Supporting Information

Improvement of humidity stability of ethyl gallate by cocrystal strategy and study of dissolution behavior of the cocrystal

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Content

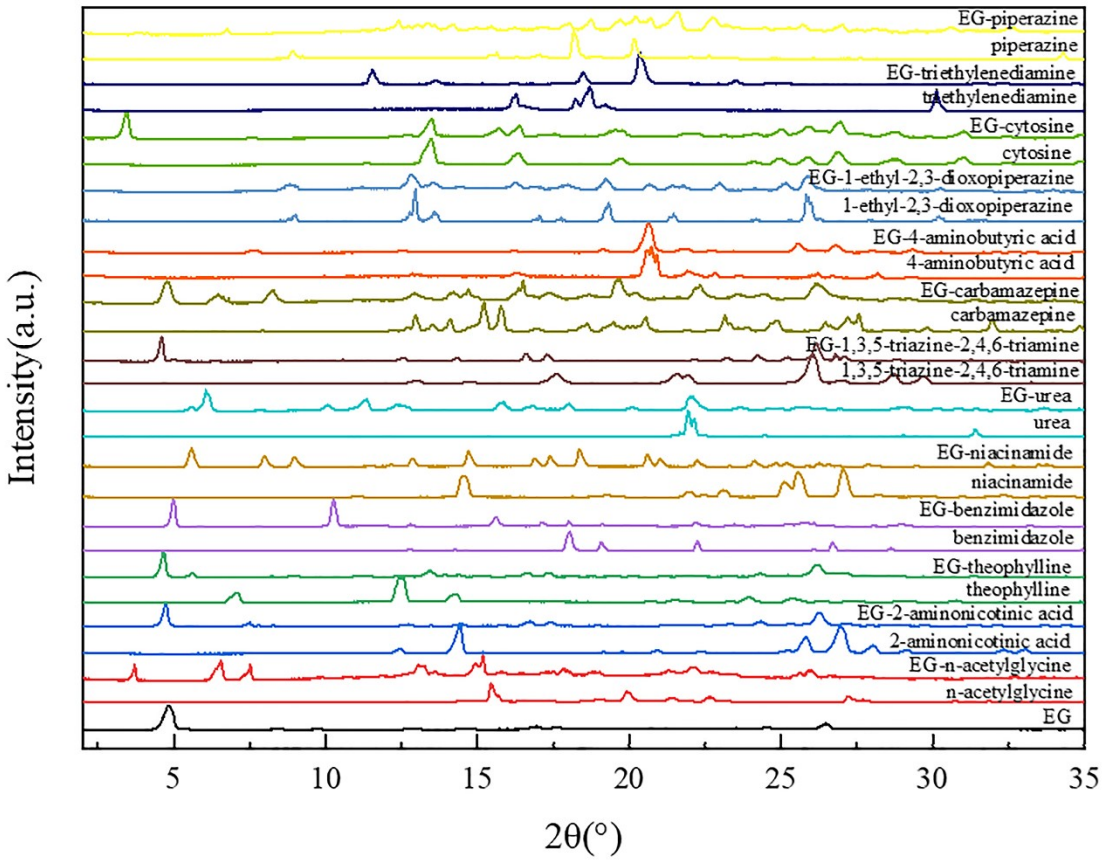

Fig. S1 PXRD patterns of LAG experiment product with new phases.

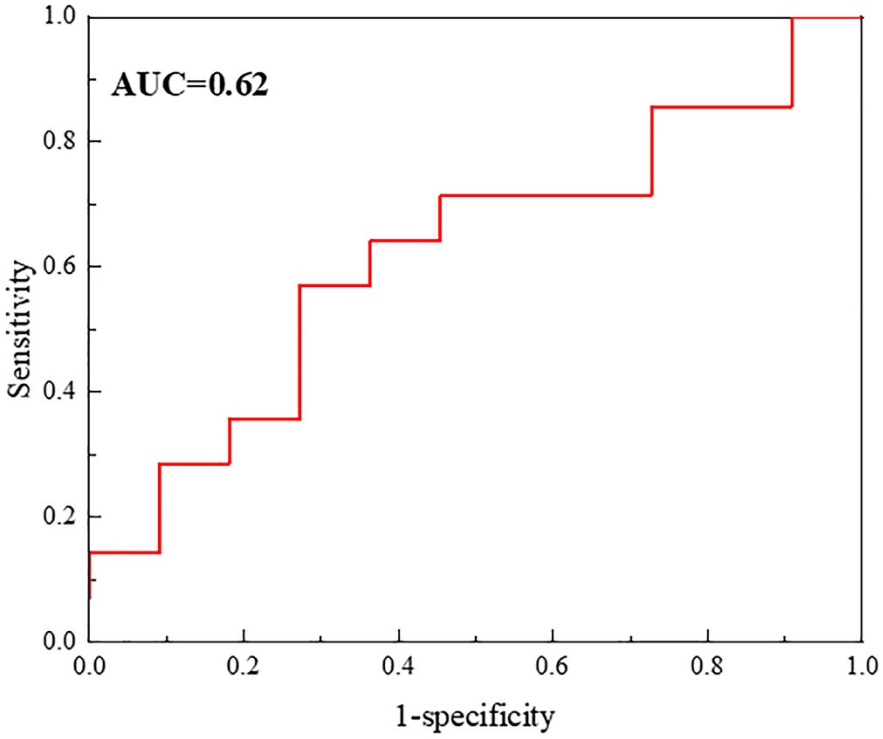

Fig. S2 ROC curve for COSMO-RS methodology.

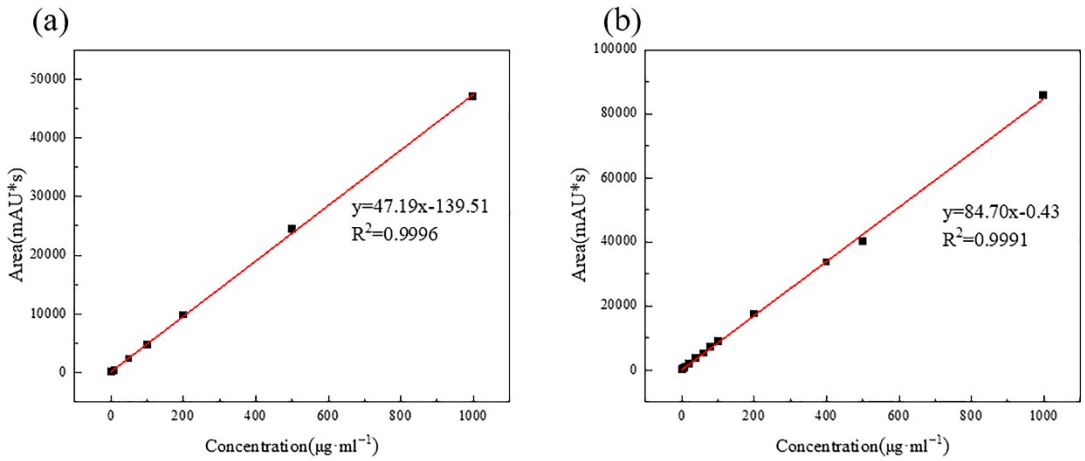

Fig. S3 The HPLC standard curve of pure EG and 2MIE: (a) EG; (b) 2MIE.

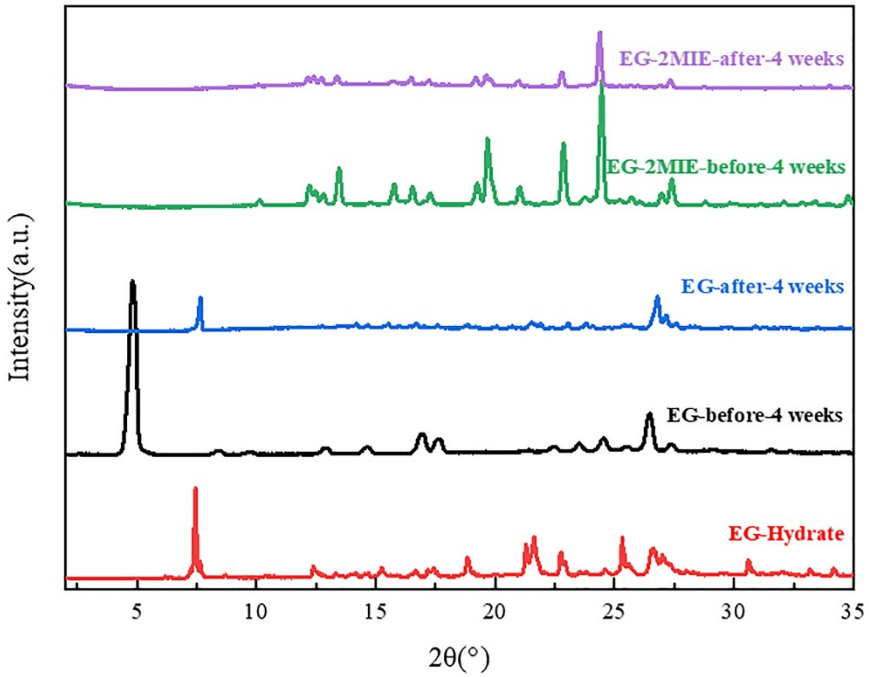

Fig. S4 PXRD patterns of EG-2MIE and EG under accelerated conditions (40 °C, 75% RH) for 4 weeks.

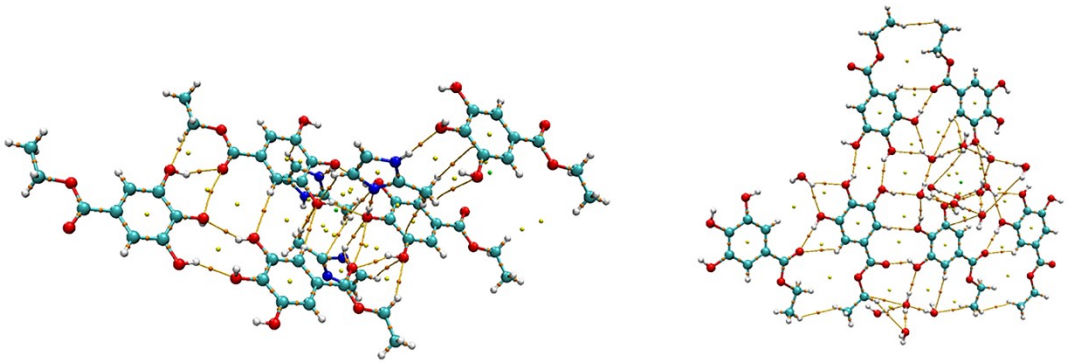

Fig. S5 The topological geometric structures of EG-2MIE and EG-Hydrate, with purple, orange, yellow, and green spheres corresponding to the (3, −3), (3, −1), (3, +1), and (3, +3) critical points of electron density (nuclear critical point, bond critical point, ring critical point, and cage critical point), respectively, the orange curve corresponds to the key path.

Table S1. The excess enthalpy (ΔH_{ex}) values and PXRD result of EG and the coformers.

API	Coformer	ΔH_{ex}(kcal·mol^{-1})	New form
EG	piperazine	−5.89	Yes
	triethylenediamine	−5.78	Yes
	nizatidine	−4.94	No
	cytosine	−4.60	Yes
	1-ethyl-2, 3-dioxopiperazine	−4.49	Yes
	palbociclib	−4.39	No
	4-aminobutyric acid	−3.83	Yes
	2-Imidazolidone	−3.50	No
	carbamazepine	−3.12	Yes
	1, 3, 5-triazine-2, 4, 6-triamine	−3.10	Yes
	2-methylimidazole	−3.00	Yes
	glutamine	−2.93	No
	urea	−2.87	Yes
	taurine	−2.61	No
	niacinamide	−2.58	Yes
	lansoprazole	−2.49	No
	2-aminopyrimidine	−2.39	No
	picolinamide	−2.04	No
	benzimidazole	−1.91	Yes
	theophylline	−1.80	Yes
	serine	−1.69	No
	mannitol	−1.37	No
	2-aminonicotinicacid	−1.26	Yes

API	Coformer	ΔH_{ex}(kcal·mol^{-1})	New form
	N-acetylglycine	−1.10	Yes
	oleanolic acid	−1.09	No

Table S2. Hydrogen bond parameters of EG-2MIE and EG-Hydrate.

D−H···A	D−H (Å)	H···A (Å)	D···A (Å)	D−H···A (°)	Symmetry
EG-2MIE					
O_5−H_5···O_9	0.66	2.18	2.6575(15)	131	
O_{10}−H_{10}···O_4	0.65	2.14	2.6457(14)	136	
O_9−H_9···N_4	0.82	1.91	2.6709(15)	154	
O_4−H_4···N_2	0.82	1.90	2.7062(18)	166	
O_8−H_8···O_7	0.84	2.01	2.8067(15)	158	1 + x, y, z
C_{10}−H_{10A}···O_8	0.97	2.59	3.2176(18)	123	−1 + x, y, z
O_3−H_3···O_2	0.88	1.91	2.7615(15)	163	−1 + x, y, z
N_3−H_{3A}···O_4	0.88	1.88	2.7431(16)	166	1 − x, 1 − y, 2 − z
N_1−H_1···O_9	0.88	1.93	2.7380(2)	152	1 − x, 1 − y, 1 − z
C_1−H_{1B}···O_5	0.96	2.51	3.4410(3)	163	1 − x, 1 − y, 1 − z
EG-Hydrate					
O_3−H_3···O_{13}	0.84	1.83	2.6647(11)	175	
O_4−H_4···O_{12}	0.84	1.95	2.7307(12)	153	
O_5−H_5···O_7	0.84	1.97	2.6486(12)	137	
O_8−H_8···O_{12}	0.84	1.86	2.6902(12)	170	
O_9−H_{9A}···O_8	0.84	2.08	2.7887(12)	142	1 − x, −y, 2 − z
O_{10}−H_{10}···O_2	0.84	1.81	2.6539(12)	178	−1 + x, y, 1 + z
O_{11}−H_{11C}···O_5	0.87	1.87	2.7358(11)	173	
O_{11}−H_{11D}···O_{13}	0.87	2.02	2.8643(12)	164	1 − x, 1 − y, 1 − z
O_{12}−H_{12A}···O_{14}	0.87	1.91	2.7805(12)	174	2 − x, −y, 1 − z
O_{12}−H_{12B}···O_{15}	0.87	1.97	2.8250(12)	168	1 − x, −y, 1 − z
O_{13}−H_{13A}···O_{15}	0.87	1.88	2.7475(12)	177	
O_{13}−H_{13B}···O_{14}	0.87	1.90	2.7687(12)	174	
O_{14}−H_{14A}···O_{11}	0.87	1.92	2.7853(12)	178	2 − x, 1 − y, 1 − z
O_{14}−H_{14B}···O_9	0.87	2.23	2.9704(12)	142	1 + x, y, −1 + z
O_{14}−H_{14B}···O_{10}	0.87	2.11	2.8528(12)	143	1 + x, y, −1 + z

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)	Symmetry
O_{15}–H_{15A}···O_{11}	0.87	1.89	2.7616(12)	178	x, −1 + y, z
O_{15}–H_{15B}···O_3	0.87	2.05	2.8892(12)	161	2 − x, −y, 1 − z
C_{14}–H_{14}···O_4	0.95	2.48	3.4226(14)	172	

Table S3. C–H···π weak interaction information of EG-2MIE and EG-Hydrate.

C–H···Cg_i*	H···Cg_i (Å)	C–H···Cg_i (°)	Symmetry
EG-2MIE			
C_9–H_{9A}···Cg_4	2.94	118	1 − x, 2 − y, 2 − z
EG-Hydrate			
C_2–H_{2A}···Cg_2	2.77	153	1 − x, 1 − y, 1 − z

*EG-2MIE: Cg_4=N_3–C_6–N_4–C_7–C_8; EG-Hydrate: Cg_2=C_{13}–C_{14}–C_{15}–C_{16}–C_{17}–C_{18}.

Table S4. π···π weak interaction information of EG-2MIE and EG-Hydrate.

Cg_i···Cg_j	Cg_i···Cg_j (Å)	Dihedral Angle between Cg_i and Cg_j (°)	Slippage (Å)	Symmetry
EG-2MIE				
Cg_4···Cg_4	3.68	0	0.528	1 − x, 1 − y, 2 − z
EG-Hydrate				
Cg_1···Cg_1	3.50	0	1.159	2 − x, 1 − y, 1 − z

*EG-2MIE: Cg_4=N_3–C_6–N_4–C_7–C_8; EG-Hydrate: Cg_1=C_4–C_5–C_6–C_7–C_8–C_9.

Table S5. Experimental solid-liquid equilibrium data (mass fraction) of EG-2MIE-EtOH system at 298.15 K, 303.15 K and 308.15 K.

	Mass fraction			
T(K)	EG	2MIE	Ethanol	Equilibrium solid phase
298.15	0.6232	0.0000	0.3768	EG
	0.5897	0.0068	0.4035	EG
	0.4793	0.0109	0.5098	EG + Cocrystal
	0.3161	0.0115	0.6724	Cocrystal
	0.2844	0.0149	0.7007	Cocrystal
	0.1687	0.0202	0.8111	Cocrystal
	0.1016	0.0294	0.8690	Cocrystal

T(K)	Mass fraction			Equilibrium solid phase
	EG	2MIE	Ethanol	
	0.0736	0.0352	0.8912	Cocrystal
	0.0312	0.0566	0.9122	Cocrystal
	0.0118	0.0852	0.9030	Cocrystal
	0.0104	0.1249	0.8647	Cocrystal
	0.0108	0.4290	0.5602	2MIE + Cocrystal
	0.0056	0.4706	0.5238	2MIE
	0.0000	0.5272	0.4728	2MIE
303.15	0.6396	0.0000	0.3604	EG
	0.5629	0.0076	0.4295	EG
	0.5168	0.0107	0.4725	EG + Cocrystal
	0.4256	0.0114	0.5630	Cocrystal
	0.3370	0.0124	0.6506	Cocrystal
	0.2183	0.0191	0.7626	Cocrystal
	0.1697	0.0235	0.8068	Cocrystal
	0.1046	0.0362	0.8592	Cocrystal
	0.0542	0.0546	0.8912	Cocrystal
	0.0334	0.0834	0.8832	Cocrystal
	0.0153	0.1511	0.8336	Cocrystal
	0.0160	0.4688	0.5152	2MIE + Cocrystal
	0.0121	0.5016	0.4863	2MIE
	0.0000	0.6099	0.3901	2MIE
308.15	0.7993	0.0000	0.2007	EG
	0.6722	0.0079	0.3199	EG
	0.5250	0.0143	0.4607	EG + Cocrystal
	0.4528	0.0108	0.5364	Cocrystal
	0.4073	0.0138	0.5789	Cocrystal
	0.3363	0.0143	0.6494	Cocrystal
	0.2622	0.0129	0.7249	Cocrystal
	0.1224	0.0234	0.8542	Cocrystal
	0.0686	0.0504	0.8810	Cocrystal
	0.0262	0.1028	0.8710	Cocrystal
	0.0125	0.2102	0.7773	Cocrystal

T(K)	Mass fraction			Equilibrium solid phase
	EG	2MIE	Ethanol	
	0.0089	0.4850	0.5061	2MIE + Cocrystal
	0.0049	0.5388	0.4563	2MIE
	0.0000	0.6922	0.3078	2MIE