Supporting Information

Salts and Cocrystals of the Antidiabetic Drugs, Gliclazide, Tolbutamide and Glipizide: Solubility Enhancements through Drug−Coformer Interactions.

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Table S1. Contents

Table S2. Neutron normalized intermolecular hydrogen bond geometrical parameters (intermolecular O···H, N···H and C···H distances, PLATON generated).

Compound	Interaction	D–H/Å	H···A/Å	D···A/Å	∠D···A°	Symmetry
GCZ–CAT	O_{16}–H_{16}···O_1	0.98	1.79	2.687(4)	150	
	O_{17}–H_{17}···O_{16}	0.98	1.98	2.796(4)	138	1-x,-y,1-z
	N_2–H_{2N}···O_{17}	1.01	2.03	3.024(4)	170	1-x,-y,1-z
	N_1–H_{1N}···O_3	1.01	2.17	3.064(4)	146	2-x,-y,-z
GCZ–RES	O_{16}–H_{16}···O_{18}	0.98	1.88	2.700(4)	139	-1/2+x,1/2-y,-1/2+z
	O_{18}–H_{18B}···O_1	0.98	1.73	2.697(4)	168	1/2+x,1/2-y,-1/2+z
	N_2–H_{2N}···O_{16}	1.01	1.97	2.968(5)	171	x,y,1+z
	N_1–H_{1N}···O_3	1.01	2.22	3.023(5)	135	1-x,-y,1-z
	C_3–H_3···O_3	1.08	2.37	3.403(5)	159	1-x,-y,1-z
	C_{21}–H_{21}···O_2	1.08	2.573	3.547	148	-1/2+x,1/2-y,-1/2+z
	C_{19}–H_{19}···O_2	1.08	2.39	3.453(5)	168	
GCZ–PPZ	N_5–H_{5B}···O_1	1.01	2.18	2.974(6)	134	x,1+y,z
	N_4–H_{4A}···N_1	1.01	1.96	2.962(7)	170	
	N_5–H_{5A}···N_2	1.01	1.91	2.909(7)	168	1/2+x,1/2+y,z
	N_4–H_{4B}···O_3	1.01	2.21	2.986(6)	132	-1/2+x,1/2+y,z
	N_4–H_{4B}···O_1	1.01	1.89	2.723(6)	137	-1/2+x,1/2+y,z
	C_8–H_{8B}···O_2	1.08	2.41	3.310(8)	139	x,-1+y,z
	C_{19}–H_{19B}···O_2	1.08	2.54	3.212(8)	119	
TOL–PPZ(II)	N_6–H_{6A}···O_4	1.01	1.67	2.640(8)	159	
	N_6–H_{6A}···O_5	1.01	2.42	2.954(9)	112	
	N_6–H_{6B}···N_1	1.01	1.77	2.733(8)	158	
	N_6–H_{6A}···O_3	1.01	2.52	3.255(9)	129	
	N_5–H_{5A}···O_1	1.01	1.80	2.715(8)	149	-1/2+x,1/2-y,z
	N_5–H_{5A}···O_2	1.01	2.27	2.899(9)	119	-1/2+x,1/2-y,z
	N_5–H_{5B}···N_3	1.01	1.86	2.847(9)	164	
	N_4–H_{4N}···O_2	1.01	1.90	2.906(9)	176	1/2+x,1/2-y,z
	N_2–H_{2N}···O_5	1.01	2.10	3.108(9)	173	
	C_{28}–H_{28A}···O_4	1.08	2.45	3.212(9)	127	1-x,-y,z
	C_{27}–H_{27A}···O_5	1.08	2.43	3.105(9)	119	
	C_{25}–H_{25A} ···O_2	1.08	2.37	3.003(9)	116	-1/2+x,1/2-y,z
	C_7–H_{7C}···O_3	1.08	2.48	3.279(12)	130	3/2-x,-1/2+y,z

Table S3. Melting points of salt/cocrystal/coformer/APIs.

Cocrystal/Salt	API MP(^{o}C)	Coformer MP(^{o}C)	Cocrystal/Salt MP(^{o}C)
GCZ−CAT	182	105	122
GCZ−RES	182	110	117
GCZ−PTSA	182	107	178
GCZ−PPZ	182	106	157
TOL−PPZ(I)	129	106	113
TOL−PPZ(II)	129	106	104

Table S4. Buffer/Water solubility of salt/cocrystal/APIs.

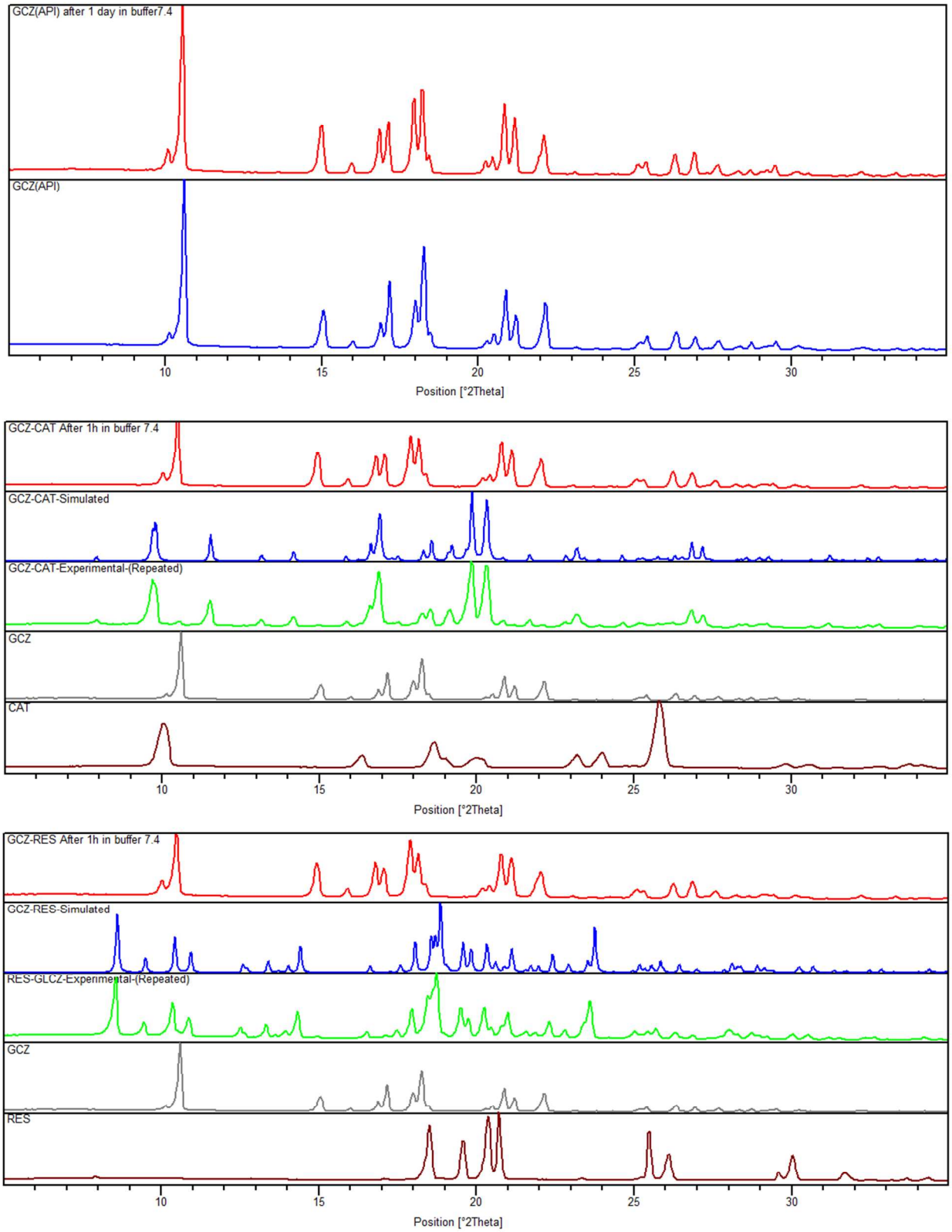
Cocrystal/salt	API buffer solubility/Water Solubility*(mg/L)	Cocrystal/Salt buffer solubility(mg/L)
GCZ−CAT	1170/1900	7113
GCZ−RES	1170/1900	4113
GCZ−PTSA	1170/1900	3129
GCZ−PPZ	1170/1900	15417.7
TOL−PPZ(I)	4179/2020	331896
TOL−PPZ(II)	4179/2020	9987

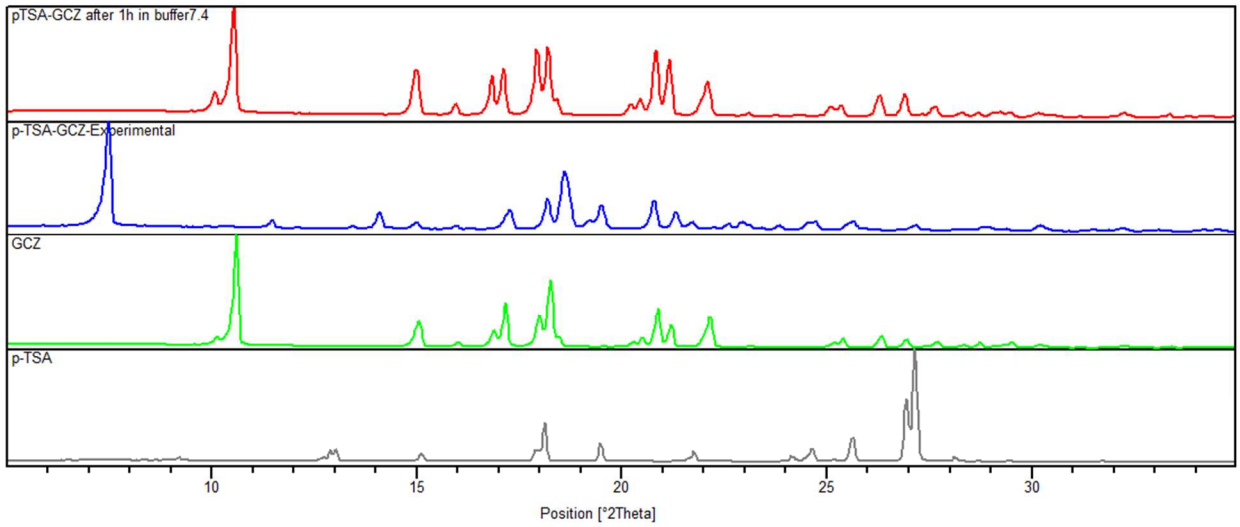
*reported in pubmed
Coformers' solubility are reported for CAT, RES, PTSA equal to 460, 710, 670 mg/mL and freely soluble for PPZ.

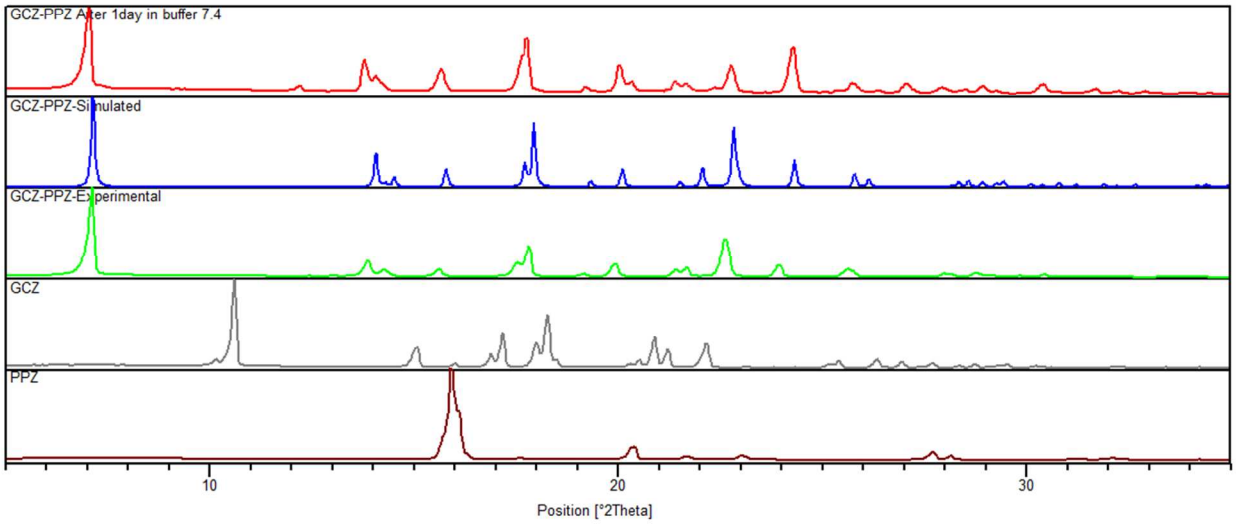
Table S5. pH variation after solubility experiments.

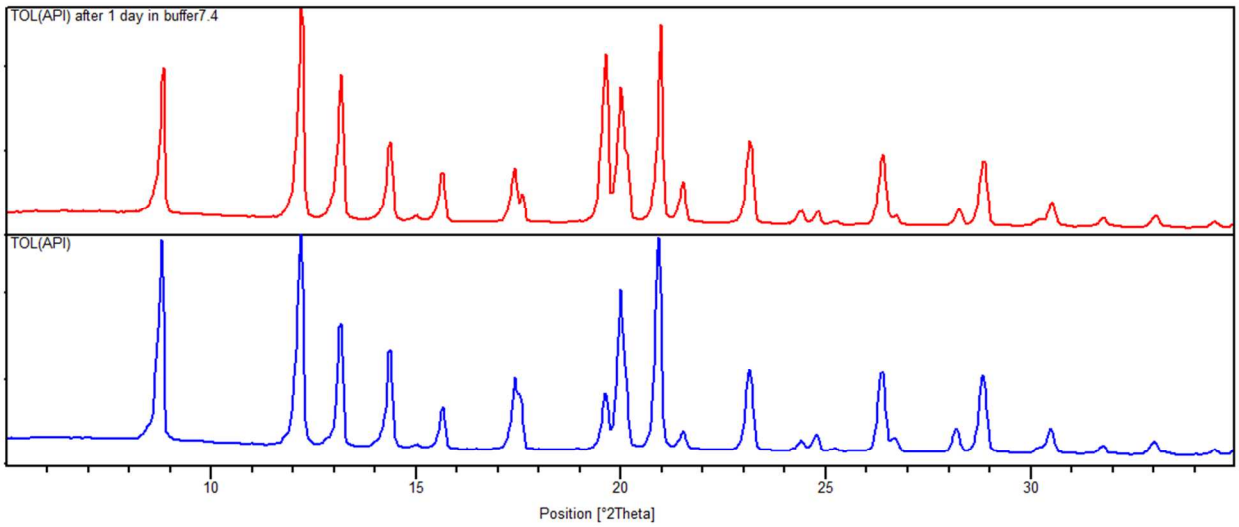
API/Cocrystals/Salts	pH (after 1h)
GCZ(API)	7.3
GCZ−CAT	7.4
GCZ−RES	7.3
GCZ−PTSA	7.2
GCZ−PPZ	7.5
TOL(API)	7.0
TOL−PPZ(I)	7.5
TOL−PPZ(II)	7.2
GPZ(API)	6.7

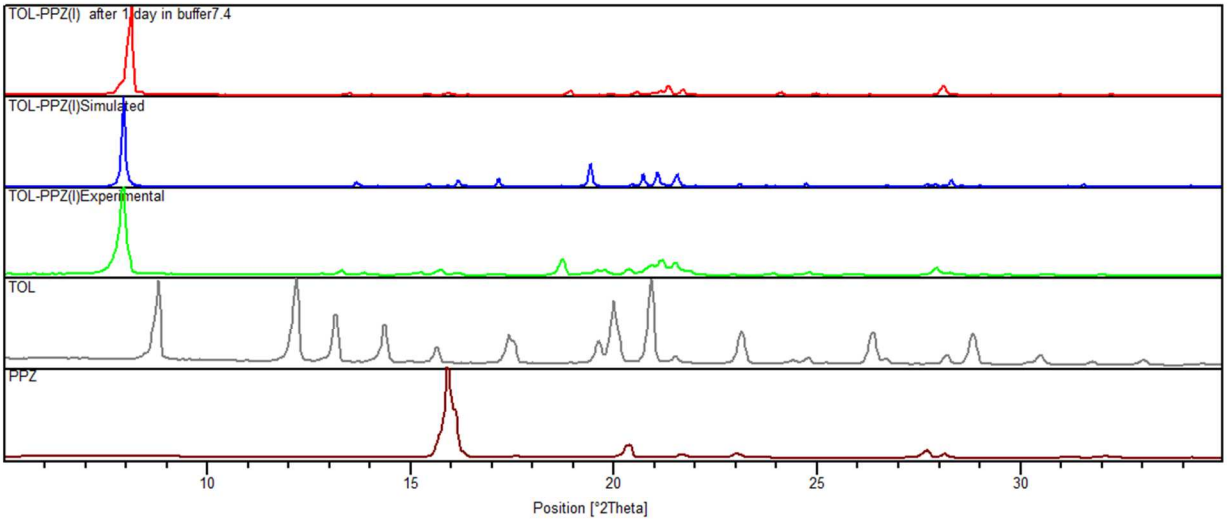
Figure S1. Powder x-ray diffraction patterns for solid forms of GCZ/TOL/GPZ.

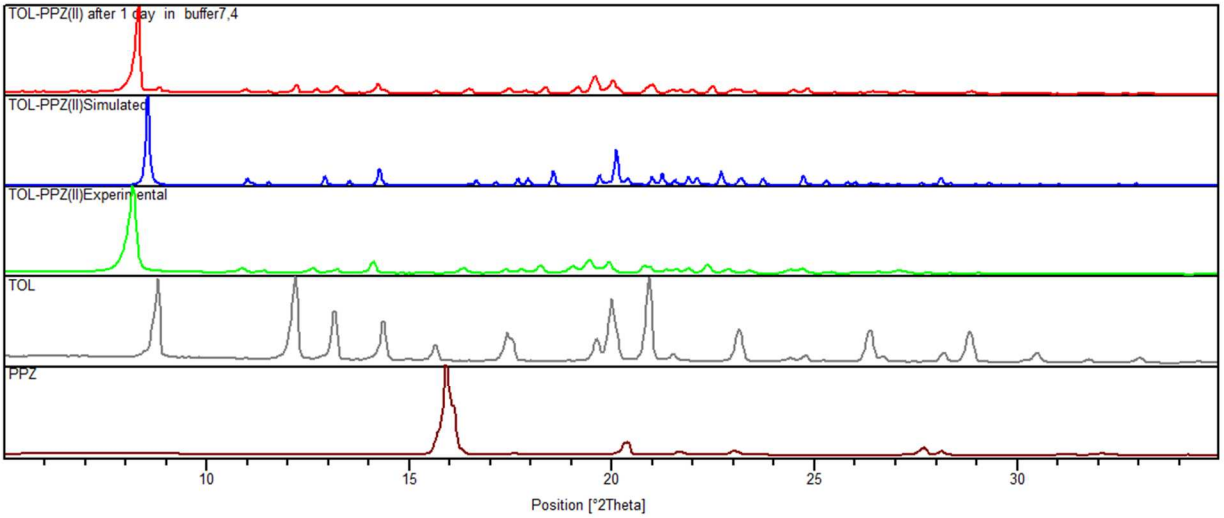


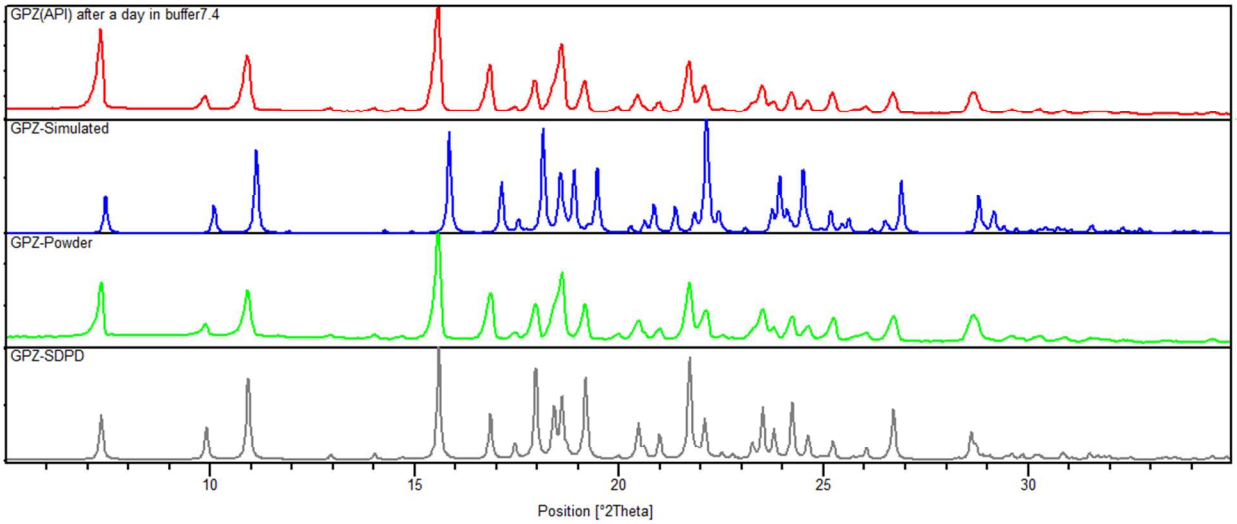

pTSA-GCZ after 1h in buffer7.4
p-TSA-GCZ-Experimental
GCZ
p-TSA
10
15
20
25
30
Position [°2Theta]


GCZ-PPZ After 1day in buffer 7.4
GCZ-PPZ-Simulated
GCZ-PPZ-Experimental
GCZ
PPZ
10
20
30
Position [°2Theta]


TOL(API) after 1 day in buffer7.4
TOL(API)
10
15
20
25
30
Position [°2Theta]


TOL-PPZ(I) after 1 day in buffer7.4
TOL-PPZ(I)Simulated
TOL-PPZ(I)Experimental
TOL
PPZ
10
15
20
25
30
Position [°2Theta]


TOL-PPZ(II) after 1 day in buffer7.4
TOL-PPZ(II)Simulated
TOL-PPZ(II)Experimental
TOL
PPZ
10
15
20
25
30
Position [°2Theta]


GPZ(API) after a day in buffer7.4
GPZ-Simulated
GPZ-Powder
GPZ-SDPD
10
15
20
25
30
Position [°2Theta]

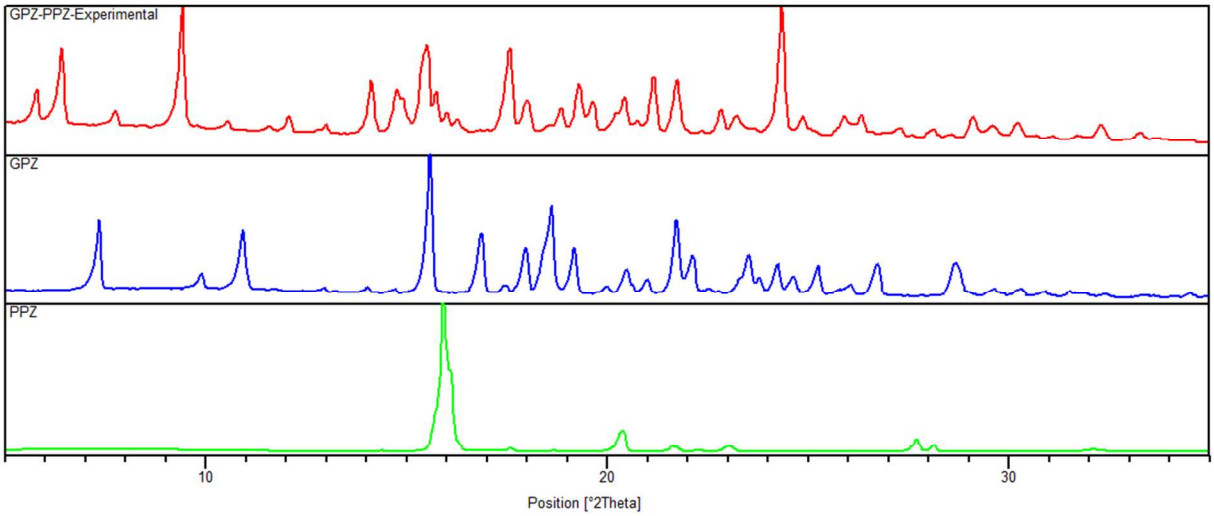
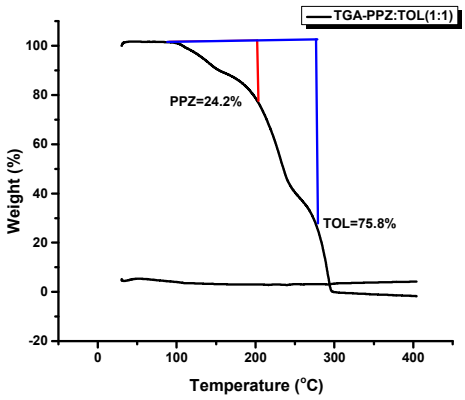
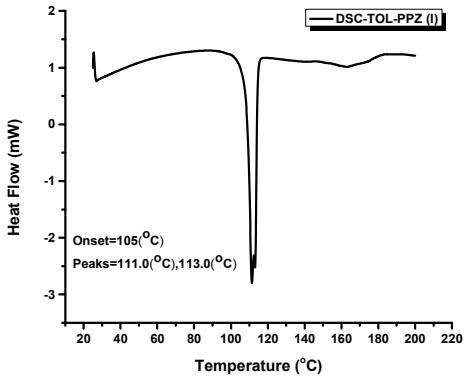
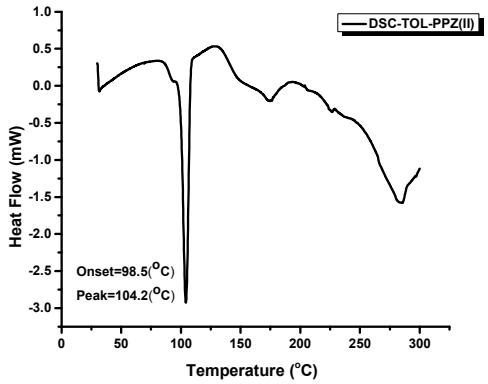
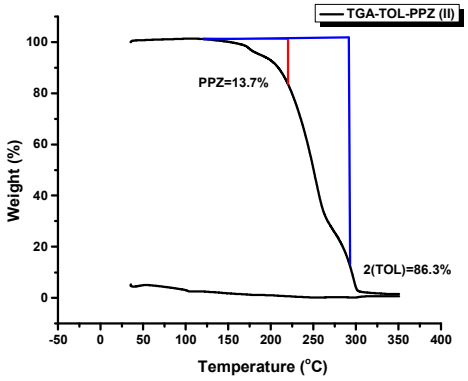


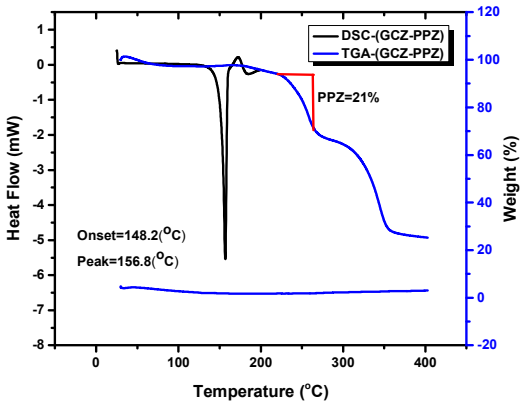
Figure S2. DSC and TGA plots of GCZ/TOL/GPZ salt/cocrystals.


TGA-PPZ:TOL(1:1)
PPZ=24.2%
TOL=75.8%
Weight (%)
Temperature (°C)


DSC-TOL-PPZ (I)
Onset=105(°C)
Peaks=111.0(°C),113.0(°C)
Heat Flow (mW)
Temperature (°C)


DSC-TOL-PPZ(II)
Onset=98.5(°C)
Peak=104.2(°C)
Heat Flow (mW)
Temperature (°C)


TGA-TOL-PPZ (II)
PPZ=13.7%
2(TOL)=86.3%
Weight (%)
Temperature (°C)


DSC-(GCZ-PPZ)
TGA-(GCZ-PPZ)
PPZ=21%
Onset=148.2(°C)
Peak=156.8(°C)
Heat Flow (mW)
Weight (%)
Temperature (°C)

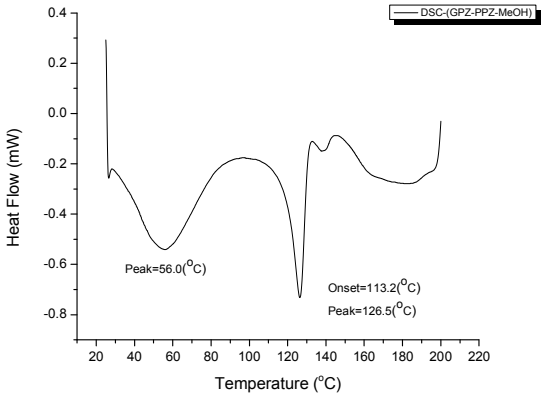

DSC-(GPZ-PPZ-MeOH)
Peak=56.0(°C)
Onset=113.2(°C)
Peak=126.5(°C)
Heat Flow (mW)
Temperature (°C)

Figure S3. FTIR spectra of GCZ/TOL/GPZ and its salt/cocrystals.

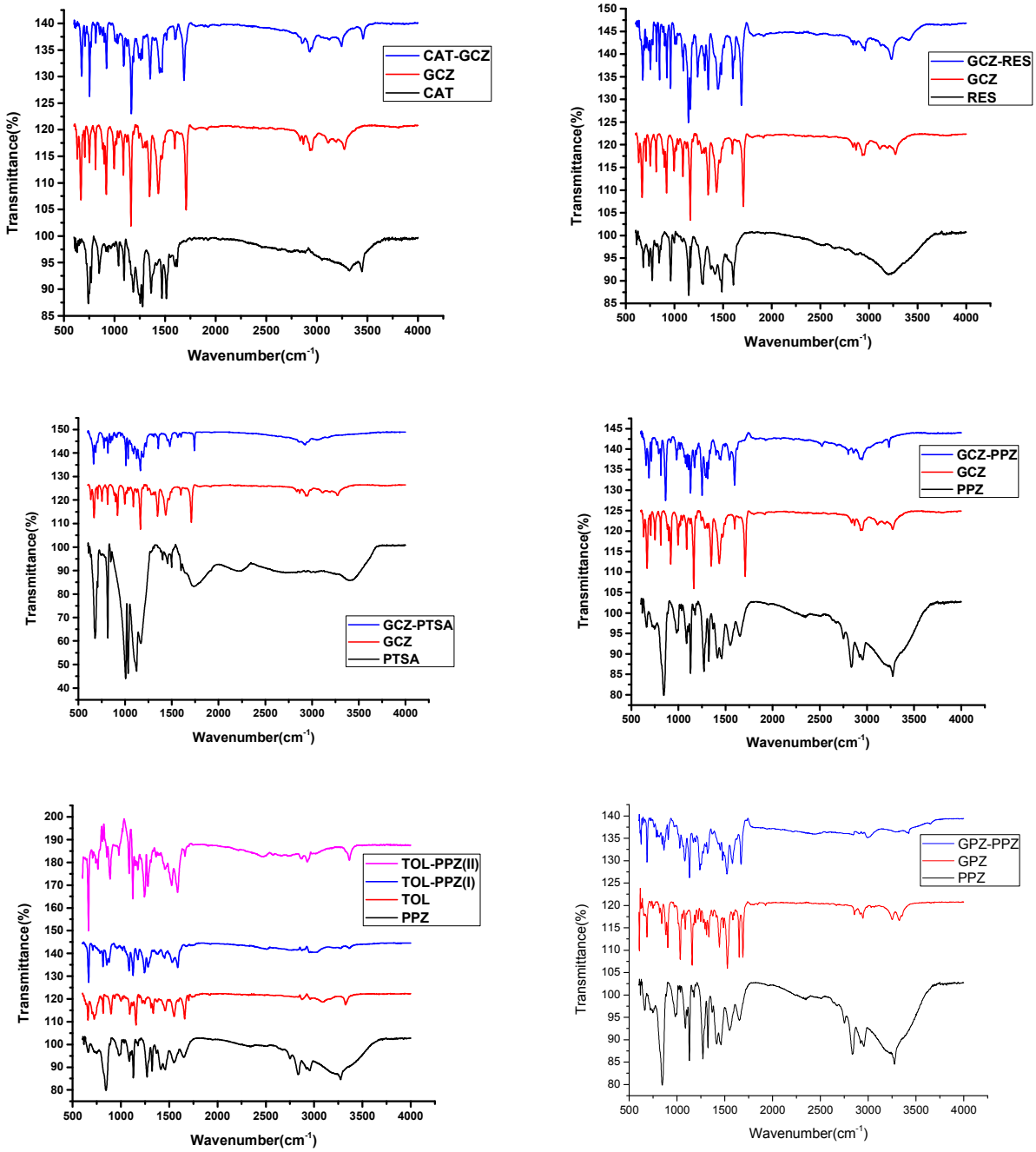


Table S6. Comparison of GPZ (Single crystal and SDPD).

	GPZ From SDPB		GPZ Crystal
emp formula	$C_{21}H_{27}N_5O_4S$		$C_{21}H_{27}N_5O_4S$
formula wt	445.06		445.54
crystal system	Triclinic		Triclinic
space group	$P\bar{1}$		$P\bar{1}$
T/K	283-303	Reduced Cell	100(2)
a/Å	9.1487(3)	5.179	5.1578(3)
b/Å	24.2873(8)	9.149	8.9760(5)
c/Å	5.1794(1)	24.287	23.9704(13)
α/°	93.118(3)	83.48	83.247(2)
β/°	101.154(2)	86.88	85.543(2)
γ/°	83.479(2)	78.85	78.987(2)
volume/Å3	1121.20(7)	1121.184	1080.01(11)
Z	2		2
*D*calcd(g.cm−3)	1.318		1.370
μ (mm−1)	0		0.189
R_1 (I > 2σ(I))	0.0541		0.0541
2*θ* range	2-79.99		3.030-26.997
CCDC No.	292334		1516974
MP(K)	481		481

Table S7. Time (min) vs cumulative amount (mg/cm^{-2}) with standard deviations.

Time	GCZ	Std	GCZ−CAT	Std	GCZ−RES	Std
0	0	0	0	0	0	0
3	1.10834	0.05542	2.21621	0.11081	1.94957	0.09748
6	1.48313	0.07416	4.35043	0.21752	3.96656	0.19833
9	2.09186	0.10459	6.38459	0.31923	5.84764	0.29238
12	2.50325	0.12516	7.78138	0.38907	7.17582	0.35879
15	2.76748	0.13837	9.22102	0.46105	8.57891	0.42895
18	3.46821	0.17341	10.46379	0.52319	9.71937	0.48597
21	3.80893	0.19045	11.42005	0.571	10.66844	0.53342
24	4.23005	0.2115	12.48027	0.62401	11.33514	0.56676

Time	GCZ−PTSA	Std	GCZ−PPZ	Std
0	0	0	0	0
3	3.8959	0.1948	5.0283	0.25142
6	5.3399	0.26699	8.245	0.41225
9	7.638	0.3819	11.159	0.55795
12	8.8288	0.44144	12.806	0.6403
15	10.765	0.53825	14.28	0.714
18	12.766	0.6383	15.964	0.7982
21	13.408	0.6704	17.197	0.85985
24	14.408	0.7204	19.249	0.96245

Time	TOL	Std	TOL−PPZ(I)	Std	TOL−PPZ(II)	Std
0	0	0	0	0	0	0
3	3.32916	0.16646	70.287	3.51435	5.91178	0.29559
6	5.3766	0.26883	120.92	6.046	10.26481	0.51324
9	7.67601	0.3838	163.72	8.186	14.00377	0.70019
12	9.94862	0.49743	204.76	10.238	16.70167	0.83508
15	13.41081	0.67054	254.23	12.7115	19.73592	0.9868
18	15.03503	0.75175	274.53	13.7265	22.78848	1.13942
21	16.79928	0.83996	293.66	14.683	25.26801	1.2634
24	18.64006	0.932	310.36	15.518	28.45163	1.42258

Table S8. Solubility and stability profiles (after 24hour) of GCZ/TOL/GPZ compounds in pH 7.4 buffer.

Compound	Solubility**1** (after **24**h) (mg/L)	Solubility**2** (after **24**h) (mg/L)	Solubility**3** (after **24**h) (mg/L)	Average Solubility (mg/L)	standard deviation	Residue (after 24 h)
GCZ	1335	1300	1313	1316	13.2	GCZ
GCZ−PPZ	8111	8139	8170	8140	29.5	GCZ−PPZ
TOL	4235	4242	4216	4231	13.9	TOL
TOL−PPZ(I)	332193	332221	332186	332200	18.5	TOL−PPZ(I)
TOL−PPZ(II)	10102	10144	10123	10123	21.0	TOL−PPZ(II)
GPZ	193	182	192	189	6.1	GPZ