Synthesis, Characterization and structure-activity relationship study of a novel pregabalin sustained-release cocrystal

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Supporting Tables:

Table S1. Detailed information of all chemicals used

Chemical Name	Chemical Abbreviation	CAS Number	Purity	Source
Pregabalin	PGB	148553-50-8	≥99%	Tianjin Heowns Technology Co., Ltd
Ascorbic acid	VC	50-81-7	≥99%	Tianjin Heowns Technology Co., Ltd
Citric acid	CitA	77-92-9	≥99%	Tianjin Heowns Technology Co., Ltd
Fumaric acid	FA	110-17-8	≥99%	Tianjin Heowns Technology Co., Ltd
Vanillic acid	VA	121-34-6	≥99%	Tianjin Heowns Technology Co., Ltd
Cinnamic acid	CA	140-10-3	≥99%	Tianjin Heowns Technology Co., Ltd
Caffeic acid	CafA	331-39-5	≥99%	Tianjin Heowns Technology Co., Ltd
Gallic acid	GA	149-91-7	≥99%	Tianjin Heowns Technology Co., Ltd
p-Methylbenzoic acid	pMBA	99-94-5	≥99%	Tianjin Heowns Technology Co., Ltd
Protocatechuic acid	PCA	99-50-3	≥99%	Tianjin Heowns Technology Co., Ltd
Quercetin	Que	117-39-5	≥99%	Tianjin Heowns Technology Co., Ltd
4-Hydroxymethylbenzoic acid	4HBA	99-96-7	≥99%	Tianjin Heowns Technology Co., Ltd
Glutaric acid	GluA	110-94-1	≥99%	Tianjin Heowns Technology Co., Ltd
Malonic acid	MaloA	141-82-2	≥99%	Tianjin Heowns Technology Co., Ltd
Maleic acid	MaleA	110-16-7	≥99%	Tianjin Heowns Technology Co., Ltd
Thymol	Thy	89-83-8	≥99%	Tianjin Heowns Technology Co., Ltd
α-Ketoglutaric acid	α-KG	328-50-7	≥99%	Tianjin Heowns Technology Co., Ltd
Deuterated methanol	MeOD	68917-16-6	99.9 atom% D, 0.03% (v/v) TMS	SIGMA-ALDRICH Co., USA
Methanol	MeOH	67-56-1	≥99%	Tianjin Jiangtian Chemical Co. Ltd
Ethanol	EtOH	64-17-5	≥99%	Tianjin Jiangtian Chemical Co. Ltd
Acetonitrile	ACN	75-05-8	≥99%	Tianjin Jiangtian Chemical Co. Ltd
Acetone	AcOH	67-64-1	≥99%	Tianjin Jiangtian Chemical Co. Ltd

Table S2. Overview of computational screening and experimental screening

No.	Coformer	ΔH_{ex}(kcal/mol)	Hit Rate(%)	New phase
1	Sulfosalicylic acid	-7.92452	0	No
2	Tartronic acid	-7.87624	0	No
3	Gallic acid	-7.61575	100	No
4	3,5-Dihydroxybenzoic acid	-7.24223	0	No
5	2,4-Dihydroxybenzoic acid	-6.43624	0	No
6	Citric acid	-6.39372	100	No
7	Protocatechuic acid	-6.37362	100	No
8	Quercetin	-6.18709	100	No
9	Fumaric acid	-5.93309	100	No
10	α-Ketoglutaric acid	-5.82211	100	No
11	m-Hydroxybenzoic acid	-5.20765	0	No

12	4-Hydroxybenzoic acid	-4.90778	100	No
13	Caffeic acid	-4.67968	100	No
14	Malonic acid	-4.66960	100	No
15	Ascorbic acid	-4.32079	100	No
16	Glutaric acid	-4.01933	100	No
17	Vanillic acid	-3.80878	100	Yes
18	Adipic acid	-3.71973	0	No
19	Maleic acid	-3.54875	100	No
20	Thymol	-3.51132	100	No
21	Orotic acid	-3.29845	0	No
22	Glycolic acid	-2.93066	0	No
23	Furoic acid	-2.53981	0	No
24	m-Methylbenzoic acid	-2.47681	0	No
25	Methyl 4-hydroxybenzoate	-2.45952	0	No
26	Acetylsalicylic acid	-2.45776	0	No
27	4-Hydroxymethylbenzoic acid	-2.44318	0	No
28	Phenylacetic acid	-2.43232	0	No
29	Maleic hydrazide	-2.38268	0	No
30	o-Methylbenzoic acid	-2.34341	0	No
31	p-Methylbenzoic acid	-2.32828	100	Yes
32	Hydrocinnamic acid	-2.27929	0	No
33	Salicyl alcohol	-2.12034	0	No
34	Cinnamic acid	-2.00098	100	Yes

Table S3. pKa and ΔpKa values of PGB and CCFs

Substance	PGB	pMBA	VA	CA
pKa	4.23	4.36	4.53	4.46
ΔpKa		-0.13	-0.30	-0.23
forms		cocrystal	cocrystal	cocrystal

Table S4. FTIR stretching vibration frequencies of PGB and its cocrystal

Material	$-NH_3^+(cm^{-1})$	$-COO^-(cm^{-1})$
PGB	3290	1619
PGB-pMBA	3345	1701
PGB-VA	3346	1625
PGB-CA	3320	1604

Table S5. Liquid chromatography conditions

Parameter	Details
Column	C18 column (6 μm, 4.6 mm × 150 mm)
Mobile phase	Acetonitrile-water (v:v=5:95)
Flow rate	1 ml/min
Inject volume	20 μL

Column temperature	37 °C
Sample temperature	37 °C
λ_{max}	190nm
Retention time	11.2min
Equation	y=2.76445E+08x-52824.9733
Regression coefficient (R^2)	0.9993
Calibration range	5-30 mg/L

Table S6. The equilibrium solubility (mg·mL^{-1}) of PGB and its cocrystals at 37 ℃

Material	pH=1.2	pH=4.0	pH=6.8
PGB	141.0026	6.2078	4.1420
PGB-pMBA Cocrystal	2.4215	0.1903	2.0890
PGB-VA Cocrystal	3.0627	0.2306	2.2460
PGB-CA Cocrystal	2.5791	0.2048	2.1537

Table S7. IDR values of PGB and its cocrystals in pH 6.8 buffers at 37 ℃

Material	IDR (mg·cm^{-2}·min^{-1})
PGB	2.0411
PGB-pMBA Cocrystal	0.3051
PGB-VA Cocrystal	0.8294
PGB-CA Cocrystal	0.4104

Table S8. pH values of PGB and its cocrystals before and after solution and dissolution experiment

Material	Before SE	After SE	Before DE	After DE
PGB	6.80±0.02	6.80±0.02	6.80±0.02	6.80±0.02
PGB-pMBA Cocrystal	6.80±0.02	6.73±0.02	6.80±0.02	6.79±0.02
PGB-VA Cocrystal	6.80±0.02	6.77±0.02	6.80±0.02	6.80±0.02
PGB-CA Cocrystal	6.80±0.02	6.69±0.02	6.80±0.02	6.78±0.02

Table S9. Hydrogen bond geometric parameters of PGB and its cocrystals

D-H…A	ARU	D-H	H-A	D-A	D-H…A	Symmetry
PGB						
N_1-H_6…O_1	3566.01	0.91	1.85	2.757	170	1/2+x,3/2-y,1-z
N_1-H_7…O_1	1545.01	0.93	1.80	2.731	174	x,-1+y,z
N_1-H_8…O_2	3466.01	0.91	1.86	2.767	172	-1/2+x,3/2-y,1-z,
C_2-H_2…O_2	3466.01	1.08	2.45	3.418	148	-1/2+x,3/2-y,1-z,
PGB-pMBA Cocrystal						
N_1-H_{1A}…O_1	3566.01	0.91	1.99	2.878	165	1/2+x,3/2-y,1-z
N_1-H_{1B}…O_2	3466.01	0.91	1.90	2.799	167	-1/2+x,3/2-y,1-z
N_1-H_{1C}…O_2	1545.01	0.91	1.83	2.732	174	x,-1+y,z
O_4-H_4…O_1	1645.01	0.84	1.81	2.647	171	1+x,-1+y,z
PGB-VA Cocrystal						
N_1-H_{1A}…O_1	1545.02	0.97	1.79	2.736	163	x,-1+y,z

N_1-H_{1B}…O_4	1455.03	0.91	1.97	2.850	164	-1+x,y,z
N_1-H_{1C}…O_3	1555.03	0.90	1.96	2.831	161	
N_2-H_{2A}…O_2	1555.02	0.93	1.92	2.839	170	
N_2-H_{2B}…O_3	1565.03	0.91	1.82	2.726	174	x,1+y,z
N_2-H_{2C}…O_1	1655.02	0.88	1.94	2.803	164	1+x,y,z
O_5-H_5…O_4	1555.03	0.82	1.83	2.652	172	
O_8-H_8…O_2	1646.02	0.89	1.95	2.763	152	1+x,-1+y,1+z
C_1-H_{1E}…O_7	1454.01	0.99	2.56	3.270	129	-1+x,y,-1+z
PGB-CA Cocrystal						
N_1-H_{1A}…O_3	3556.02	0.91	1.93	2.836	170	1/2+x,1/2-y,1-z
N_1-H_{1B}…O_4	3456.02	0.91	1.87	2.769	168	1/2+x,1/2-y,1-z
N_1-H_{1C}…O_4	1545.02	0.91	1.85	2.752	170	x,-1+y,z
O_2-H_2…O_3	1555.02	0.84	1.76	2.598	174	
C_{11}-H_{11B}…O_3	3556.02	0.99	2.52	3.432	154	1/2+x,1/2-y,1-z

Table S10. Hydrogen bond parameters in AIM analysis

Bond Type	Bond Length(Å)	Bond Angle(°)	ρ(a.u.)	$\nabla^2\rho$ (a.u.)	G (a.u.)	V (a.u.)	H (a.u.)	E_H (kJ/mol)
PGB								
N_1-H_6…O_1	1.855	170.24	0.04324	0.12741	0.03590	-0.03995	-0.00405	-8.90
N_1-H_7…O_1	1.802	173.99	0.04623	0.11078	0.03442	-0.04114	-0.00672	-9.57
N_1-H_8…O_2	1.859	171.85	0.04849	0.13157	0.03960	-0.04632	-0.00671	-10.08
C_2-H_2…O_2	2.453	147.94	0.01178	0.03454	0.00797	-0.00730	0.00067	-1.89
PGB-pMBA Cocrystal								
N_1-H_{1A}…O_1	1.991	164.65	0.03010	0.10660	0.02571	-0.02477	0.00094	-5.97
N_1-H_{1B}…O_2	1.904	167.20	0.03869	0.12382	0.03275	-0.03454	-0.00179	-7.89
N_1-H_{1C}…O_2	1.825	173.83	0.05057	0.12881	0.04035	-0.04851	-0.00815	-10.54
O_4-H_4…O_1	1.813	171.50	0.04676	0.15359	0.04337	-0.04834	-0.00497	-9.69
PGB-VA Cocrystal								
N_1-H_{1A}…O_1	1.792	162.48	0.04575	0.13433	0.03842	-0.04325	-0.00483	-9.46
N_1-H_{1B}…O_4	1.966	163.98	0.03088	0.11630	0.02771	-0.02635	0.00136	-6.15
N_1-H_{1C}…O_3	1.963	160.59	0.03290	0.11621	0.02849	-0.02793	0.00056	-6.60
N_2-H_{2A}…O_2	1.920	170.26	0.03259	0.11853	0.02890	-0.02817	0.00073	-6.53
N_2-H_{2B}…O_3	1.823	173.62	0.05067	0.13092	0.04078	-0.04883	-0.00805	-10.56
N_2-H_{2C}…O_1	1.944	163.56	0.03826	0.10929	0.02986	-0.03240	-0.00254	-7.79
O_5-H_5…O_4	1.834	172.00	0.04708	0.14225	0.04137	-0.04717	-0.00581	-9.76
O_8-H_8…O_2	1.951	151.75	0.02891	0.10986	0.02594	-0.02441	0.00153	-5.71
C_1-H_{1E}…O_7	2.559	128.59	0.01007	0.03276	0.00728	-0.00637	0.00091	-1.50
PGB-CA Cocrystal								
N_1-H_{1A}…O_3	1.935	170.28	0.03505	0.11321	0.02910	-0.02989	-0.00080	-7.08
N_1-H_{1B}…O_4	1.873	167.71	0.04383	0.12000	0.03475	-0.03949	-0.00475	-9.04
N_1-H_{1C}…O_4	1.851	170.24	0.04738	0.12766	0.03824	-0.04456	-0.00632	-9.83
O_2-H_2…O_3	1.761	174.36	0.05433	0.16341	0.04982	-0.05878	-0.00897	-11.38

C_{11}-H_{11B}…O_3	2.517	153.55	0.01158	0.03439	0.00789	-0.00719	0.00070	-1.848

Supporting Figures:

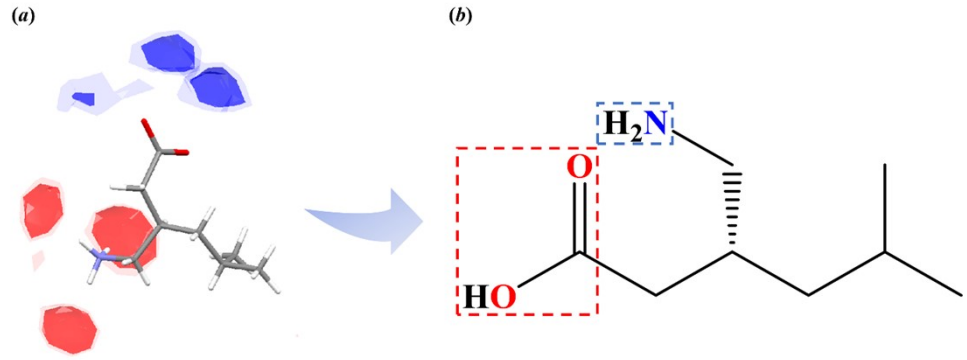

Figure S1. (a) FIM of PGB; (b)Potential sites for intermolecular interactions of PGB.

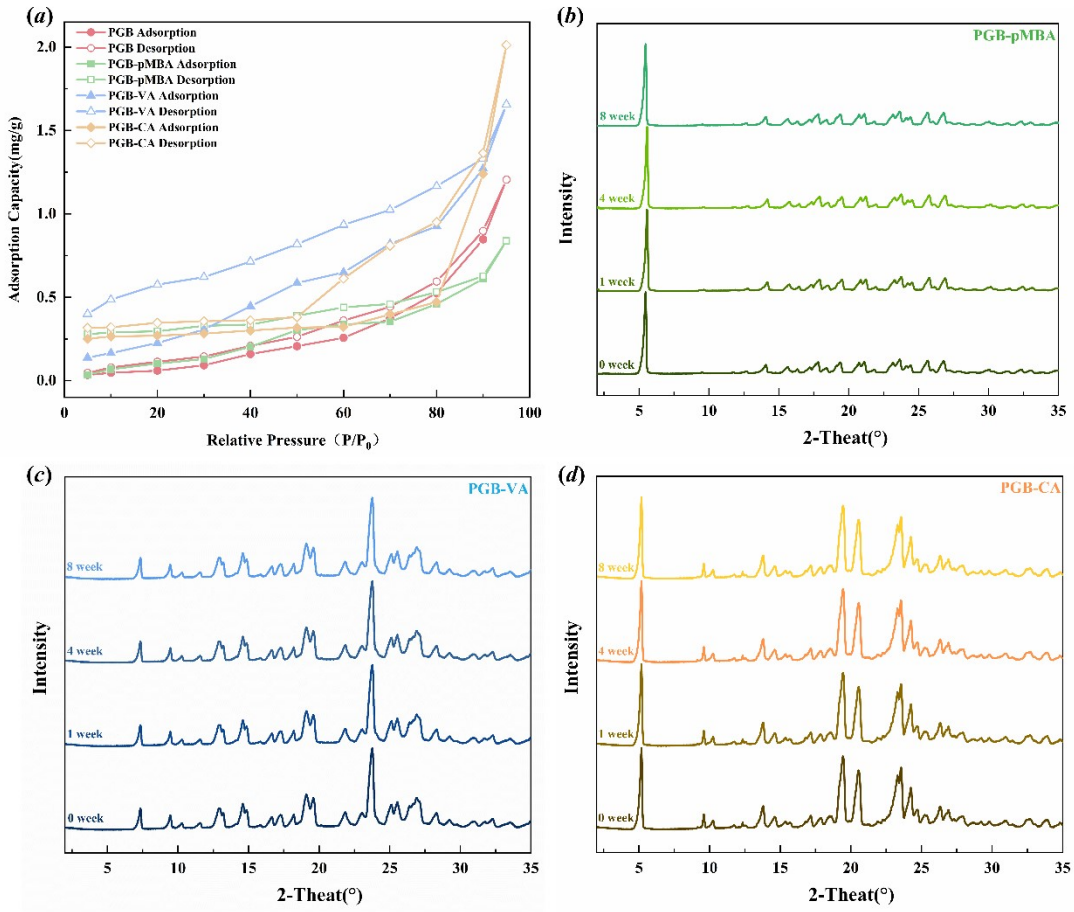

Figure S2. PGB cocrystals: (a) Hygroscopic Stability Results; (b-d) Accelerated Stability Results.

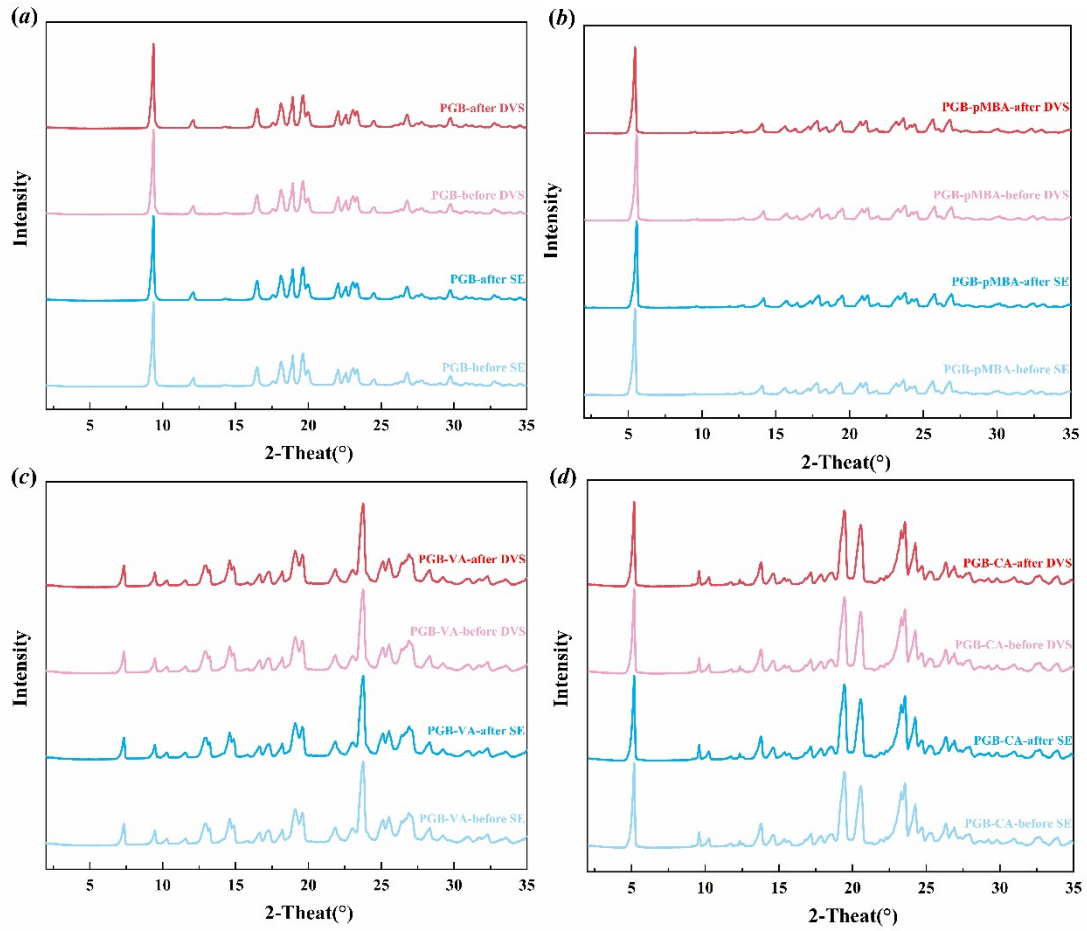

Figure S3. PXRD patterns of PGB and its cocrystals before and after solubility tests and DVS tests: (a) PGB crystal; (b) PGB-pMBA cocrystal; (c) PGB-VA cocrystal; (d) PGB-CA cocrystal.

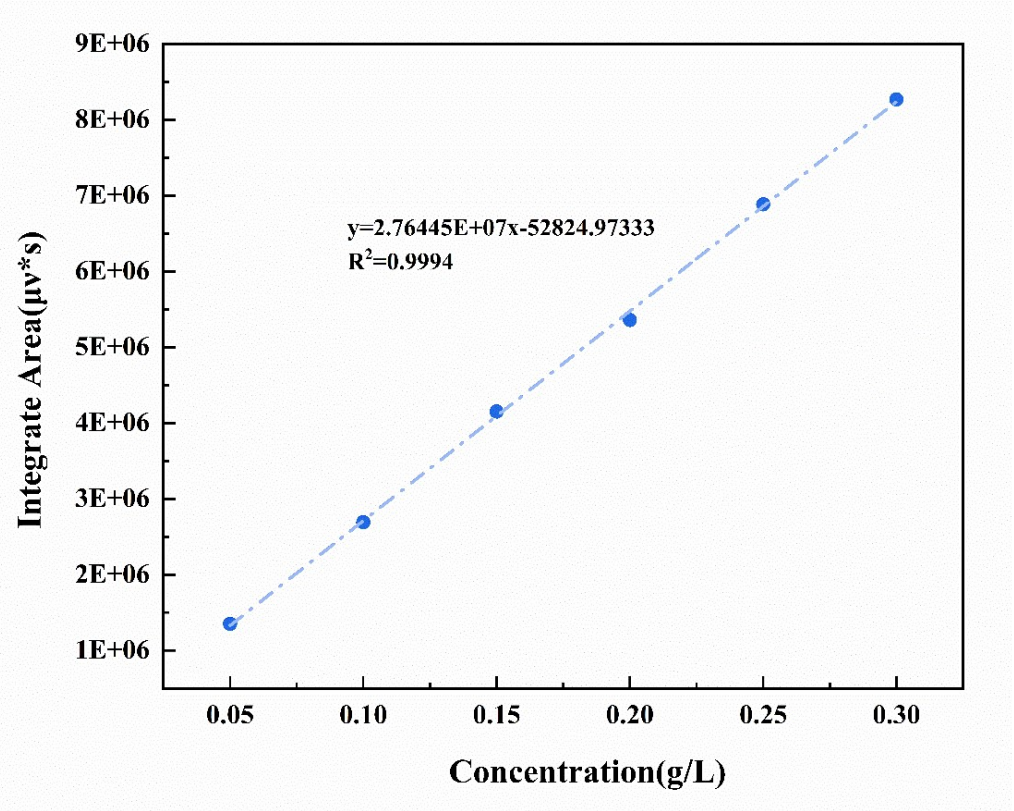

Figure S4. Solubility Standard Curve of PGB

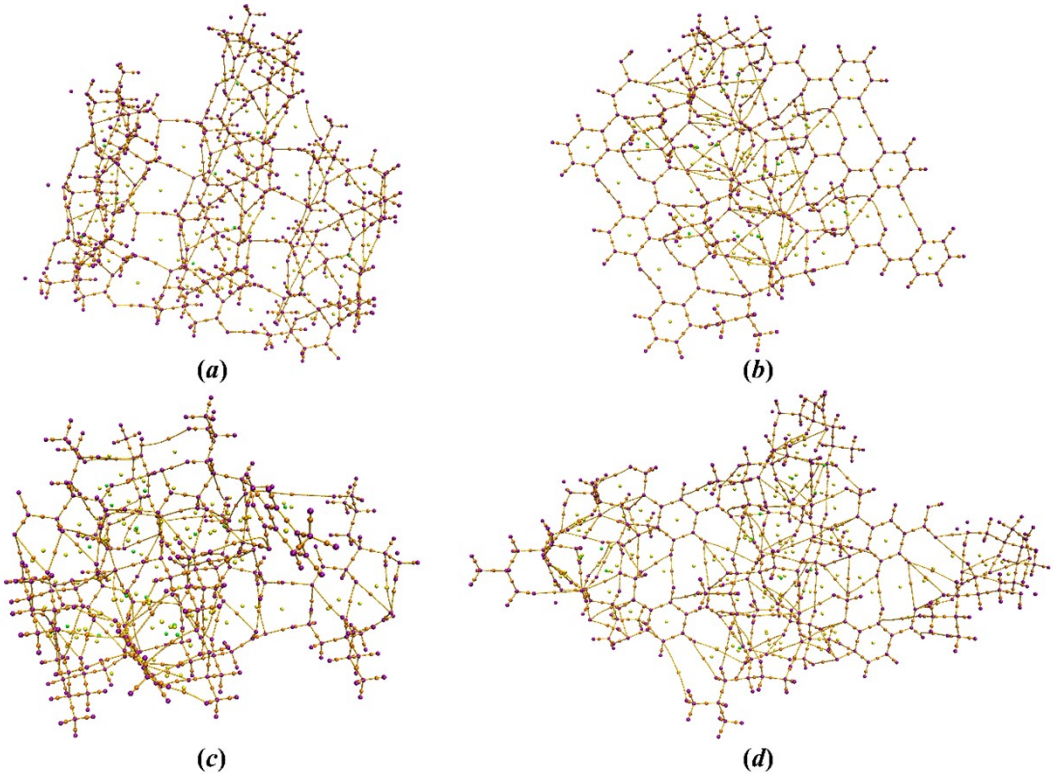

Figure S5. Topological geometries of PGB and its cocrystals: (a) PGB crystal; (b) PGB-pMBA cocrystal; (c) PGB-VA cocrystal; (d) PGB-CA cocrystal.

Supporting Information：

Information S1. Detailed pH-Dependent Solubility Profiles

The equilibrium solubility of PGB and its cocrystals was determined at 37 °C in three buffer media: pH 1.2 (simulated gastric fluid), pH 4.0 (acetate buffer), and pH 6.8 (simulated intestinal fluid). The complete dataset is presented in Figure 7a, Table S6.

Pure PGB exhibits strong pH-dependent solubility: extremely high at pH 1.2 (141.00 $mg \cdot mL^{-1}$), dramatically decreasing to 6.21 $mg \cdot mL^{-1}$ at pH 4.0 and 4.14 $mg \cdot mL^{-1}$ at pH 6.8. This behavior stems from its zwitterionic nature (pKa_1 ~4.2, pKa_2 ~10.6). At pH 1.2, protonation of both functional groups imparts a net positive charge, enhancing solubility through electrostatic repulsion and solvation. Near the isoelectric region (pH 4-6), as shown in Table S3, PGB exists predominantly as a zwitterion with minimized net charge, reducing electrostatic repulsion and promoting molecular aggregation via intermolecular hydrogen bonding, thus yielding minimum solubility. All three cocrystals display a U-shaped pH-dependent profile: moderate at pH 1.2 (2.4-3.1 $mg \cdot mL^{-1}$), lowest at pH 4.0 (0.19-0.23 $mg \cdot mL^{-1}$), and increased at pH 6.8 (2.1-2.2 $mg \cdot mL^{-1}$). This trend reflects the interplay between lattice stability and ionization states: protonation at pH 1.2 disrupts hydrogen-bonding networks; neutral forms at pH 4.0 maximize lattice stability; deprotonation at pH 6.8 introduces charges that partially disrupt the lattice and enhance solvation.