Electronic Supporting Information†

Can we exchange water ina hydrate structure: a case study of Etoricoxib†

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Reported X-ray crystal structures of Etoricoxib:
Four crystal structures of Etoricoxib and its hydrates are reported in the current version of the Cambridge Structural Database (ver. 5.36, May 2015 update 3).
WEVGIW, space group Pca21, Etoricoxib anhydrate Form 1
WECGIW01, space group P-1, Etoricoxib anhydrate Form 4
WECGUI, space group Pccn, Etoricoxib hemihydrate Form 1 (stable form)
WECHAP, space group P21/c, Etoricoxib hemihydrate Form 2.

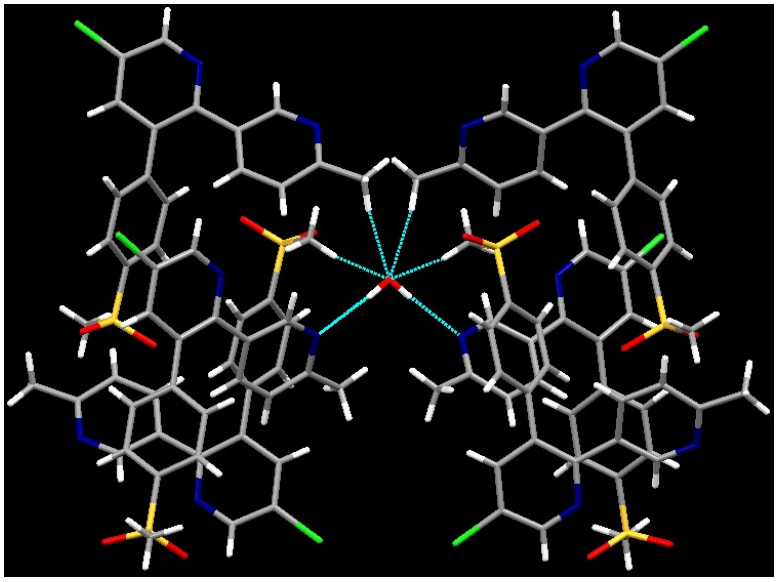


Figure S1 Crystal structure of ETR hemihydrate Form I (stable form). The packing diagram is drawn using CSD Refcode WECGUI (space group *Pccn*). Both O–H···N and C–H···O hydrogen bonds are shown.

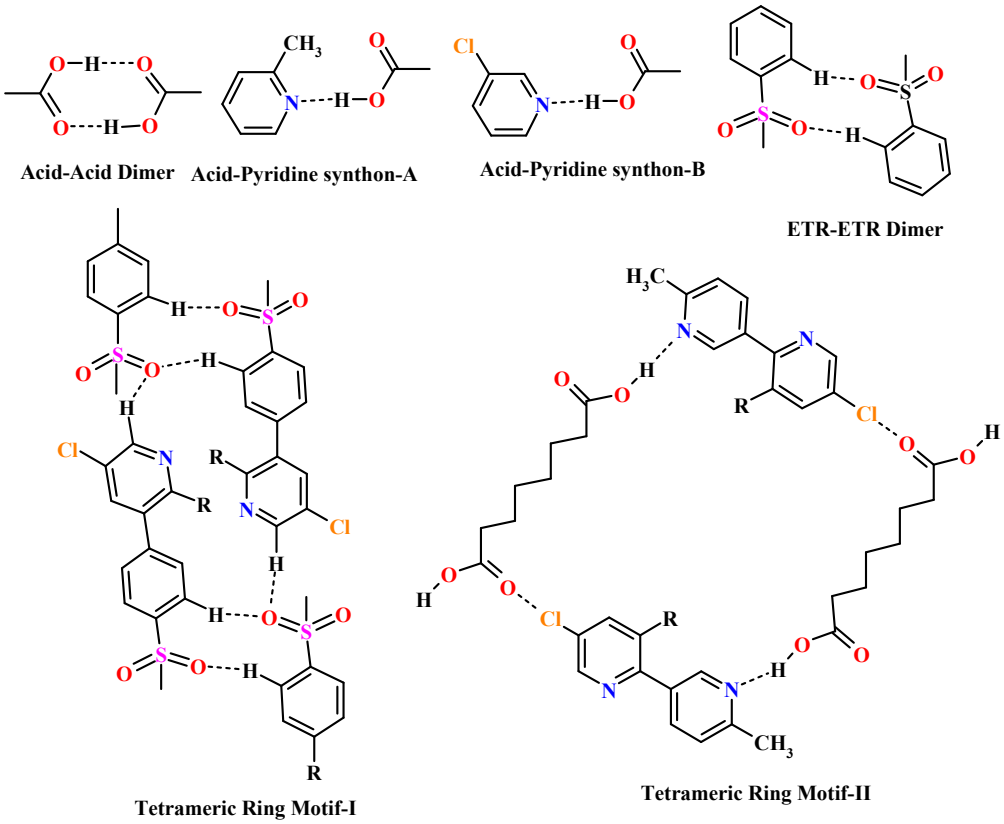


Figure S2 Different types of hydrogen bonding interactions observed in cocrystal structures.

Table S1 Crystallographic information.[a]

	ETR–GA (1:1)	**ETR–ADA (2:1)**	**ETR–SBA (1:1)**	**ETR–SBA Tri Hydrate (4:1:6)**	**ETR–CPR Dihydrate (2:1:2)**
CCDC No.	444656	1444654	1444657	1444658	1444655
Empirical Formula	C18 H15 Cl N2 O2 S, C5 H8 O4	C18 H15 Cl N2 O2 S, 0.5(C6 H10 O4)	C18 H15 Cl N2 O2 S, C8 H14 O4	2(C18 H15 Cl N2 O2 S), 0.5(C8 H14 O4), 2(H2 O), O	2(C18 H15 Cl N2 O2 S), C6 H11 N O, 2(H2 O)
Formula weight	490.94	431.90	533.02	856.79	866.85
Crystal system	$P2_1/n$	$P2_1/n$	P–1	P–1	P–1
Space group	Monoclinic	Monoclinic	Triclinic	Triclinic	Triclinic
T (K)	298	298	298	298	298
a (Å)	11.8317(15)	16.6417(18)	9.0238(3)	12.2796(15)	12.552(3)
b (Å)	12.7266(16)	5.4913(6)	10.1284(5)	12.4817(10)	12.574(3)
c (Å)	15.772(2)	23.838(3)	14.8544(9)	14.8713(18)	14.989(3)
α (deg)	90	90	82.766(5)	95.187(8)	96.690(3)
B (deg)	90.203(2)	98.603(2)	77.640(4)	113.754(12)	114.553(2)
γ (deg)	90	90	85.387(4)	91.242(8)	90.099(3)

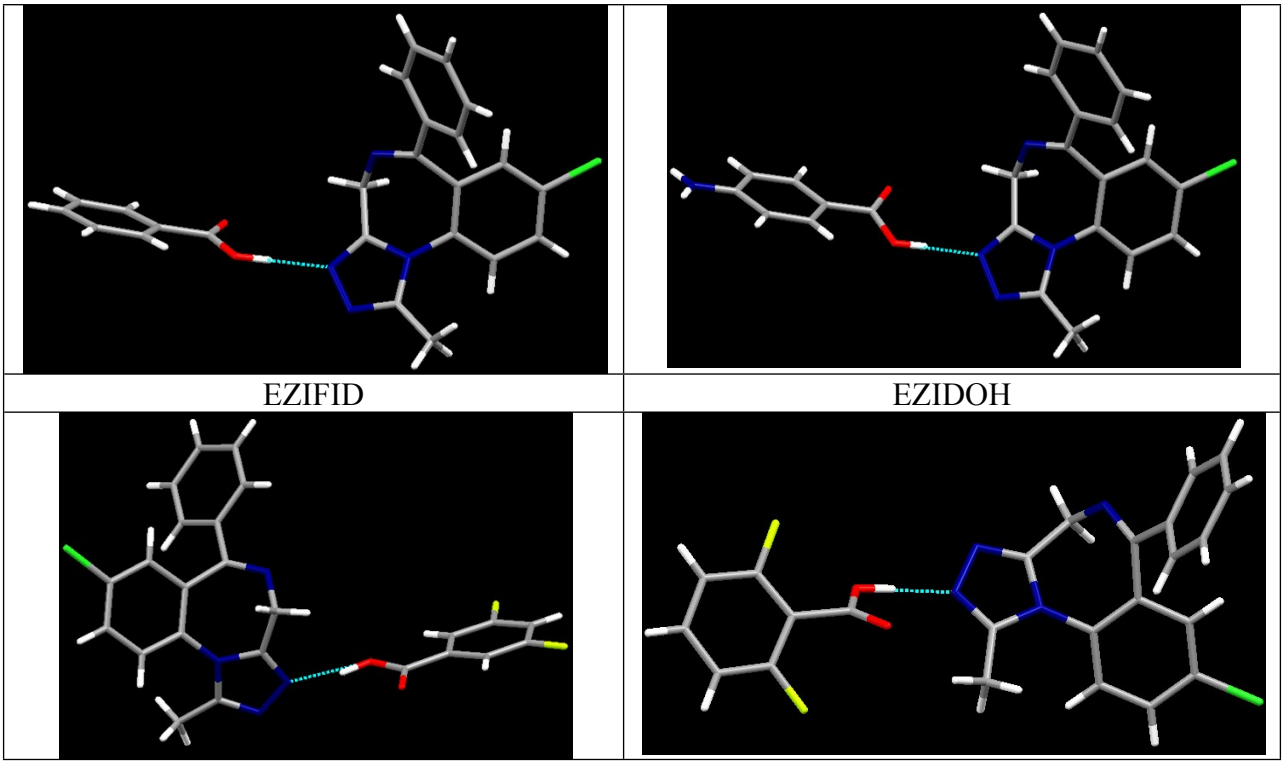
V (Å^3)	2375.0(5)	2153.9(4)	1313.62(11)	2073.4(4)	2133.7(8)
D_{calcd} (gcm^{-3})	1.373	1.332	1.348	1.372	1.349
μ(mm^{-1})	0.290	0.303	2.396	0.316	0.305
θ range	2.06 to 26.40	1.40 to 26.38	3.06 to 66.59	2.79 to 25.06	1.51 to 26.45
Z/Z[1]	4	4	2	2	2
Range h	–14 to 14	–20 to 20	–10 to 6	–11 to 14	–15 to 15
Range k	–15 to 15	–6 to 6	–12 to 11	–14 to 14	–15 to 15
Range l	–19 to 19	–29 to 29	–16 to 17	–17 to 17	–18 to 18
Reflections collected	24676	21794	7910	13766	22864
Total reflections	4862	4406	4615	7303	8692
Observed reflections	4098	3765	3886	3338	7183
R_1 [I> 2 σ (I)]	0.0445	0.0556	0.0424	0.0649	0.0440
wR$_2$ (all)	0.1271	0.1516	0.1219	0.1307	0.1295
Goodness-of-fit	1.035	1.025	1.045	0.962	1.037
X-ray diffractometer	Bruker	Bruker	Oxford	Bruker	Bruker

[a] The X-ray crystal structure of ETR-SA was extracted from the CSD for analysis in this work. CCDC No. 1018390

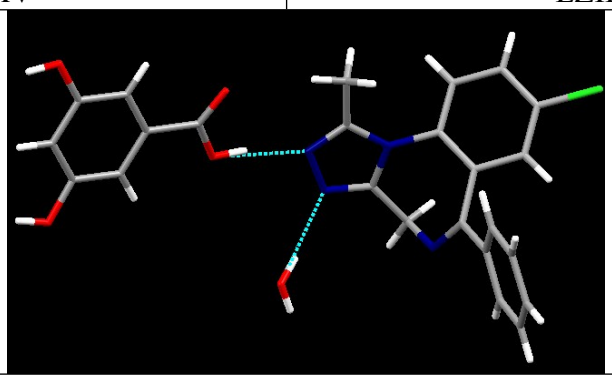
Table S2 Neutron-normalized hydrogen bond geometry in ETR cocrystals and hydrates.

Cocrystal/Cocrystal hydrate	Interaction	D–H/Å	H···A/Å	D···A/Å	∠D–H···A/Å	Symmetry code
ETR–GA	O3–H3A···N1	0.88(3)	1.85(4)	2.664(3)	152(3)	1/2+x,-1/2-y,3/2+z
	O6–H6A···O5	0.98(4)	1.66(4)	2.633(3)	172(3)	-x,2-y,1-z
	C1–H1B···O4	0.96	2.43	3.391(3)	175	1-x,1-y,1-z
	C4–H4···O1	0.93	2.41	3.260(2)	152	1/2-x,-1/2+y,3/2-z
	C7–H7···O2	0.93	2.43	3.138(2)	132	1-x,1-y,1-z
	C12–H12···O2	0.93	2.60	3.512(2)	167	x,-1+y,z
	C21–H21A···Cl1	0.97	2.81	3.728(2)	158	-1/2+x,1/2-y,-1/2+z
ETR–ADA	O3–H3A···N1	0.83(3)	1.86(3)	2.675(3)	171(3)	x,1+y,z
	C1–H1C···O1	0.96	2.29	3.207(3)	161	x,-1+y,z
	C4–H4···O2	0.93	2.53	3.429(3)	163	3/2-x,-1/2+y,1/2-z
ETR–SBA	O4–H4A···O3	0.82	1.84	2.659(2)	179	2-x,1-y,-z
	O5–H5A···N1	0.82	1.89	2.705(2)	169	-x,1-y,1-z
	C1–H1B···O6	0.96	2.50	3.462(4)	178	x,-1+y,z
	C14–H14···O6	0.93	2.56	3.225(3)	129	-x,1-y,1-z
	C25–H25B···O1	0.97	2.50	3.400(3)	153	-x,1-y,1-z

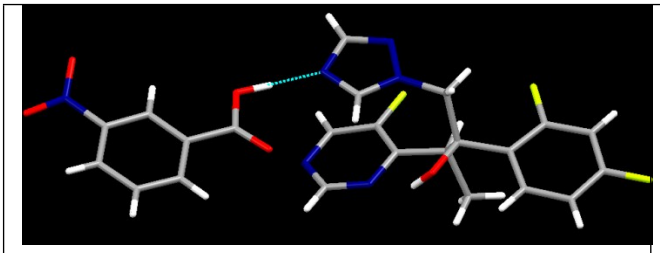
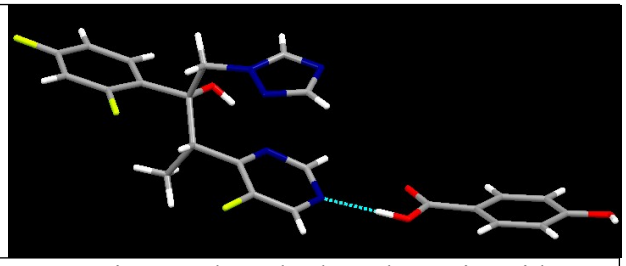
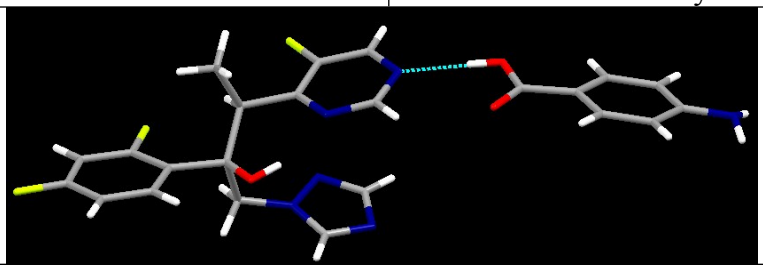
ETR–SBA Tri Hydrate	O5–H5A···O7	0.89(6)	1.98(6)	2.860(7)	172(7)	-1+x,y,z
	O5–H5B···N1	0.87(4)	2.13(5)	2.944(7)	156(4)	1-x,1-y,1-z
	O6–H6A···O8	0.91(5)	2.22(5)	2.901(8)	131(5)	x,y,z
	O6–H6B···O7	0.92(6)	2.00(7)	2.891(7)	164(10)	1-x,1-y,-z
	O9–H9A···N2	0.82	2.06	2.797(6)	150	x,1+y,z
	C12–H12···O2	0.93	2.35	3.256(5)	163	x,-1+y,z
	C1–H1A···N4	0.95	2.67	3.52(5)	146	1-x,1-y,1-z
ETR–CPR Di Hydrate	N5–H5A···O5	0.98	2.01	2.9374(7)	157	x,1+y,z
	O5–H5B···O6	0.94	1.87	2.8026(7)	172	X,y,z
	O5–H5C···N1	0.86	2.04	2.8940(7)	173	x,y,-1+z
	O6–H6A···N4	0.94	2.02	2.8578(7)	148	1-x,1-y,1-z
	O6–H6B···O7	0.77	2.07	2.8352(7)	169	1-x,1-y,1-z
	C1–H1A···O5	0.96	2.58	3.5118(8)	165	-x,-y,1-z
	C12–H12···O1	0.93	2.40	3.3099(8)	167	x,1+y,z
ETR–SA	O4–H4A···N1	0.90(4)	1.82(4)	2.708(4)	170(3)	1/2-x,1/2+y,1/2-z
	C1–H1C···O1	0.96	2.19	3.137(5)	170	x,-1+y,z
	C4–H4···O2	0.93	2.54	3.449(4)	165	1/2-x,-1/2+y,1/2-z



EZIFID EZIDOH

EZIFAV	EZIDUN
	
EZIFEZ	

(a)

	
Voriconazole–3-nitrobenzoic acid	Voriconazole–4-hydroxybenzoic acid
	
Voriconazole–4-aminobenzoic acid	

(b)

Figure S3 (a) Carboxylic acid from coformer forming hydrogen bonding interactions with different nitrogen acceptor of Alprazolam.[2] **(b)** Coformer acid forming hydrogen bond with triazole and pyrimidine nitrogen of Voriconazole.[3] CSD version 5.36 (update 3, May 2015).

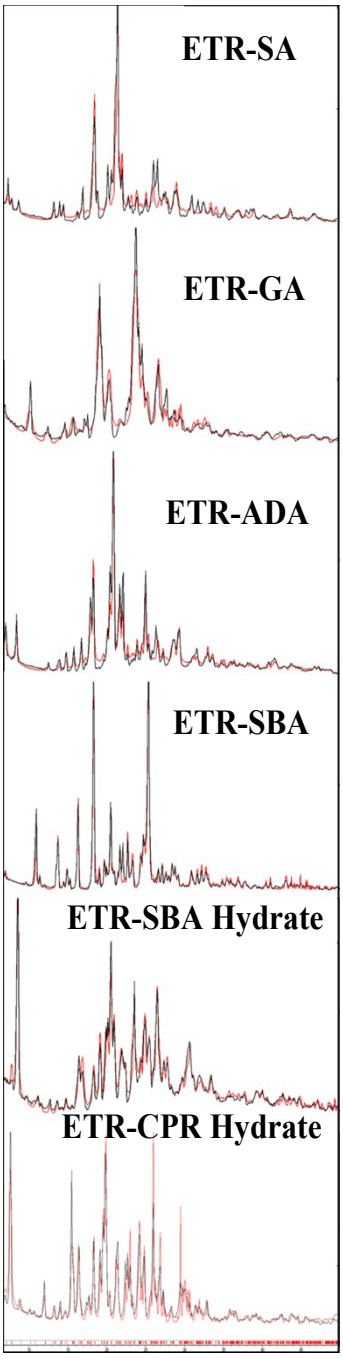


Figure S4 Overlay of experimental and calculated powder X-ray diffraction pattern of the new solid crystalline forms.

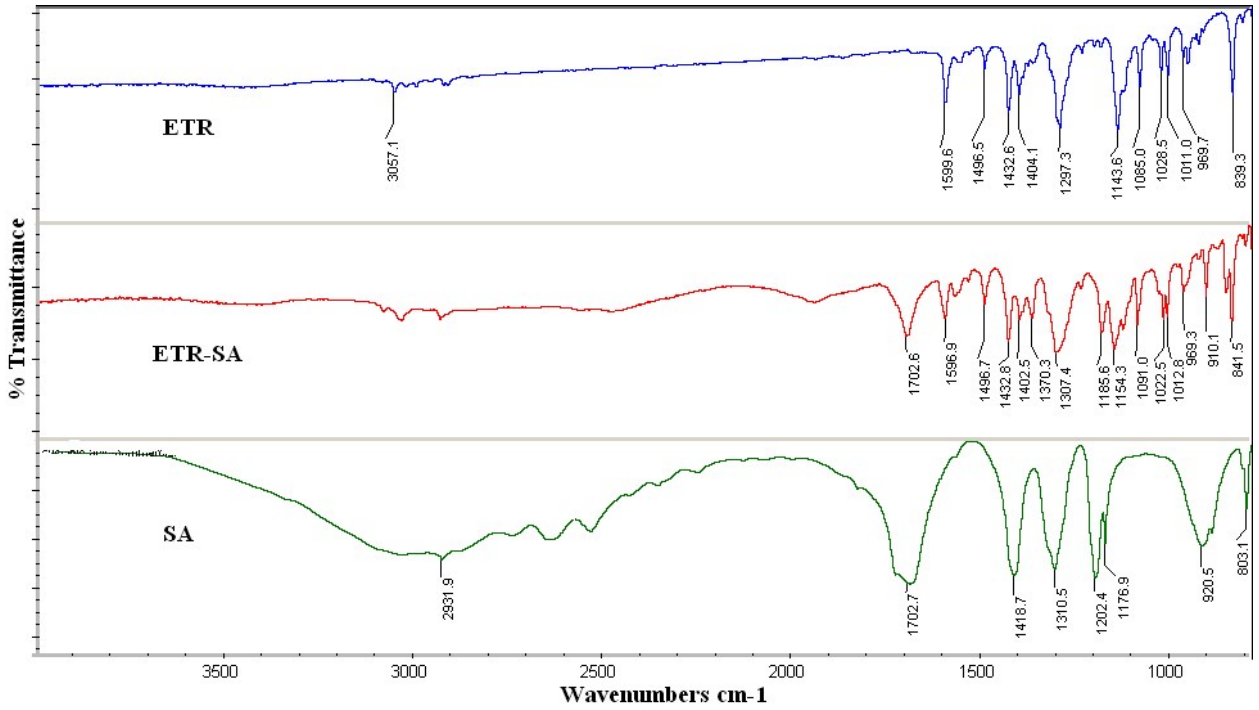


Figure S5 (a) Comparison of stretching frequencies of ETR–SA with its starting materials.

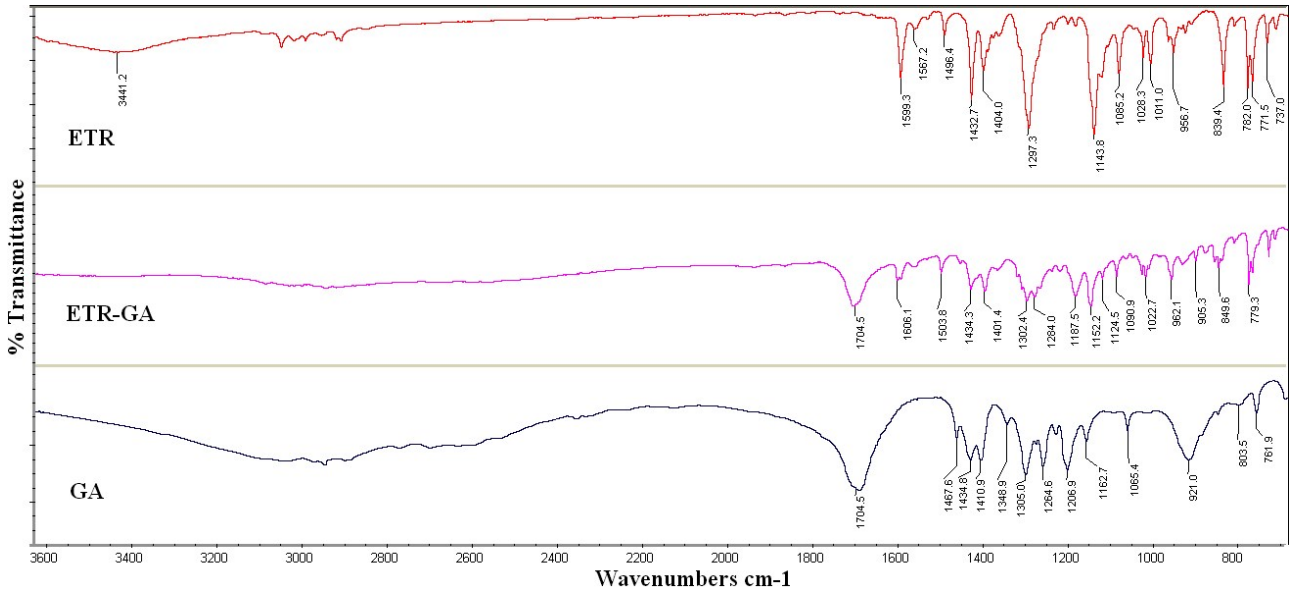


Figure S5 (b) Comparison of stretching frequencies of ETR–GA with its starting materials.

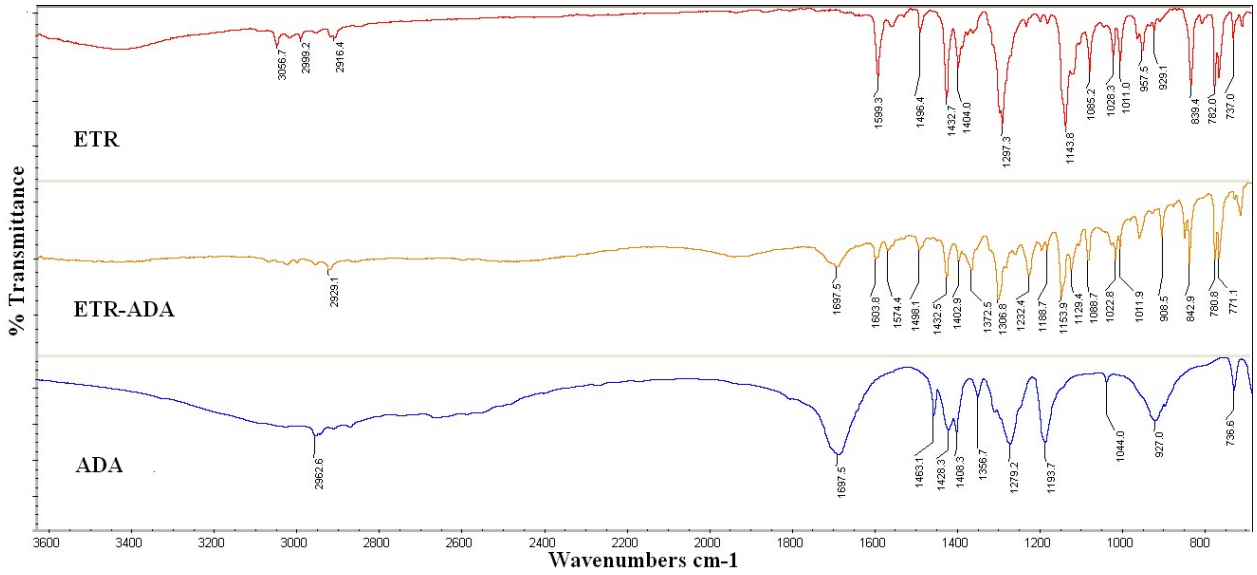


Figure S5 (c) Comparison of stretching frequencies of ETR–ADA with its starting materials.

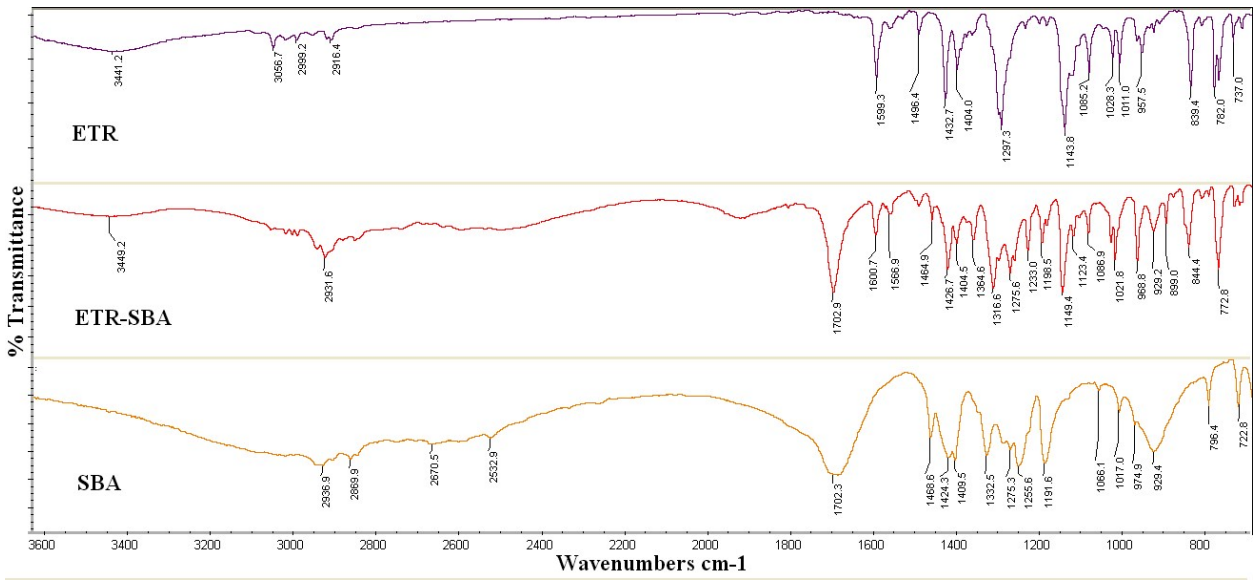


Figure S5 (d) Comparison of stretching frequencies of ETR–SBA with its starting materials.

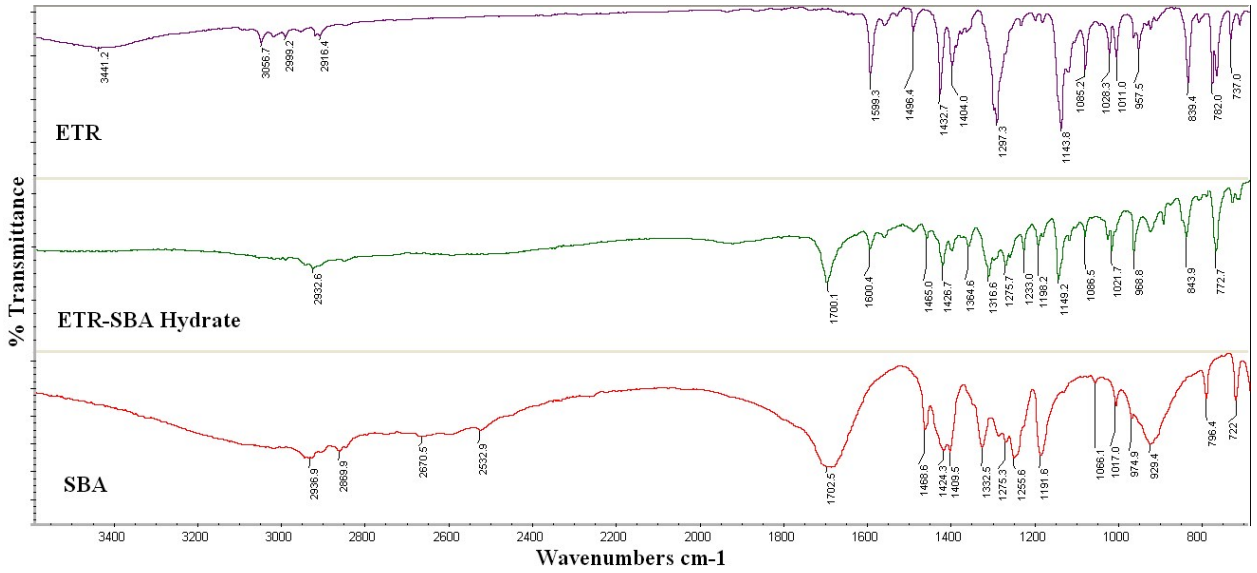
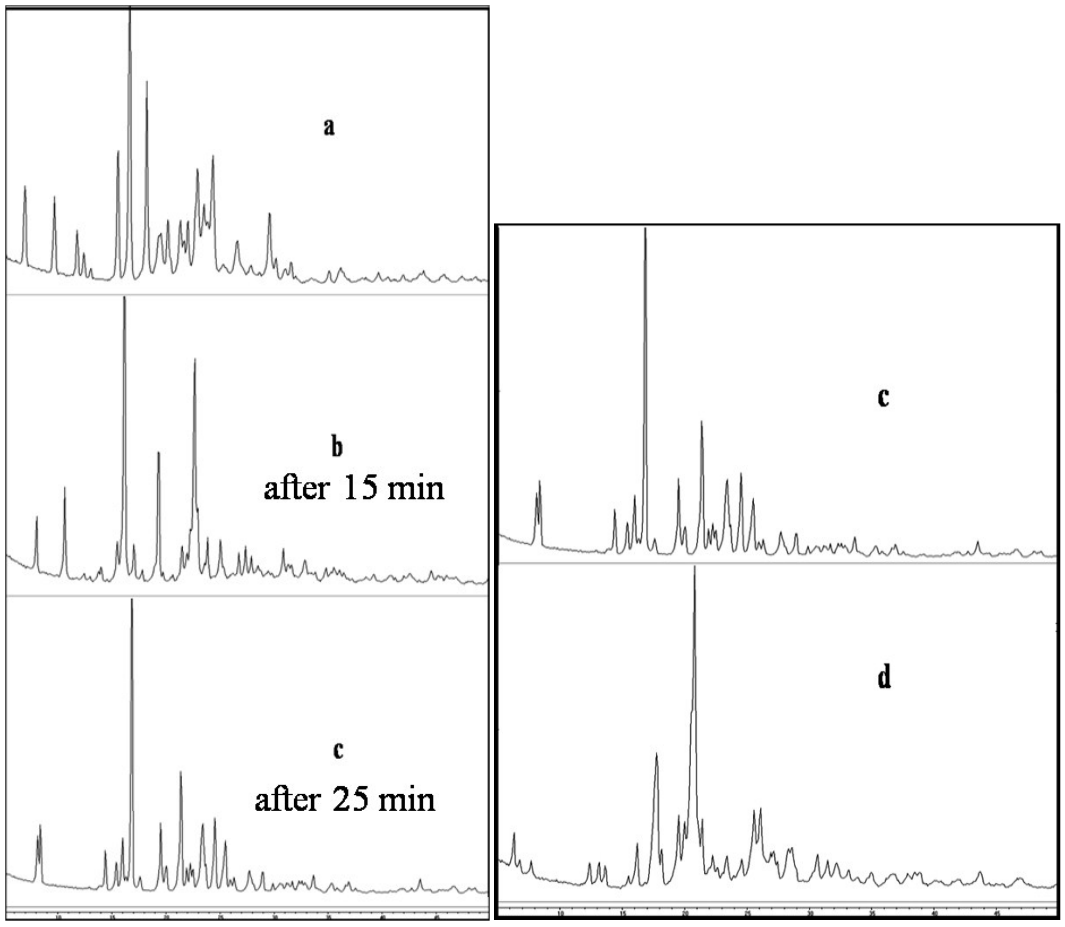
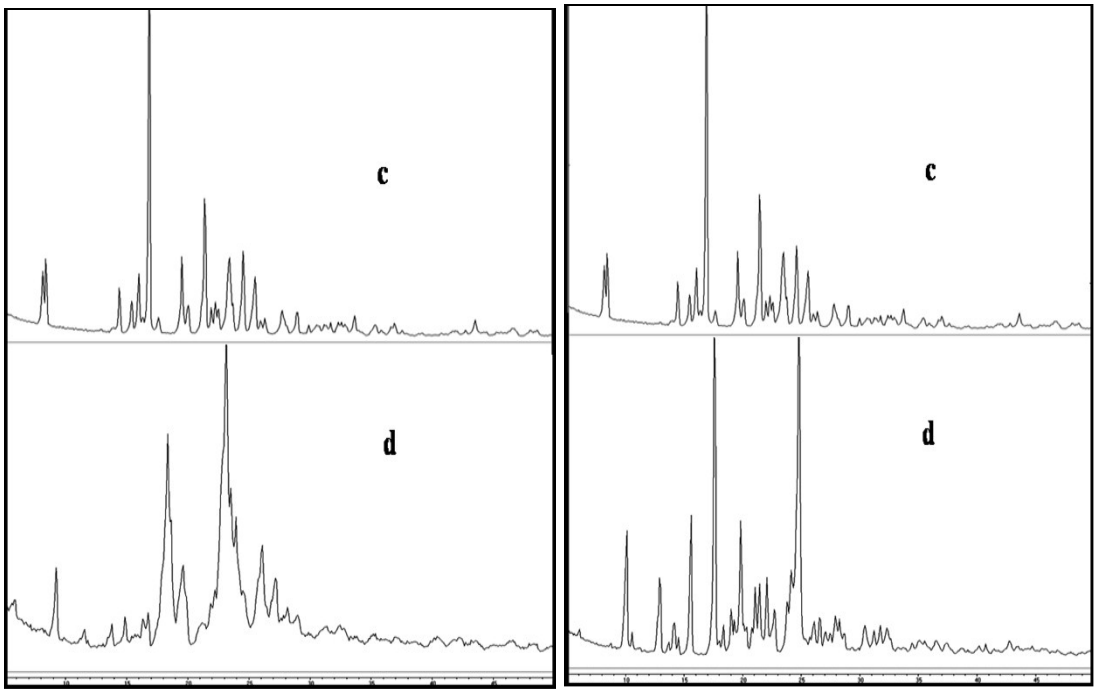


Figure S5 (e) Comparison of stretching frequencies of ETR–SBA hydrate with its starting materials.



(a) (b)



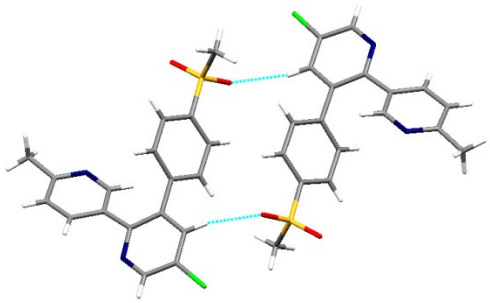
(c) (d)

Figure S6 PXRD plots to show the transformation.(a) Transformation of ETR anhydrate Form I to ETR hemihydrate Form I on grinding with water present (few drops).(b) ETR-SA cocrystalpreparation from ETR hemihydrate Form I.(c) ETR-GA cocrystalpreparation from ETR hemihydrate Form I. (d) ETR-SBA cocrystalpreparation from ETR hemihydrate Form I.

In the figures a, b, c, and d indicates, ETR anhydrate Form I, ETR hemihydrate Form II, ETR hemihydrate Form I, and cocrystal powder patterns.

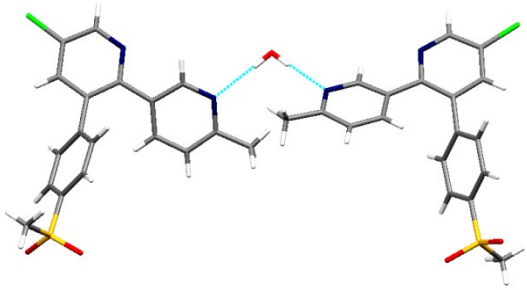
Stabilization energy calculations:

ETR Anhydrate Form I:



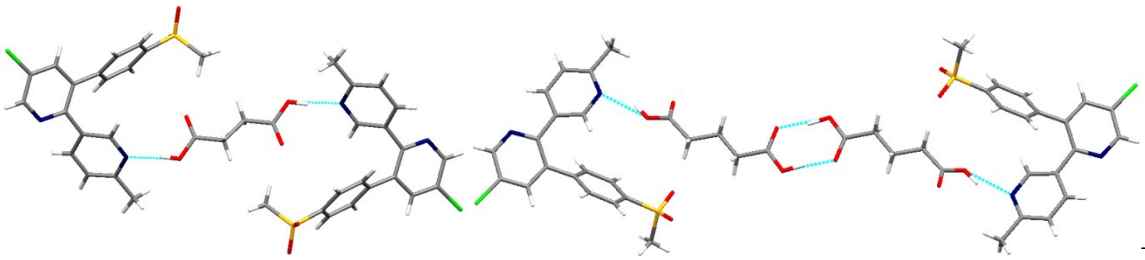
–6.54 kcal/mol

Hemihydrate Form I:



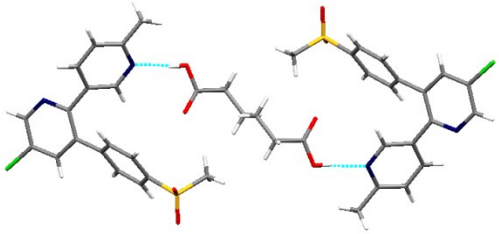
–22.97 kcal/mol

Cocrystals:

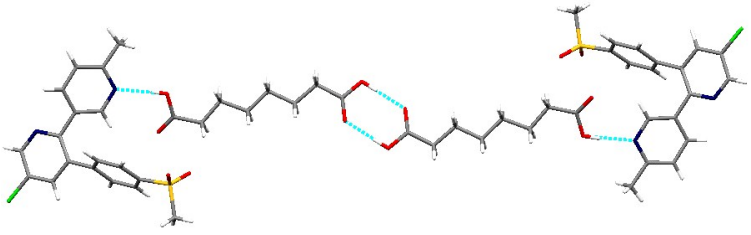


–38.37 kcal/mol (ETR-SA (2:1) cocrystal)

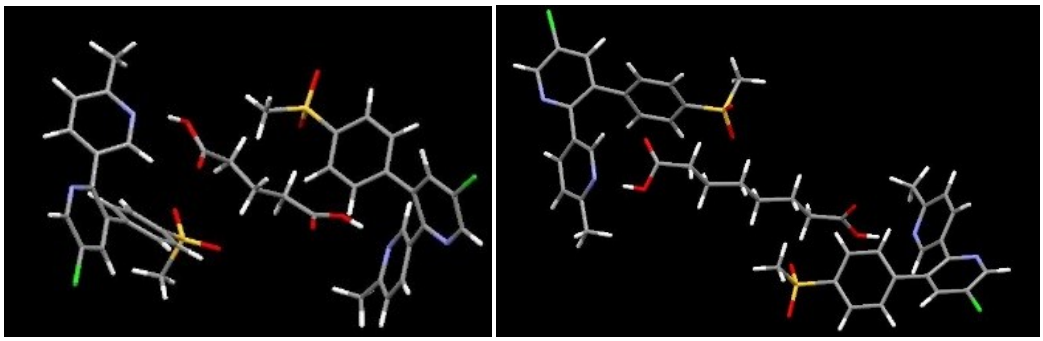
–47.97 kcal/mol (ETR-GA (1:1) cocrystal)



–30.23 kcal/mol (ETR-ADA (2:1) cocrystal)



–49.99 kcal/mol (ETR-SBA (1:1) cocrystal)



–31.09 kcal/mol (ETR-GA (2:1) cocrystal) –30.28 kcal/mol (ETR-SBA (2:1) cocrystal)

Figure S7 The stabilization energies were calculated by using M062x[1]/6-311++g (d, p)//M062x/6-311g (d, p) level of theory. These energies are BSSE (basis set superposition error) corrected using the counterpoise method.

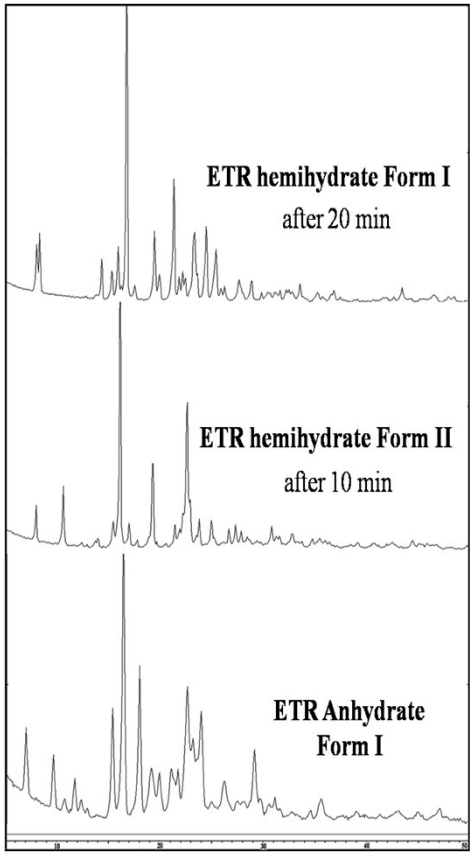


Figure S8 (a) Transformation of ETR anhydrate Form I to hemihydrate Form I in water slurry via hemihydrate Form II.

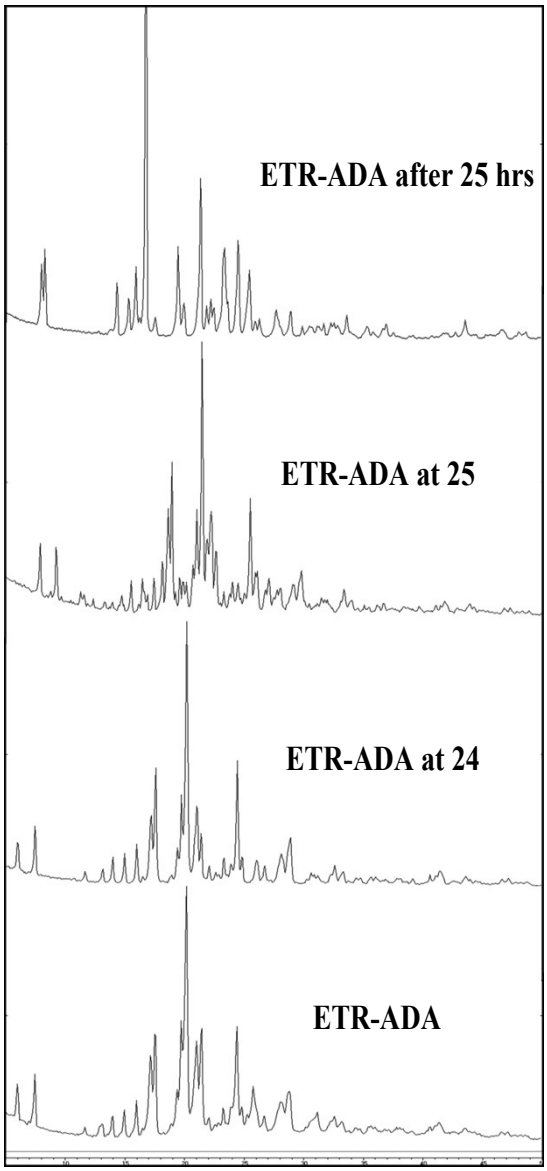


Figure S8 (b) Comparison of powder XRD pattern of ETR–ADA in water slurry experiments at different time intervals. Transformation of ETR-ADA cocrystal to ETR hemihydrate Form I after 24 h.

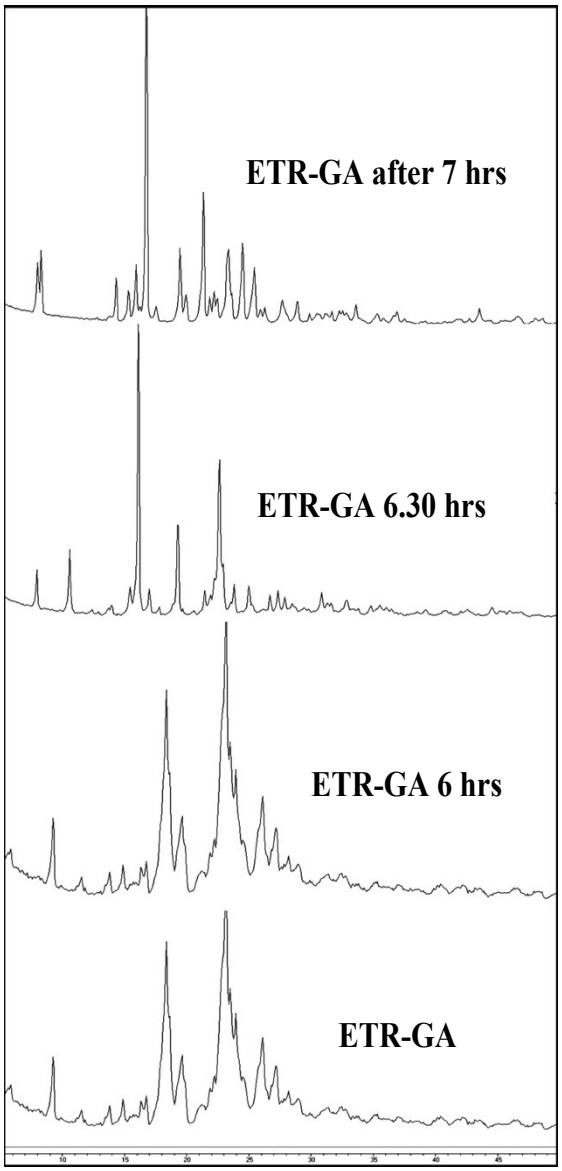
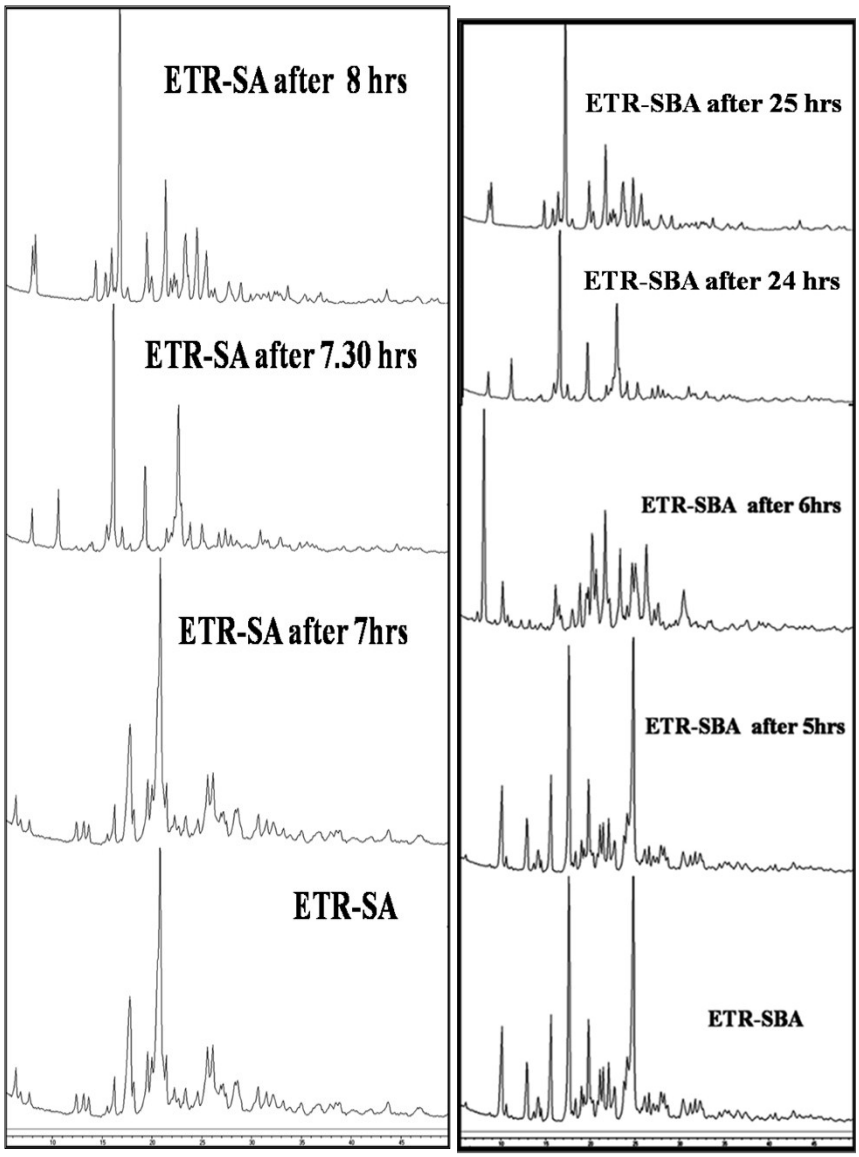


Figure S8 (c) Comparison of powder patterns ETR–GA Cocrystal water slurry experiments at different time intervals. Transformation of ETR-GA cocrystal to ETR hemihydrate Form I after 7 h.



(d) (e)

Figure S8 (d) and (e) Comparison of powder XRD pattern of ETR–SA and ETR–SBA cocrystal in water slurry experiments at different time intervals. Transformation of ETR–SA and ETR–SBA cocrystal to ETR hemihydrate Form I after 8 and 25 h, respectively.

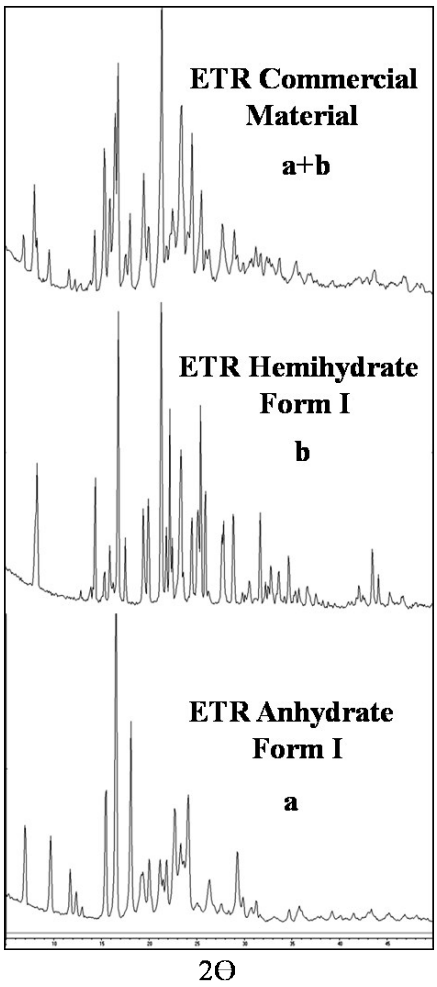


Figure S9 Powder XRD patterns of ETR anhydrate Form I (a), ETR hemihydrate (b), and ETR commercial material (a+b).

*(a+b) = mixture of (a) and (b).

Table S3 Melting point of ETR and cocrystals.

S. No.	Compound	Melting point of API/ Coformer (°C)	Melting Point of cocrystal (°C)
1	ETR	138.9	–
2	ETR–SA	184	150.4
3	ETR–GA	95-98	128.7
4	ETR–ADA	152	141.3
5	ETR–SBA	141-144	117.4
6	ETR–SBA hydrate	141-144	87.5, 115.2

7	ETR–CPR hydrate	69	90, 116

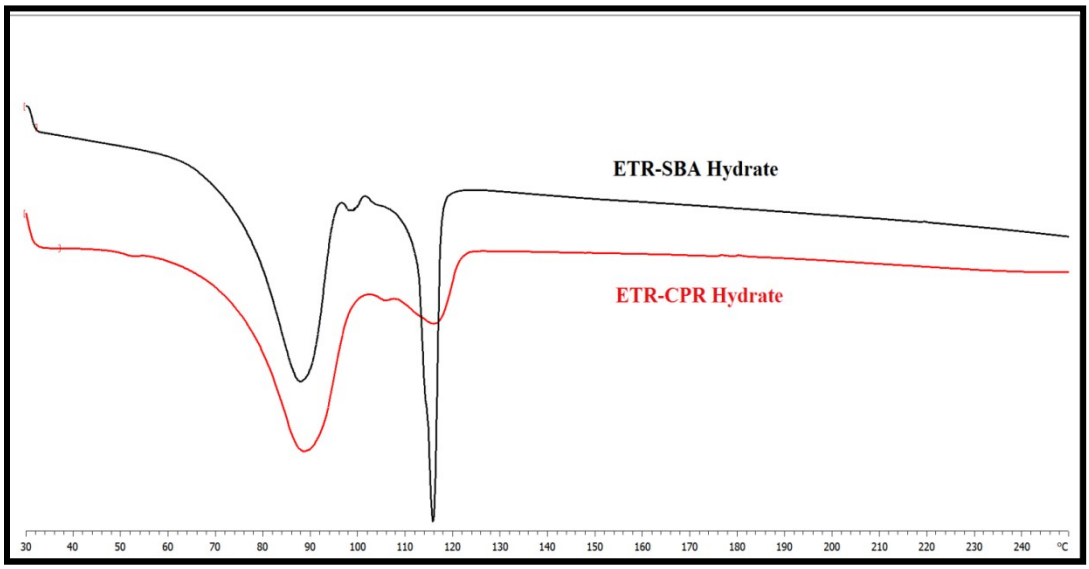


Figure S10 DSC endotherm of ETR–SBA hydrate and ETR–CPR hydrate.

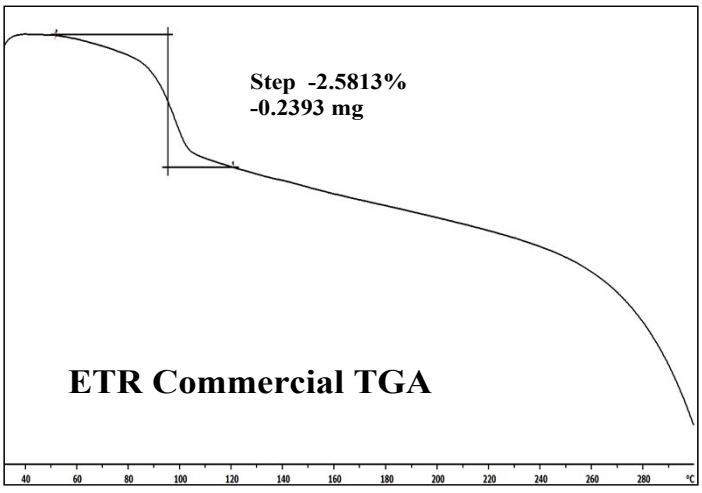


Figure S11 (a) TGA ofETR hydrate commercial material to show weight loss at 90-100 °C.

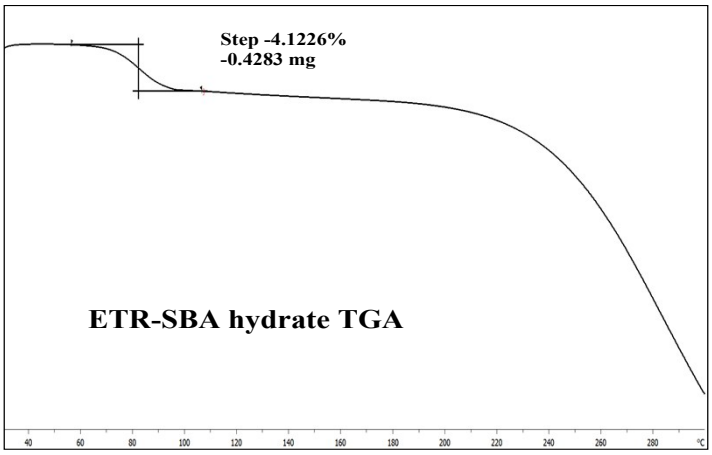


Figure S11 (b) TGA curve for ETR-SBA hydrate.

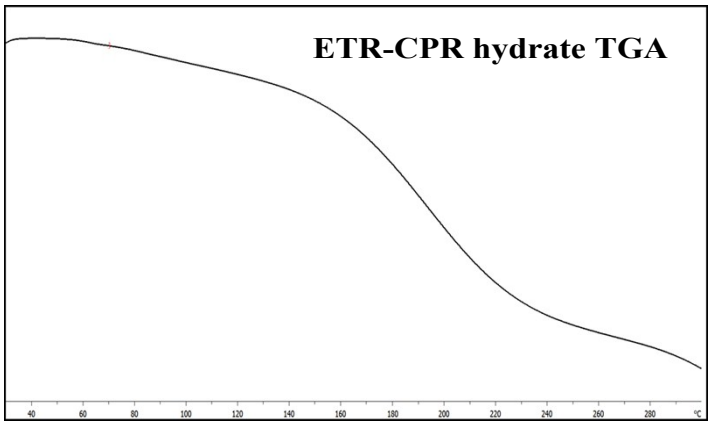


Figure S11 (c) TGA curve for ETR-CPR hydrate.

Experimental Section

ETR anhydrate Form I preparation: For the preparation of ETR anhydrate Form I, we have taken the commercial ETR (mixture of anhydrate Form I and hemihydrate Form I) and heated at 100 °C for about 1-2 h resulted ETR anhydrate Form I (confirmed by PXRD) as final product.

ETR hemihydrate Form I preparation: We have taken 400 mg of ETR anhydrate in 5 mL of water and stirred it for about 20-30 min resulted in ETR hemihydrate Form I, which was confirmed by PXRD.

ETR–SA: The Cocrystal was obtained by grinding of equimolar molar amounts (2:1) of ETR hemihydrate (Form I; 735.62 mg) and SA (118.09 mg) in a mortar pestle for 20-30 min and the resulted material was confirmed by PXRD, DSC, and IR. M.p. 150 °C.

ETR–GA: The Cocrystal was obtained by grinding of equimolar molar amounts (1:1) of ETR hemihydrate (Form I; 367.81 mg) and GA (132.12 mg) in a mortar pestle for 20-30 min and the resulted material was confirmed by PXRD, IR, DSC and finally by single crystal XRD. M.p. 128 °C.

ETR–ADA: crystallization of ground material of ETR hemihydrate and ADA in 2:1 stoichiometric ratio(ETR hemihydrate Form I 735.62 mg, ADA 146.14 mg) afforded block crystals in EtOAc/MeOH solvent mixture and the resulted material was confirmed by PXRD, IR, DSC and finally by single crystal XRD. Crystal structure was solved and refined under monoclinic crystal system with $P2_1/n$ space group and it's having one ETR and one half of the ADA molecules in one asymmetric unit.M.p. 141 °C.

ETR–SBA: The Cocrystal was obtained by dissolving equimolar amounts (1:1) of ETR hemihydrate Form I (367.81 mg) and SBA (174.2 mg) in anhydrous methanol afforded good quality crystals, and the crystal structure was solved and refined under triclinic crystal system with P-1 space group. The asymmetric unit contains each one of ETR and SBA molecules. M.p. 117 °C.

ETR–SBA trihydrate: The Cocrystal hydrate was prepared by grinding of ETR hemi hydrate Form I and SBA in 1:1 stoichiometric ratios and the resulted powder material was crystallized from methanol/water (1:1) solvent mixture. Crystal structure was solved and refined under triclinic crystal system with P-1 space group which is having two ETR, three water, and half unit SBA molecules in asymmetric unit. M.p. 115 °C.

ETR–CPR dihydrate: The Cocrystal was obtained by dissolving equimolar amounts (2:1) of ETR hemihydrate Form I (735.62 mg) and CPR (113.16 mg) in methanol solvent afforded good quality crystals after 3-4 days. The crystal structure of ETR–CPR dihydrate was solved and refined under triclinic crystal system with P-1 space group and the asymmetric unit contains two ETR, one CPR and two water molecules. M.p. 53 °C.

X–ray crystallography: X-ray reflections for the ETR–GA, ETR–ADA,ETR–SBA hydrate, and ETR–CPR hydrate were collected on Bruker SMART-APEX CCD diffractometer equipped with a graphite monochromator and Mo-Kα fine-focus sealed tube (λ = 0.71073 Å). ETR–SBA Data collected on Oxford Xcalibur Gemini Eos CCD diffractometer at 298 K using Cu-Kα radiation ((λ = 1.54184 Å) and reduction was performed using CrysAlisPro (version1.171.33.55)[4]and OLEX2[5] was to solve and refine the structures. X-ray reflections for ETR–GA, ETR–ADA, ETR–SBA hydrate, and ETR–CPR hydrate reduction was performed using Bruker SAINTSoftware.[6] Intensities were corrected for absorption using SADABS,[7] and the structure was solved and refined using SHELX-97.[8]All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on hetero atoms were located from difference electron density maps and all C–H hydrogens were fixed geometrically. Hydrogen bond geometries were determined in Platon.[9]X-Seed[10]was used to prepare packing diagrams. Crystal structures are deposited as part of the Supporting Information and may be accessed at www.ccdc.cam.ac.uk/data_request/cif

Powder X-ray diffraction: Powder X-ray diffraction was recorded on Bruker D8 Advance diffractometer (Bruker-AXS, Karlsruhe, Germany) using Cu-Kα X-radiation (λ = 1.5406 Å) at 40 kV

and 30 mA power. X-ray diffraction patterns were collected over the 2θ range 5–50° at a scan rate of 1°/min.

Vibrational spectroscopy: Nicolet 6700 FT–IR spectrometer with a NXR FT–Raman Module was used to record IR spectra. IR spectra were recorded on samples dispersed in KBr pellets.

Thermal analysis: DSC was performed on a Mettler Toledo DSC 822e module. Samples were placed in crimped but vented aluminum sample pans. The typical sample size is 4–6 mg, temperature range was 30–250 °C @ 10 °C/min. Samples were purged by a stream of nitrogen flowing at 80 mL/min.

Thermogravimetric analysis (TGA): TGA was carried out using Mettler Toledo TGASDTA851eoperating with STARe software to detect solvates and thermal degradation. Accurately weighed (5-15 mg) samples were loaded in alumina crucibles and heated at a rate of 10 ºC/min over a temperature range of 30 to 300 ºC under a nitrogen purge of 60 mL/min.

Gaussian 09 calculations: Cocrystal structures were optimized by using M062x/6-311g (d, p) level of theory.The initial geometry parameters for the structural motifs were taken from the crystal data. Single point energy calculations were done using M062x/6-311++g (d,p) level of theory to calculate the stabilization energies.

Stabilization energy calculations:

The stabilization energies were calculated using the following formula.

$$E_{stabilization} = E_{co-crystal} - m\,E_{ETR} - n\,E_{acid/water}$$

In the above equation, $E_{co-crystal}$ is the counterpoise corrected energy of co-crystal. $E_{ETR}$and $E_{acid/water}$are the energies corresponding to ETR drug and acid/water molecules respectively. $m\&n$ are the number of ETR molecules and acid or water molecules in the co-crystal.

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