Supporting Information

Tuning Diffusion Permeability of an Anti-Retroviral Drug, Emtricitabine, via Multicomponent Crystallizations

Vasanthi Palanisamy,[a] Palash Sanphui,*[a] Vaskuri G S Sainaga Jyothi,[b] Nalini R Shastri,[b] Geetha Bolla,*[c] Kandhan Palanisamy,[a] Muthuramalingam Prakash[a] and Venu R. Vangala[d]

[a]Department of Chemistry, Faculty of Engineering and Technology, SRM Institute of Science and Technology, SRM Nagar, Kattankulathur, Chennai TN-603203, India. Email: palashi@srmist.edu.in.

[b]Solid State Pharmaceutical Research Group, Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Hyderabad-500037, India.

[c]Department of Chemistry, National University of Singapore, Science Drive 3, Singapore 117543 (Singapore). Email: bolla.geetha25@gmail.com

[d]Centre for Pharmaceutical Engineering Science, School of Pharmacy and Medical Sciences, University of Bradford, Richmond Road, Bradford BD7 1DP, United Kingdom.

Table of Contents

Table S1. Neutron normalized hydrogen bond geometry (Å/°).

	d (H···A/ Å)	D (D···A/Å)	<D–H···A/°	Symmetry codes
ECB-CPR				
O2–H2···O4	2.05	2.839(5)	161	1-x,1/2+y,1/2-z
N2–H2A···O4	2.19	3.019(6)	170	-1+x,y,z
N2–H2B···O2	2.15	2.957(6)	158	1-x,-1/2+y,1/2-z
N4–H4···N3	2.08	2.942(5)	176	1+x,y,z
C7–H7···O4	2.45	3.252(5)	145	1-x,1/2+y,1/2-z
C19–H19B···O3	2.32	3.225(6)	156	1+x,y,z
ECB-DHBA				
N1–H1···O3	1.80	2.6611(2)	177	1-x,-1/2+y,1-z
N3–H3A···O4	1.90	2.7592(2)	176	1-x,-1/2+y,1-z
N3–H3B···O5	1.90	2.7468(2)	168	1-x,1/2+y,1-z
O6–H6···O2	2.12	2.8487(2)	148	-x,1/2+y,-z
C19–H19A···O7	2.54	3.3009(2)	135	1-x,-1/2+y,-z
ECB-MLN				
N2–H2A···O6	1.90	2.7539(11)	170	2-x,-1/2+y,1-z
N2–H2B···O4	1.95	2.7760(11)	161	1+x,y,1+z
N3–H3···O7	1.81	2.6708(11)	174	2-x,-1/2+y,1-z
O3–H3A···O8	2.04	2.7404(11)	143	1-x,1/2+y,1-z
C13–H13···O3	2.55	3.5060(14)	166	-x,-1/2+y,1-z
C16–H16···O5	2.49	3.3673(14)	148	-x,-1/2+y,-z
C17–H17A···O7	2.38	3.2324(13)	147	-1+x,y,z
ECB-MLE				
N1–H1···O5	1.85	2.7102(3)	175	1-x,1/2+y,1/2-z
N2–H2A···O6	1.94	2.7951(3)	175	1-x,1/2+y,1/2-z
N2–H2B···O7	1.91	2.7503(3)	164	-x,1/2+y,1/2-z
O7–H7···O4	1.86	2.6651(3)	168	2-x,-1/2+y,1/2-z
C12–H12B···O5	2.56	3.1165(3)	116	1/2-x,-y,-1/2+z
ECB-SAC				
N1–H1A···O3	2.00	2.8038(2)	164	1-x,1/2+y,1-z
N1–H1B···O3	2.00	2.7394(2)	172	1+x,1+y,z
N4–H4···N3	2.18	2.9620(2)	170	1+x,1+y,z
O6–H6···O1	2.02	2.7369(2)	158	1+x,y,z
C7–H7···O2	2.55	3.3527(3)	139	1+x,y,z
C7–H7···O15	2.55	3.0718(3)	113	2-x,-1/2+y,-z
C8–H8A···O15	2.47	3.1516(3)	127	2-x,-1/2+y,-z

Table S2. ^{15}N SSNMR chemical shifts (ppm) of ECB binary systems.

	N(1) ppm	N(2) ppm	N(3) ppm	Conclusion
ECB	-285.5/-289.6	-179.3/-180.3	-228.3/-237.9	--
ECB–BA (Form I)	-289.1	-190.8	-225.2	Cocrystal
ECB–DHBA	-272.5	-243.6	-236.9	Salt

Table S3. Literature reports of multicomponent solids of drugs with solubility/permeability.

Sr. no.	Drug solid forms reported	Solubikity/permeability study	Possible factors responsible	References
1	**Acyclovir** (BCS class IV) Acyclovir–maleate Acyclovir–fumaric acid dihydrate Acyclovir–glutaric acid	Maleate salt decreased permeability, whereas fumaric acid/glutaric acid cocrystals improved by 2-4 fold.	Higher log *P* and solubility (coformers), lower melting points (cocrystals) than the drug lead to improved permeability.	Yan et. al., CrystEngComm, **2013**, 15, 6457–6460.
2	**Indomethacin** (BCS class II) Indomethacin–2-hydroxy, 4-methylpyridine (cocrystal 1) Indomethacin–2-methoxy, 5-nitroaniline (cocrystal 2) Indomethacin–saccharine (cocrystal 3)	Apparent permeation coefficient for cocrystals 1 and 3 increased compared to native drug and that of cocrystal 2 is decreased.	Enhanced permeability of cocrystal 1 was correlated with its improved dissolution and loss of barrier effect of the monolayer.	Ferretti et al. Mol. Pharmaceutics **2015**, 12, 1501–1511.
3	**Hydrochlorothiazide** (BCS class IV) Hydrochlorothiazide–nicotinic acid Hydrochlorothiazide–nicotinamide Hydrochlorothiazide–4-aminobenzoic acid Hydrochlorothiazide–resorcinol Hydrochlorothiazide–succinamide	All the cocrystals (except succinamide one) improved permeability/diffusion (max. 2 fold) compared to the drug.	Absence of (drug) sulfonamide dimer/catemer synthon in nicotinic acid/ nicotinamide cocrystals lead to enhance permeability. Both polar/non-polar interactions have pivotal role in improved diffusion.	Sanphui et al., Mol. Pharmaceutics **2015**, 12, 1615-1622.
4	**Theophylline** (BCS class I) Theophylline–o-aminobenzoic acid Theophylline–o-aminobenzoic acid	Flux of theophylline–o-aminobenzoic acid cocrystal hydrates and solvates	Weaker heterosynthon and layers structure between theophylline and o-	Saikia et al., Cryst. Growth Des. **2015**, 15, 5593−5603.

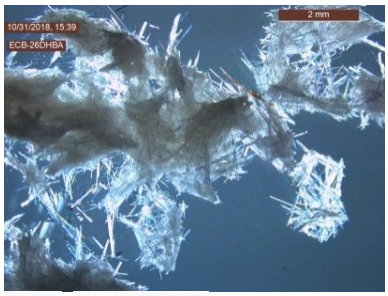
	(isobutanol solvate) Theophylline–o-aminobenzoic acid hydrates Theophylline–m-aminobenzoic acid Theophylline–p-aminobenzoic acid	exhibited improved diffusion rate (1.3-1.7 fold) compared to its anhydrous cocrystal and others including the drug.	aminobenzoic acid improved solubility and diffusion compared to m/p-aminobenzoic acid cocrystals.	
5	**5‑Fluorouracil** (BCS class III) 5‑Fluorouracil–3-hydroxybenzoic acid 5‑Fluorouracil–4-aminobenzoic acid 5‑Fluorouracil– cinnamic acid	All the cocrystals improved diffusion/flux than the drug. Cinnamic acid cocrystal showed max. diffusion/flux (1.8 fold)	Drug-coformer heterosynthons, lower crystal density of cocrystals and higher log *P* (coformers) are correlated with improved diffusion behavior.	Dai et al., Cryst. Growth Des. **2016**, 16, 4430−4438.
6	**Furosemide** (BCS class IV) Furosemide– anthranilamide Furosemide–4-toluamide Furosemide–2-picolinamide Furosemide–piperazine Furosemide–2,3,5,6-tetramethylpyrazine Furosemide–pyrazine Furosemide–2-picolinic acid Furosemide–isoniazid Furosemide–theophylline	All the cocrystals and salts improved permeability compared to the native drug. Tetramethylpiperazine cocrystal exhibited highest flux of the drug.	Heterosynthons, higher improved solubility in the cocrystals/salts and hydrophobic nature of the coformers are considered for improved diffusion of the drug.	Banik et al. Cryst. Growth Des. **2016**, 16, 5418–5428.
7	**Norfloxacin-sulfathiazole** (BCS class IV, II) Norfloxacin-sulfathiazole salt hydrate	Salt improved diffusion permeability compared to their physical mixture.	Lower melting point and higher solubility are correlated with improved diffusion behavior	Gopi et al., Mol. Pharmaceutics **2016**, 13, 3590−3594.
8	**Hydrochlorothiazide** (BCS class IV)	Piperazine and picolinamide	Higher diffusion/flux of the	Gopi et al., *Cryst. Growth*

	Hydrochlorothiazide–piperazine Hydrochlorothiazide–picolinamide Hydrochlorothiazide–malonamide Hydrochlorothiazide–isoniazide Hydrochlorothiazide–tetramethylpyrazine	cocrystals improved diffusion/flux compared to the drug alone. Other cocrystals showed comparable diffusion as the drug.	cocrystals are correlated with their higher solubility.	*Des.* **2017**, 17, 308–316.
9	**Ethenzamide** (BCS class II) Ethenzamide–2,5-dihydroxybenzoic acid Ethenzamide–2,6-dihydroxybenzoic acid Ethenzamide–3,4-dihydroxybenzoic acid Ethenzamide–3,5-dihydroxybenzoic acid	Cocrystals improved solubility and permeability compared to the native drug in pH 7 phosphate buffer medium	Improved solubility and permeability are explained based on heterosynthons, conformations of the drug and logP of the coformers.	Khatodia et al. CrystEngComm, **2017**, 19, 6992–7000.
10	**Meloxicam** (BCS class II) Meloxicam–salicylic acid	Cocrystal showed enhanced drug permeation coefficient	Drug-coformer interactions enhanced both drug solubility and cutaneous permeation.	Machado et al. *Eur. J. Pharm. Sci*., **2018**, 123, 184–190.
11	**Entacapone** (BCS class IV) Entacapone– acetamide Entacapone–nicotinamide Entacapone–isonicotinamide Entacapone–pyrazinamide Entacapone–isoniazid Entacapone–theophylline hydrate	Entacapone–theophylline hydrate exhibited improved solubility/permeability.	Higher diffusion was correlated with high solubility/permeability of coformer theophylline.	Bommaka et al. Cryst. Growth Des. **2018**, 18, 6061–6069.
12	**Acetazolamide** (BCS class IV) Acetazolamide–theophylline Acetazolamide–piperazine (salt) hydrate	Theophylline cocrystal and piperazine salt hydrate improve diffusion of the drug	Acetazolamide dimers forming layers structures and hydrophobic interactions	Zhang et al. J. Mol. Struc. **2019**, 1184, 225–232.

		by 1.5 and 2.2 fold.	between the layers promote higher diffusion of the drug	
13	**Acetazolamide** (BCS class IV) Acetazolamide–proline	The cocrystal improve cumulative diffusion by 2 fold compared to the native drug.	Higher lipophilicity of proline and heterosynthons in the cocrystal leads to low polarity and high lipophilicity/permeability.	Song et al. CrystEngComm, **2019**, 21, 3064-3073.
14	**5-Fluorouracil** (BCS class III) 5-Fluorouracil–salicylic acid 5-Fluorouracil–3-hydroxybenzoic acid 5-Fluorouracil–4-hydroxybenzoic acid (Forms I/II)	All the cocrystals improve permeability/diffusion rate compared to the native drug.	Cocrystals with higher lipid solubility and lower lattice energy are correlated with improved diffusion behavior.	Dai et al. CrystEngComm, **2019**, 21, 5095–5105.
15	**Naftopidil** (BCS class IV) Naftopidil–oxalate Naftopidil–succinate Naftopidil–D-malate Naftopidil–L-malate Naftopidil–DL-malate Naftopidil–isonicotinate Naftopidil–3,5-dinitrobenzoate	Except nicotinate salt, other salts exhibited rapid increase of flux compared to native drug. The malate salts improved flux by 4 folds and permeability up to 16 times. .	High permeability of the salts was correlated improved solubility/dissolution rates.	Mannava et al. Cryst. Growth Des. **2020**, 20, 3064–3076.
16	**Etodolac** (BCS class II) Etodolac–isopropylamine Etodolac–n-hexylamine Etodolac–cyclohexylamine	Etodolac–isopropylamine salt exhibited highest dissolution and diffusion.	Improved diffusion rate was correlated with higher molecular mobility and dissolution rate.	Rai et al. Cryst. Growth Des. **2020**, 20, 4512–4522.

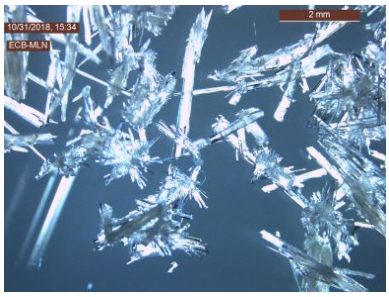
	Etodolac–2-phenylethylamine Etodolac–piperazine			
17	**Allopurinol** (BCS class IV) Allopurinol–piperazine Allopurinol–2,4-dihydroxybenzoic acid Allopurinol–isonicotinamide	Allopurinol–piperazine cocrystal improved diffusion/membrane permeability	Weaker interactions between allopurinol and piperazine and lower solubility and density lead to higher diffusion.	Dai et al. Cryst. Growth Des. **2020**, 20, 5160–5168.
18	**Furosemide** (BCS class IV) Furosemide–imidazole (salt) Furosemide–5-fluorocytosine	Binary systems improved cellular transport by 2-3 fold across Caco-2 monolayers.	Improved diffusion was correlated with enhanced solubility of the salt compared to the cocrystal.	Diniz et al. Int. J. Pharm. **2020**, 587, 119694.
19	**Nicorandil** (BCS class III) Nicorandil oxalate Nicorandil fumarate Nicorandil succinate Nicorandil–suberic acid	All the salts and cocrystal improved solubility, dissolution rate and permeability compared to the native drug.	Improved solubility was correlated with ionic nature of the salts and permeability was correlated with hydrophobicity of suberic acid.	Mannava et al. CrystEngComm, **2021**, 23, 227-237

ECB–BA Cocrystal: Form I (block), II (fibers)

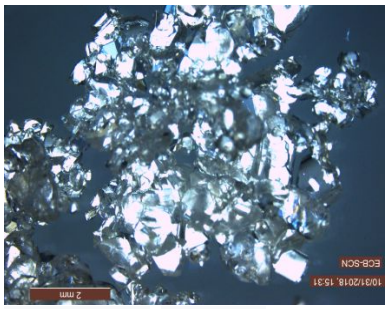


ECB–DHBA Salt

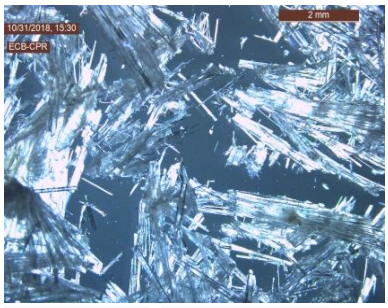
ECB–MLE Salt



ECB–MLN salt



ECB–SAC salt



ECB–CPR cocrystal

Figure S1. Microscopic images of ECB multicomponent molecular crystals.

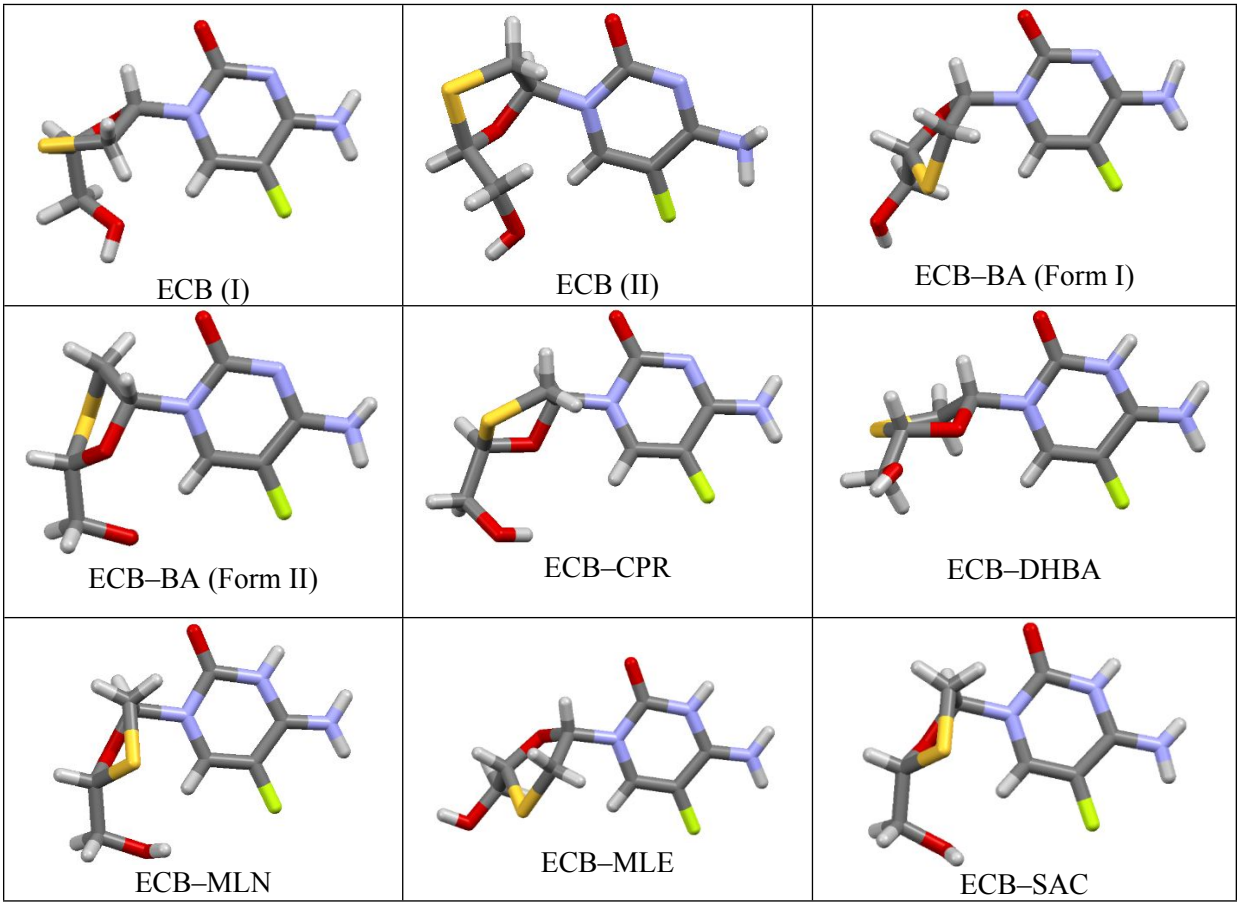
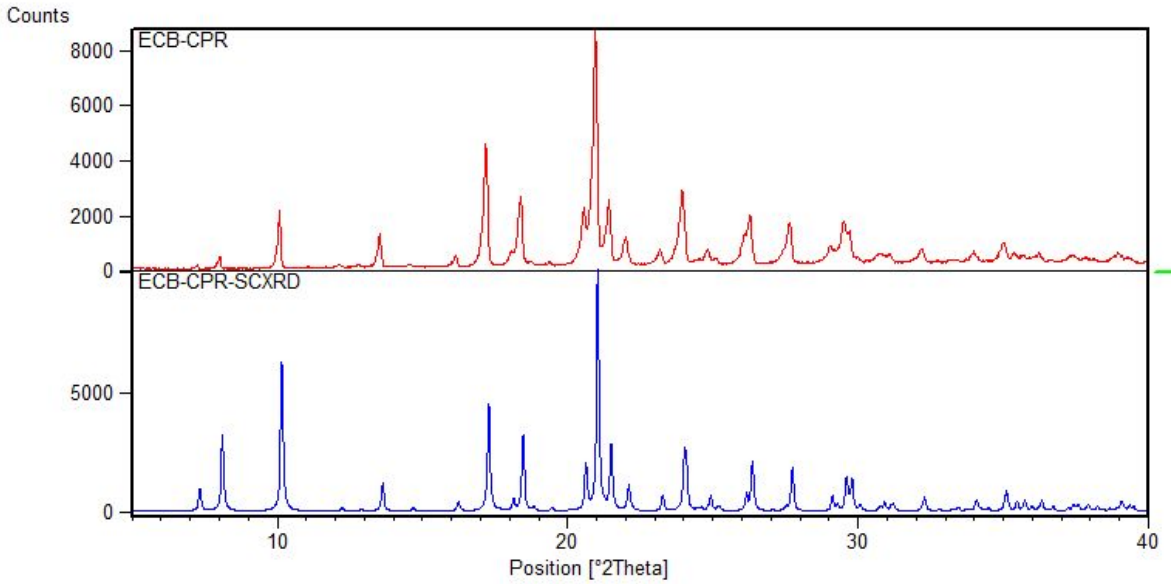
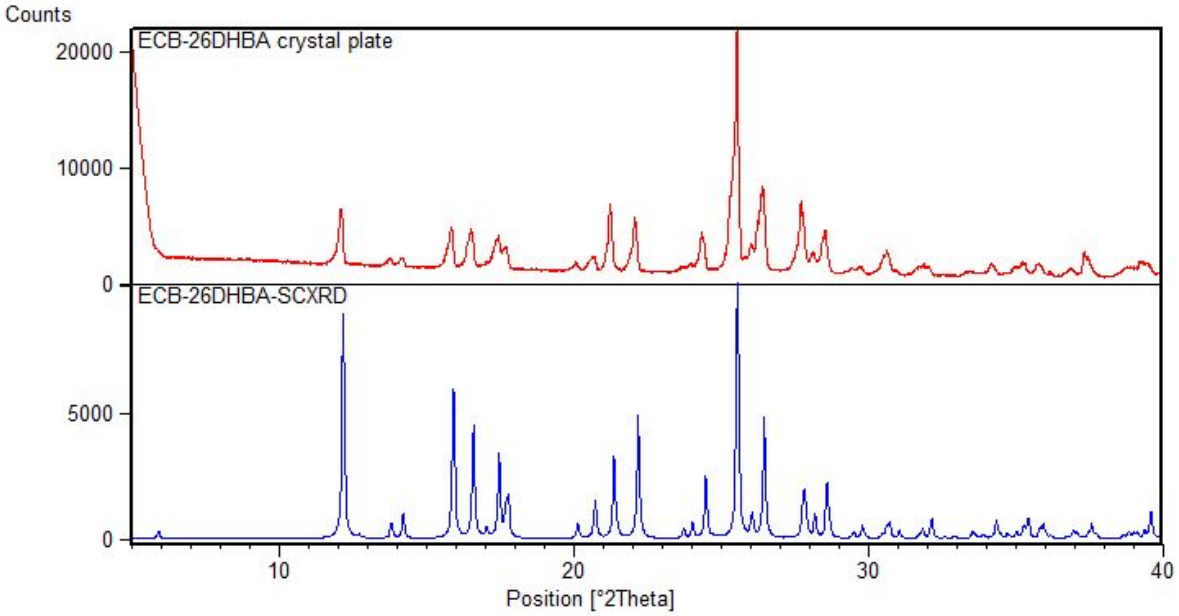


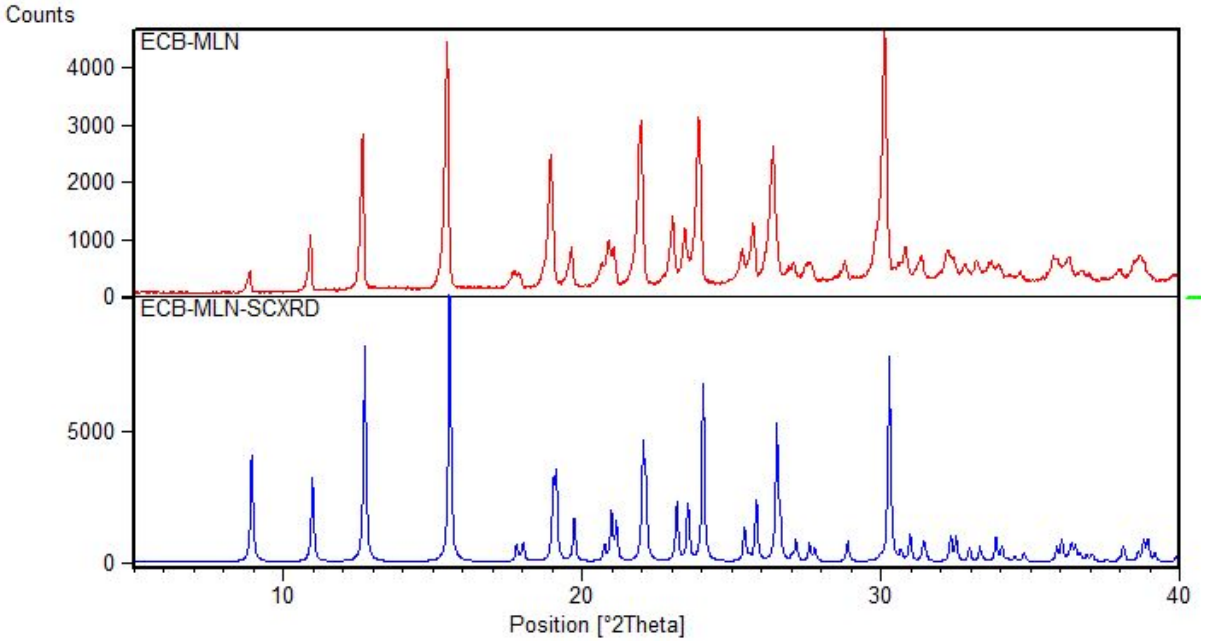
Figure S2. Molecular conformations of ECB in the drug and its multicomponent solids.


Counts
ECB-CPR
8000
6000
4000
2000
0
ECB-CPR-SCXRD
5000
0
10
20
30
40
Position [°2Theta]

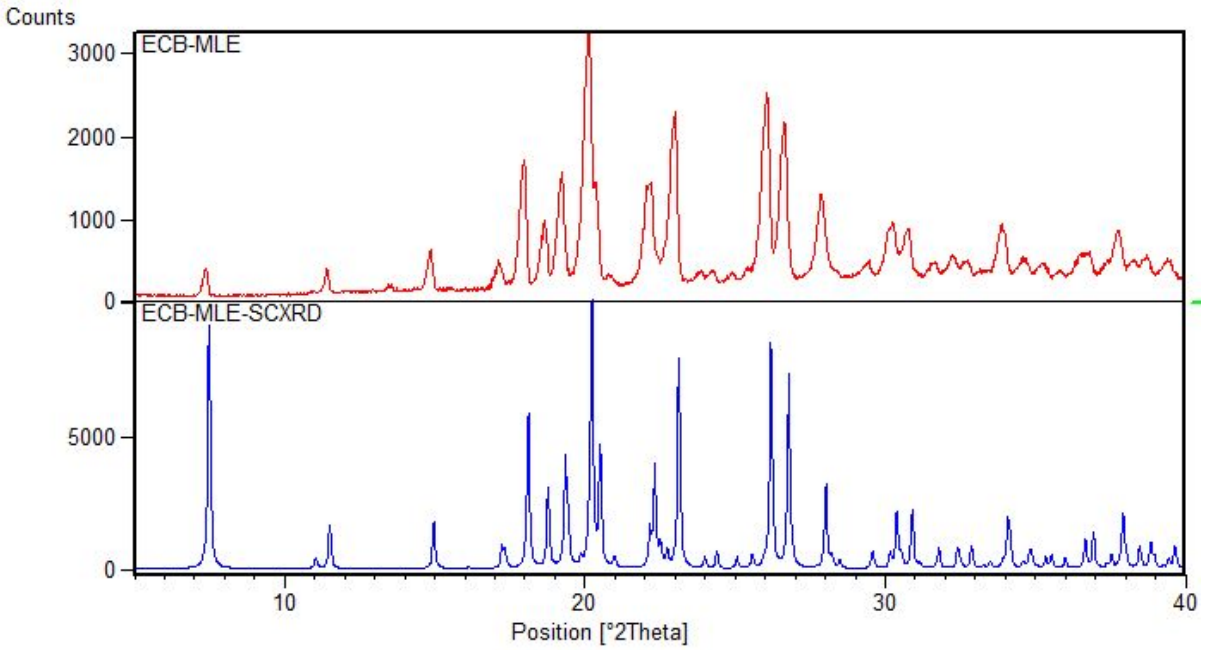
(a)


Counts
ECB-26DHBA crystal plate
20000
10000
0
ECB-26DHBA-SCXRD
5000
0
10
20
30
40
Position [°2Theta]

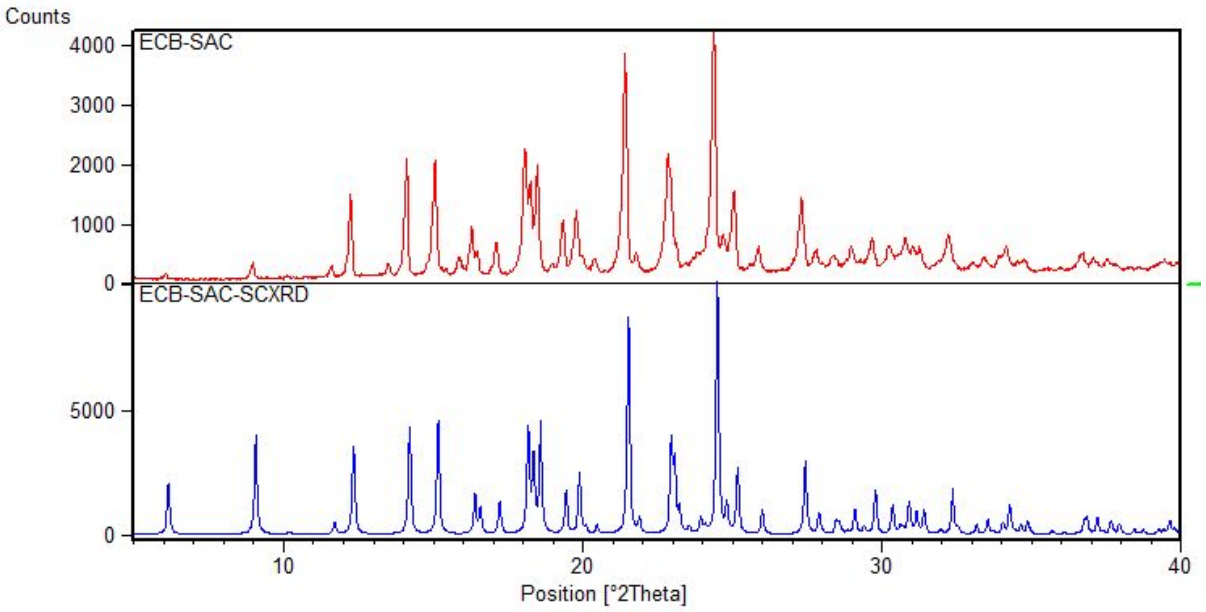
(b)


Counts
ECB-MLN
4000
3000
2000
1000
0
ECB-MLN-SCXRD
5000
0
10
20
30
40
Position [°2Theta]

(c)

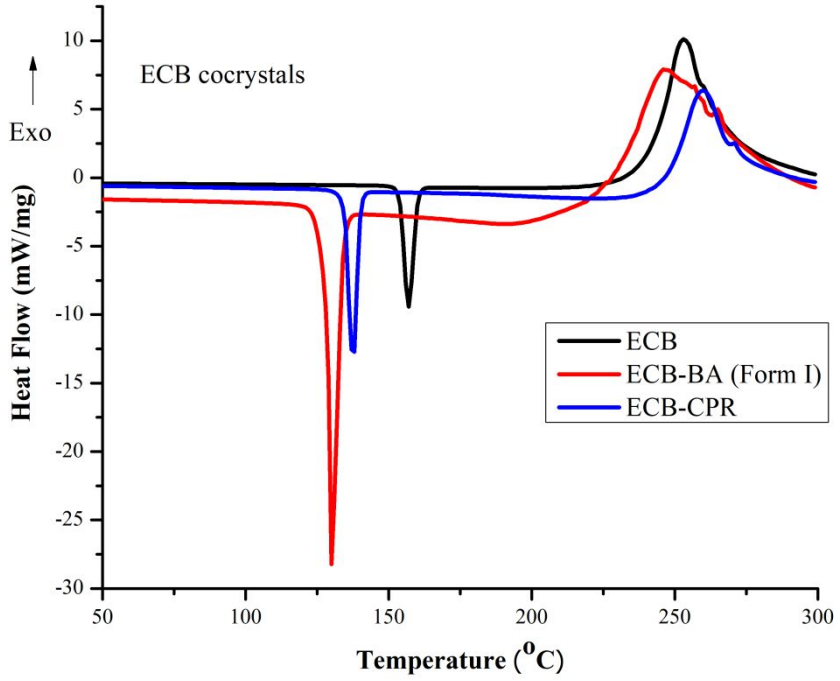

Counts
ECB-MLE
3000
2000
1000
0
ECB-MLE-SCXRD
5000
0
10
20
30
40
Position [°2Theta]

(d)

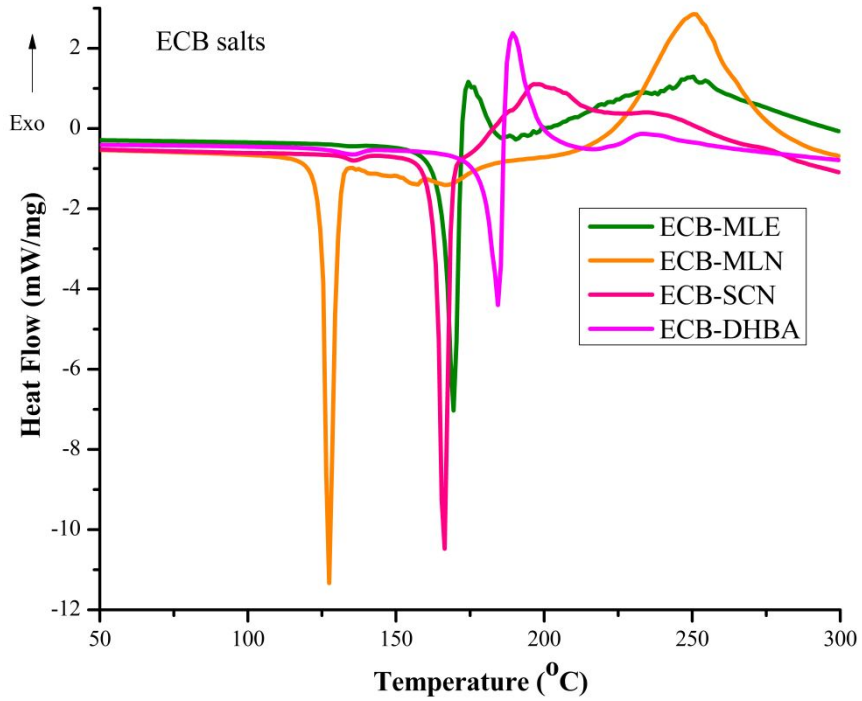


(e)

Figure S3. PXRD (red trace) comparison of (a) ECB–CPR, (b) ECB–DHBA, (c) ECB–MLN, (d) ECB–MLE, and (e) ECB–SAC with the corresponding simulated X-ray patterns (blue trace).



(a)



(b)

Figure S4. DSC endotherms of ECB cocrystals and salts indicate melting endotherms of ECB–BA/CPR (red, blue traces) is lower than that of the drug (black trace), whereas melting endotherms of salts like ECB–MLE/DHBA/SAC (except ECB–MLN salt, orange trace) are higher than that of the drug.

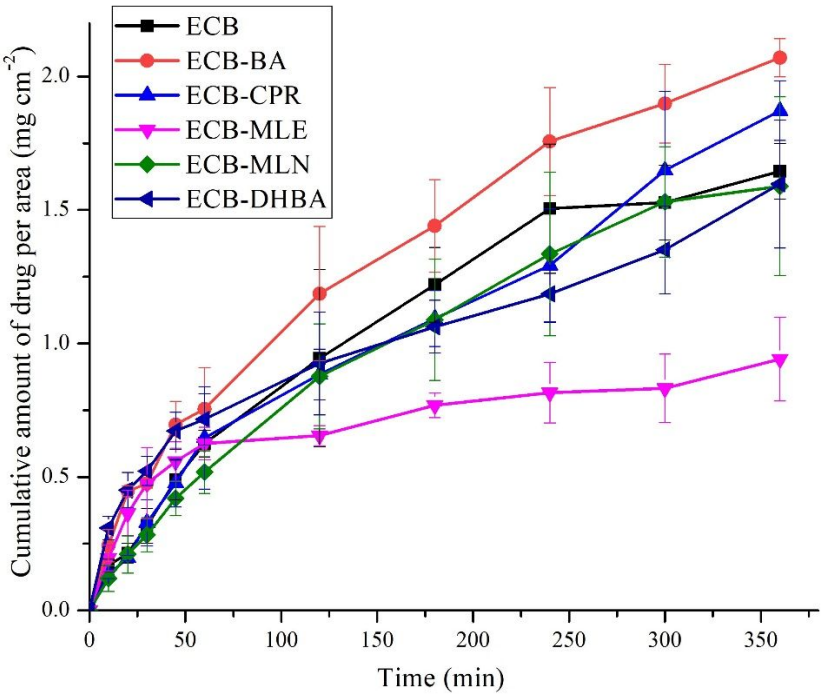


Figure S5. Cumulative amount of drug diffused per unit area vs time (min) of all the multicomponent systems.

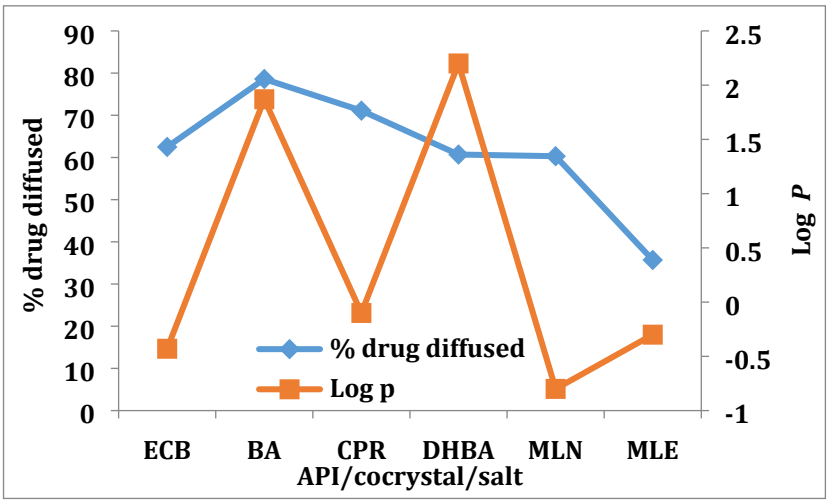
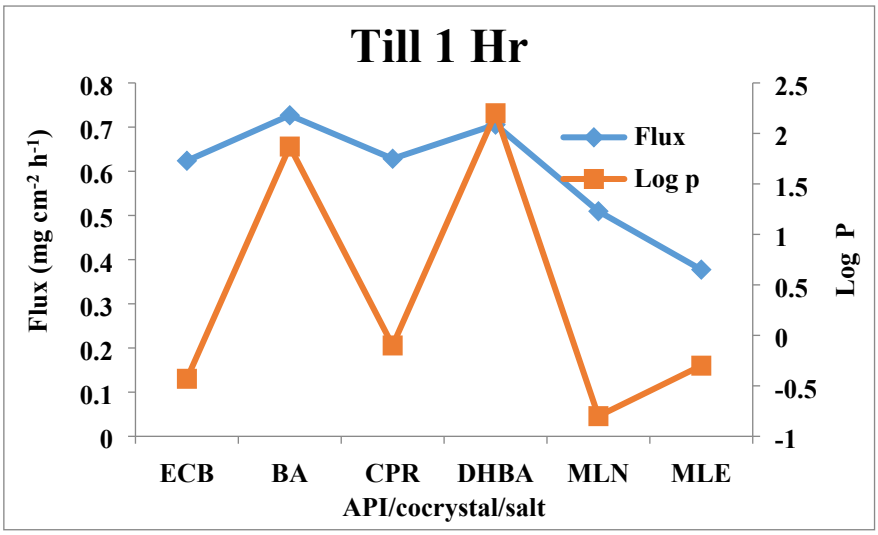
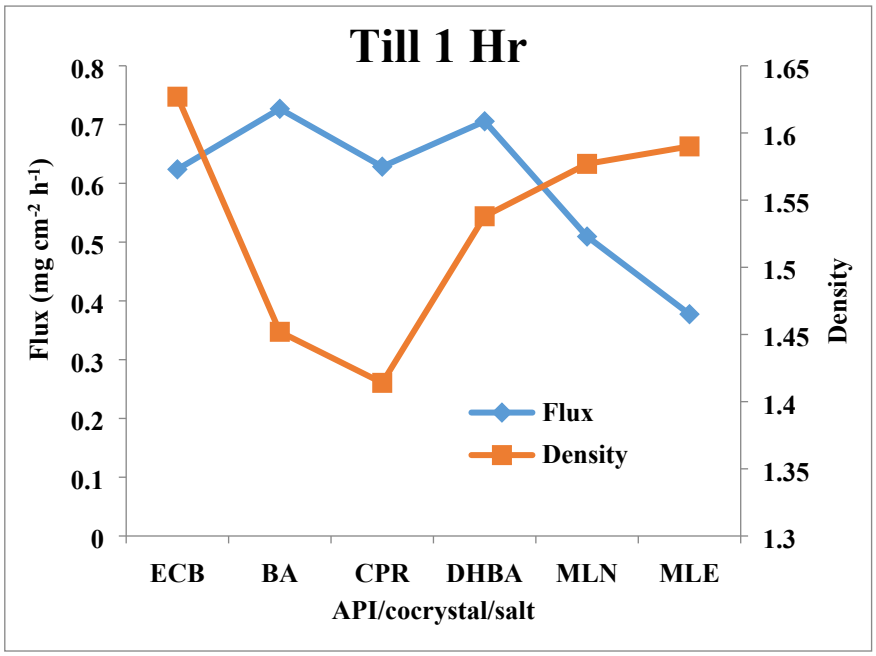


Figure S6. Correlation between % drug diffused and log *P* of the drug/coformers.



(a)



(b)

Figure S7. Correlation between (a) flux and log *P* and (b) flux and calculated density (from crystal structures) of the ECB multicomponent solids.