry independent ECB molecules, ECB cocrystallized with PABA, wherein OH is replaced by NH_2. Notably, number of H bond donors from PHBA (OH) to PABA (NH_2) is doubled which is hypothesized to alter the number of symmetry independent molecules in the asymmetric unit. ECB–PABA crystallized in monoclinic system with $P2_1$ space group [6(ECB·PABA)·2H_2O], which has six molecules each of each and two water molecules in the asymmetric unit (Z'=14, depicted in different color codes), see

Figure 3a. Each ECB as expected, constitutes two point 2-aminopyridine···acid heterosynthon with PABA by O–H···O, O–H···N interactions. The remaining two ECB conformations are hydrogen bonded with each other and coformer acid groups. ECB and PABA molecules are propagated alternatively via alcohol···amine and 2-aminopyridine···acid heterosynthons. The adjacent layers are interlinked using several auxiliary interactions like O–H···O, C–H···O and π···π stacking interactions (Cg···Cg: 3.39 Å) to constitute 2D layer structure (Figure 3b). In addition, one of water molecules is bound to three ECB conformers (O···O: 2.74, 2.83, 2.88 Å) and another water is bound with two ECBs (O···O: 2.85, 2.91 Å). These are strongly bound and not easy to elude from the crystal lattice. Both the experimental (at 298 K) and simulated (from SCXRD at 100K) PXRD patterns matched well, indicates the stability of hydrates in the crystal structure of ECB–PABA (Figure S3, SI). Thermal profiles of ECB–PABA suggest that water was lost at 128-132 ^{O}C, followed by melting during 180-183 ^{O}C (Figure S4, SI). Water loss of 1.8% (0.4 mole) corroborate well with the observed 0.33 mole of hydrate in the SCXRD. The Z''=14 in the ECB–PABA cocrystal could be rationalized with systematic manipulation of H bond donors. The crystal structure is primarily stabilized with two robust heterosynthons, (i) 2-aminopyridine···acid, and (ii) hydroxyl···carbonyl interactions. For saturation of the remaining H bond donors/acceptors, two water molecules have been incorporated in the crystal lattice.

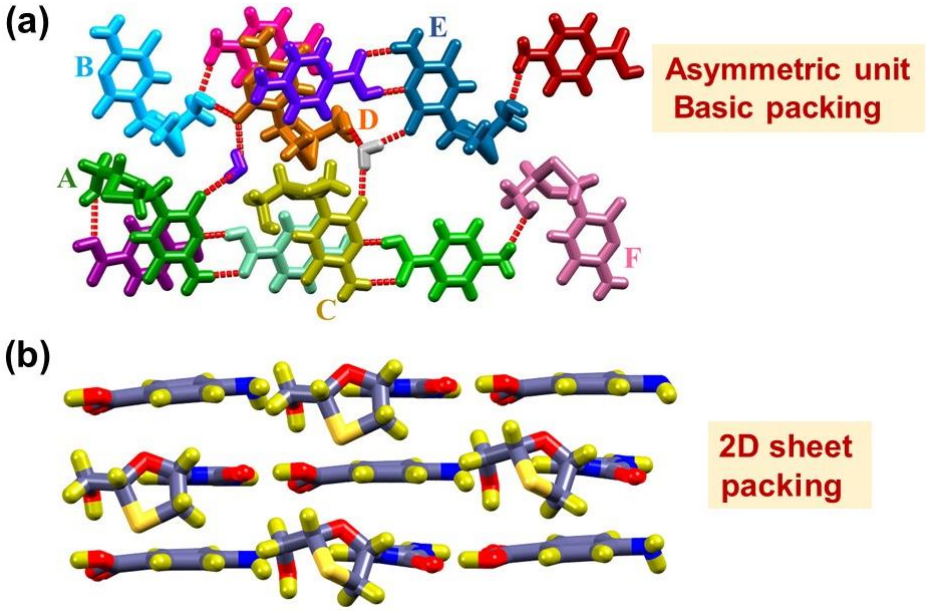


Figure 3. (a) Hydrogen bonded ECB–PABA cocrystal hydrate (6:6:2) with different color codes. Note, two water molecules are bound to four different ECB conformers (A, C, D and E). (b) ECB and PABA molecules alternately arrange to form 2D layer structure, which is stabilized by several auxiliary interactions.

A CSD statistical analysis has been performed to understand the prevalence of high Z' lattice for cocrystals. Note, Z' is considered based on the number of conformers of the solid component in the asymmetric unit. In CSD study, Z'=2-12 (no. of hits) for binary and ternary systems after excluding ionic, metal complexes and R-factor <0.1 were considered (see Figure 4, also Table S4, SI). The results indicate that cocrystals have much less tendency to crystallize in high Z' crystal structures compared to solvates/hydrates. Among multicomponent crystals, Z'≥6 is very rare. Out of 30 binary crystal structures including hydrate/solvates, only 3 hits (Refcodes:

KAYGUO, USAKEF, ZEKPIR) were noted with Z'=6. There is no report of ternary system with Z'≥6, whether it be either three solid components or two solids with one liquid component (e.g. water molecule). Herein we demonstrate ECB–PABA as the rare cocrystal hydrate with Z'=6 (Z''=14) of pharmaceutical relevance or otherwise.[35-39]

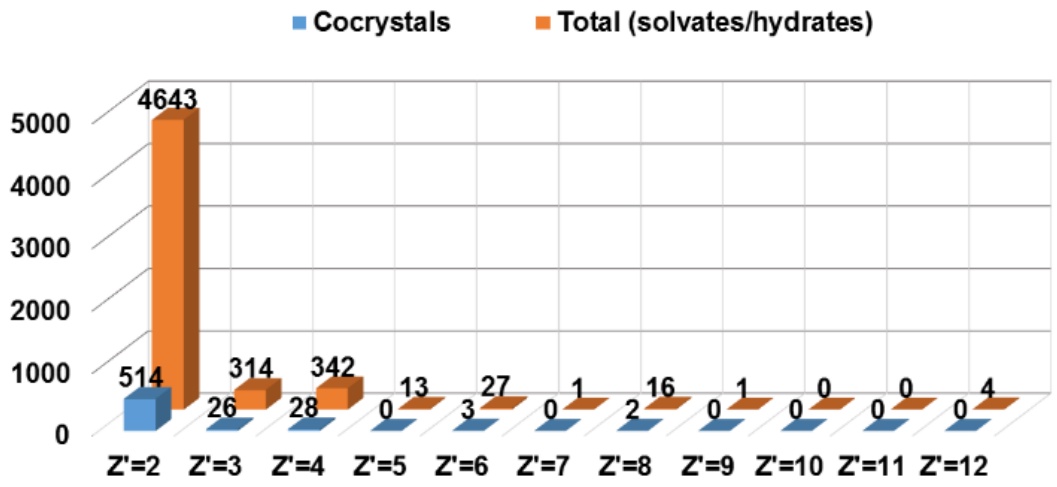


Figure 4. CSD analysis depicts that binary cocrystals with high Z' are scarce.

SSNMR of ECB cocrystals were undertaken as based on the resonances of an atom in SSNMR spectra, one can predict the number of symmetry independent molecules in the crystal lattice.[40] Protonation of amine moiety may shift SSNMR resonances towards more shielded regions.[41,42] In the ^{15}N SSNMR studies of ECB cocrystals (Figure 5, also SI), a chemical shift of ± 20 δppm from precursors were observed, which is in agreement with neutral acid-base complexes formation. SSNMR of pure ECB reveals the presence of double resonance for each of three nitrogens (N1, N2, N3) confirming Z'=2, matching the crystal structure. ECB–BA (Form I) exhibits one signal for each N atom of the drug with the change of chemical shift (±)10 δppm

that confirms its cocrystal formation with one ECB molecule in the asymmetric unit (Figure 5). ECB–PHBA cocrystal, also showed double resonances for the three nitrogens like ECB, which reaffirms that there are two molecules of ECB in the asymmetric unit (Figure S5, SI). Interestingly, SSNMR pattern of ECB–PABA is more complex due to more symmetry independent molecules in the lattice and high signal/noise ratio, which indicates minimum three (≥3) ECB conformations in the asymmetric unit (Figure S6, SI). In other words, it could be rationalized as that there are three distinct ECB conformers of which, three ECB molecules have two different conformations, whereas remaining three ECB molecules have one conformation. Accordingly, six symmetry independent drug molecules in the asymmetric unit could be attributed, see Figure S6, SI. Note, the single resonance at -318.9 ppm that could be attributed to NH_2 group of PABA, which indicates that all PABA molecules in the cocrystal appear to have taken one conformation due to its planar geometry.

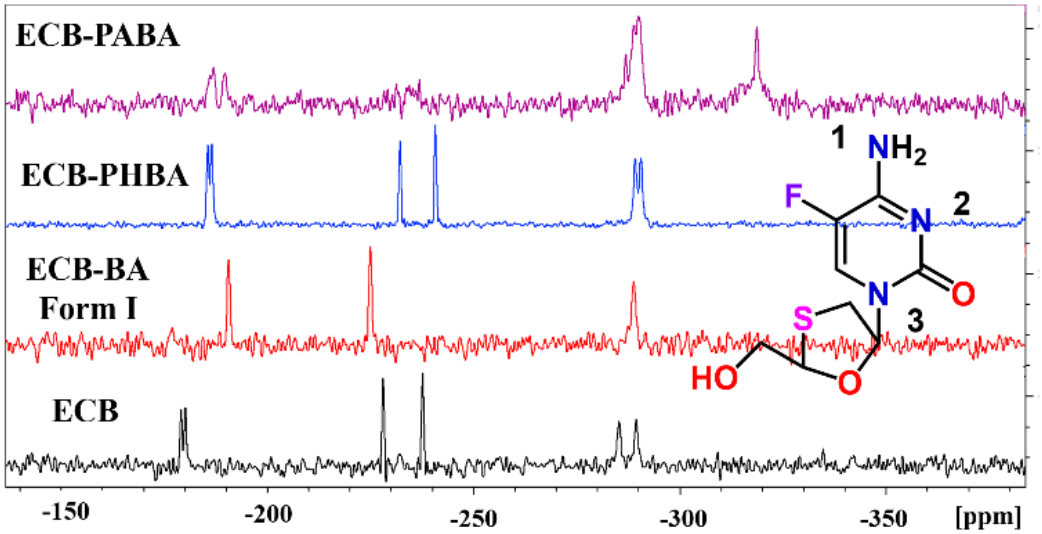


Figure 5. ^{15}N SSNMR comparison of ECB and its cocrystals that indicates the number of symmetry independent drug molecule in the asymmetric unit.

In conclusion, we demonstrated the rational understanding of high Z" cocrystals of anti-HIV drug ECB by replacing H with OH/NH_2 functional groups at the para position of benzoic acid. Z"=2 to 5.3 to 14 has been achieved by replacing coformer BA first with PHBA, followed by PABA. To counterbalance the number of hydrogen bond donors and acceptors, nonstoichiometric water molecules have been incorporated in the ECB cocrystal high Z" lattices. Aside, two cocrystal polymorphs of ECB–BA were also identified and fully characterized in this study. Further, a combination of single crystal X-ray diffraction and solid state NMR spectroscopy are found to be a promising approach to enhance the understanding of the number symmetry independent molecules in the crystalline lattice and it has provided insights to the mechanistic pathways of crystallization.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.cgd

Experimental section include cocrystal preparation, characterization details and Cambridge Structural Database (CSD) statistics; supplementary details include molecular overlay, PXRD

comparisons, DSC and TGA results, ^{15}N SSNMR results, molecular conformations and CSD statistical analysis for high Z' cocrystals.

The following files are available free of charge.

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.cgd.

Accession Codes:

SCXRD crystallographic information files (CIFs) see CCDC reference numbers, 1896473, 1896477, 1988089 and 1988090 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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Intriguing High Z" Cocrystals of Emtricitabine

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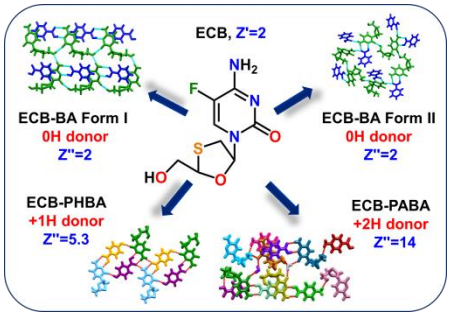

Emtricitabine, an anti-retroviral drug, afforded the *rare* pharmaceutical cocrystal of high Z"=14 (Z'=6) by systematic manipulation of H bond donors in *para* position of benzoic acid coformers. Solid state NMR spectroscopy in combination with single crystal X-ray diffraction has been demonstrated as a promising approach to advance the understanding of the number of symmetry independent molecules in the multicomponent crystals.