Crystal engineering of cystic fibrosis drug ivacaftor: Salts, solvates, and hydrate forms with solubility and stability studies

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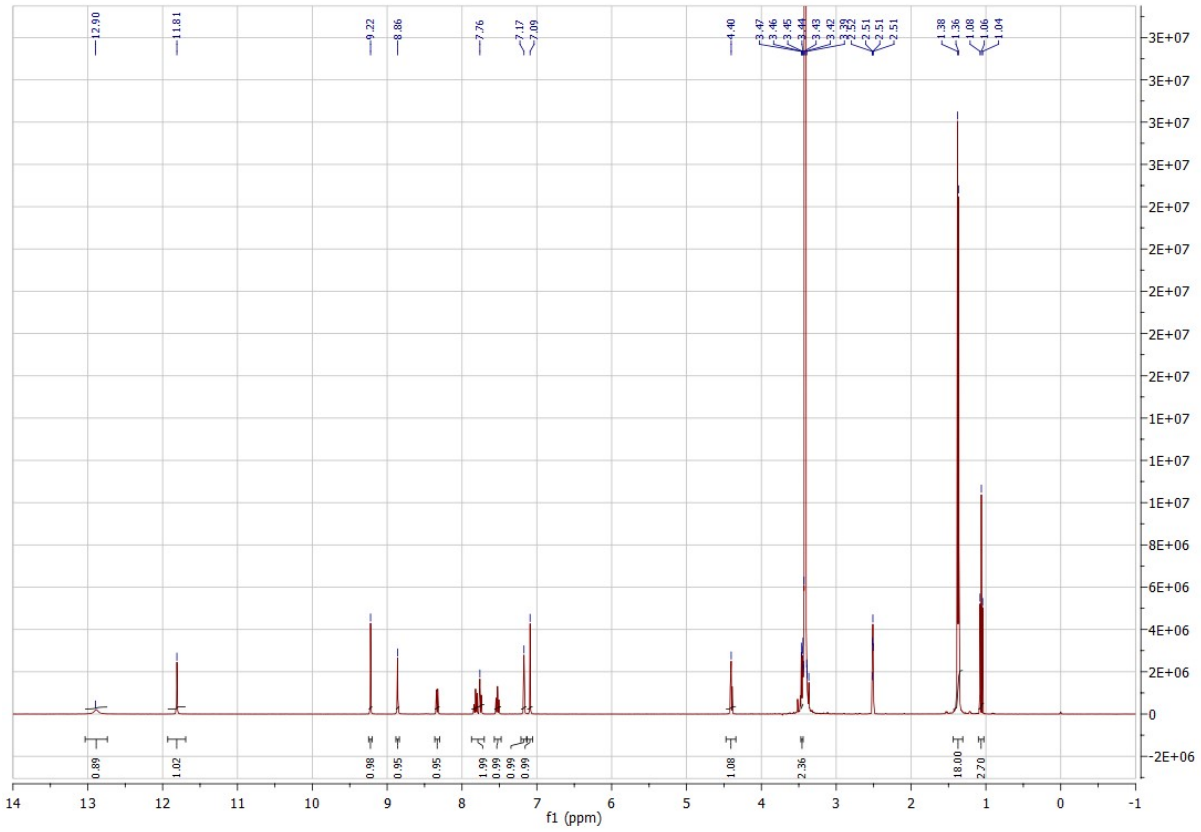


Figure S1. ^{1}H NMR of IVA-ETOH solvate.

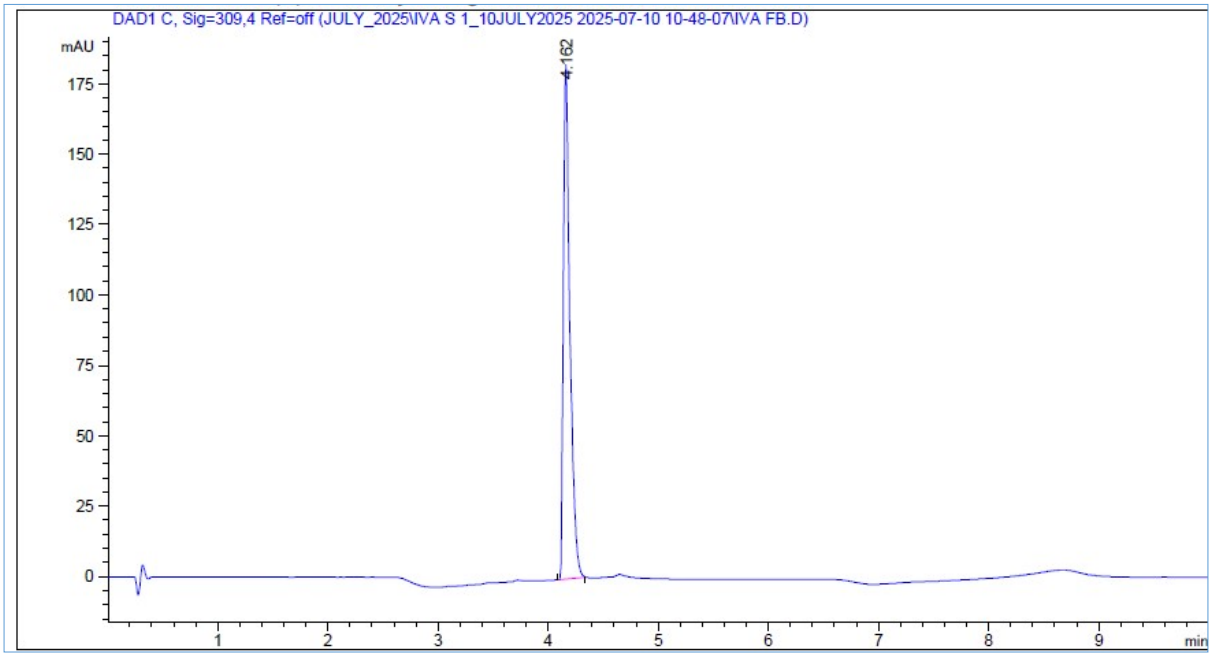


Figure S2. HPLC chromatogram of IVA-ETOH solvate.

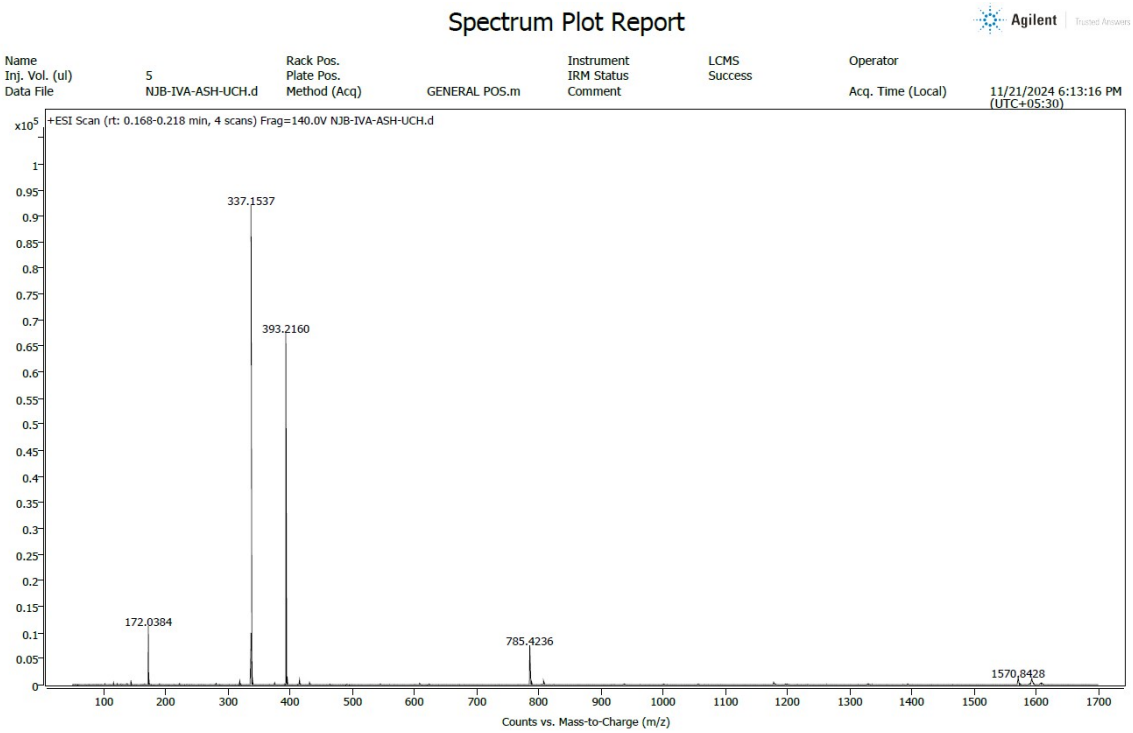


Figure S3. HRMS data of IVA-ETOH solvate.

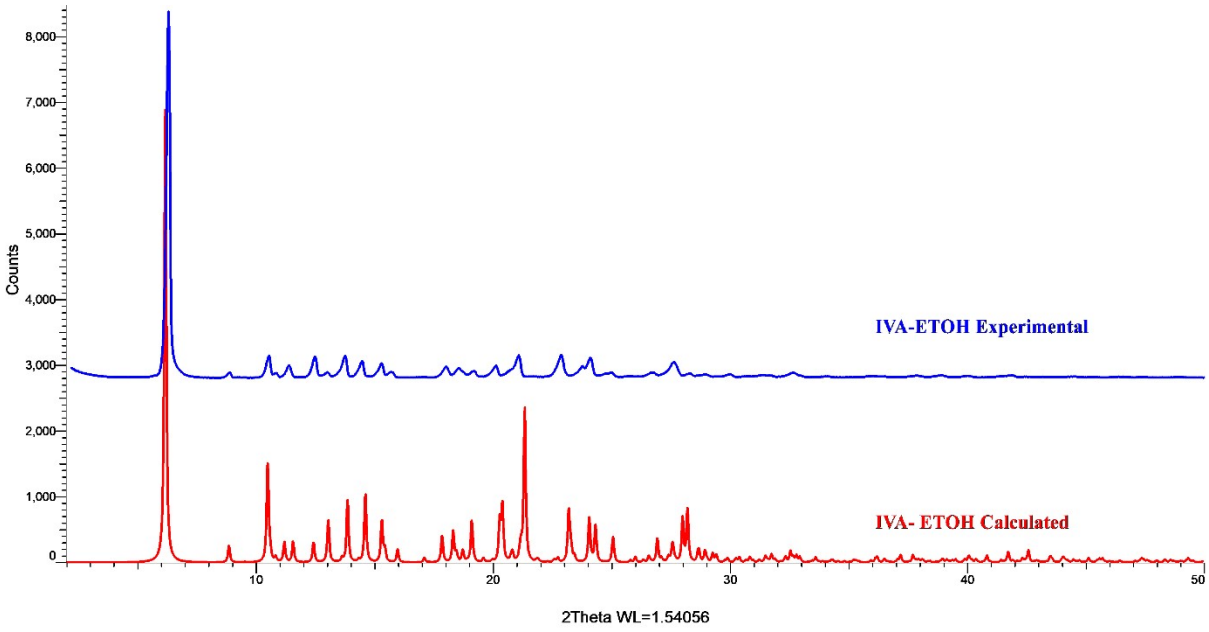


Figure S4: PXRD overlay of IVA-ETOH calculated with experimental.

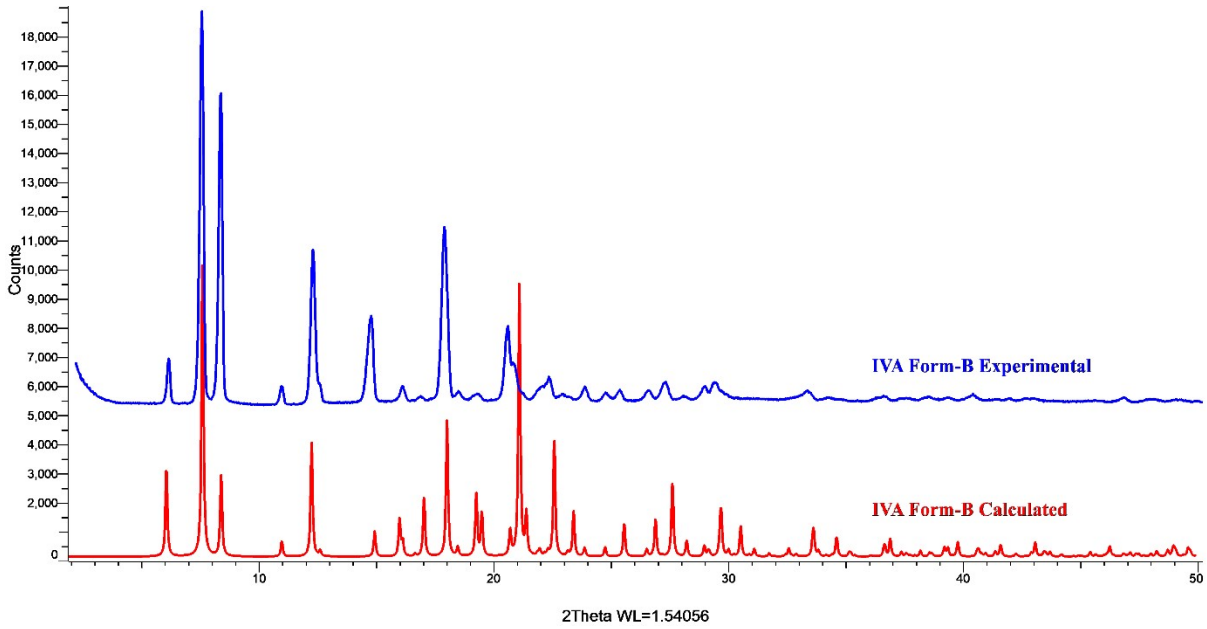


Figure S5. PXRD overlay of IVA Form-B calculated with experimental.

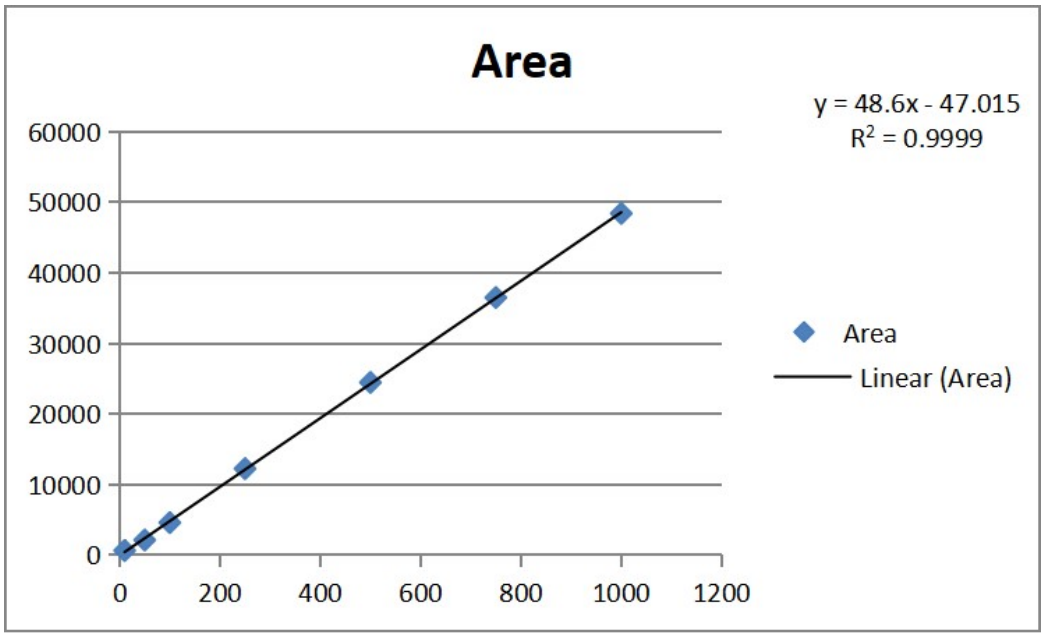


Figure S6. Standard linearity curve of IVA in the LC-MS method.

Table S1. Hydrogen bond geometry of IVA multicomponent solids.

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)
IVA Form B				
C7—H7···O2^{i}	0.95	2.65	3.398 (5)	136
C12—H12···O2^{ii}	0.95	2.45	3.194 (5)	135
O3—H3O···O2^{ii}	0.86 (1)	1.84 (2)	2.697 (4)	173 (6)
N1—H1N···O3^{iii}	0.90 (4)	2.16 (5)	3.032 (5)	164 (4)
N2—H2N···O1	0.89 (4)	1.90 (4)	2.694 (4)	147 (3)
C12—H12···O2	0.95	2.22	2.791 (5)	118
Symmetry codes: (i) −x+1, y+1/2, −z+1; (ii) −x+1, y−1/2, −z+1; (iii) −x+1, y+3/2, −z+1.				

IVA-2H$_2$O				
N1—H5···O1W	0.98 (3)	1.74 (4)	2.709 (4)	175 (3)
N2—H2A···O1	0.88	1.99	2.697 (4)	136
O3—H3O···O2W^{i}	0.87 (2)	2.00 (2)	2.866 (4)	170 (4)
O1W—H1W···O2^{ii}	0.87 (2)	2.01 (2)	2.861 (4)	164 (5)
O1W—H2W···O2W^{iii}	0.86 (2)	2.07 (3)	2.882 (4)	157 (5)
O2W—H3W···O1	0.89 (2)	1.93 (2)	2.824 (4)	177 (5)
O2W—H4W···O2^{iv}	0.88 (2)	2.03 (3)	2.881 (4)	163 (5)
Symmetry codes: (i) *x*+1, *y*−1, *z*; (ii) −*x*+1, −*y*+1, −*z*+1; (iii) −*x*, −*y*+2, −*z*+1; (iv) *x*, *y*+1, *z*.				
IVA-GER				
N1—H1N···O4^{i}	0.97 (4)	1.81 (4)	2.780 (4)	170 (3)
O1W—H1W···O4^{ii}	0.89 (2)	2.05 (2)	2.931 (4)	173 (4)
O1W—H2W···O1^{iii}	0.87 (2)	1.96 (2)	2.817 (3)	168 (4)
N2—H2N···O1	0.89 (3)	1.91 (3)	2.695 (3)	147 (3)
O3—H3O···O1W	0.89 (4)	1.87 (4)	2.756 (4)	174 (4)
O4—H4O···O2	0.84 (5)	1.83 (5)	2.666 (3)	176 (5)
Symmetry codes: (i) −*x*+1, −*y*+1, −*z*+1; (ii) *x*+1, *y*, *z*; (iii) *x*, *y*+1, *z*.				
IVA-HCl-EA				
N1—H1N···Cl01	0.90 (2)	2.14 (2)	3.0333 (18)	170 (2)
N2—H2N···Cl01^{i}	0.89 (2)	2.30 (2)	3.1845 (19)	170 (2)
O1—H1O···O2	0.88 (2)	1.58 (2)	2.429 (2)	160 (3)
O3—H2O···Cl01^{ii}	0.85 (2)	2.25 (2)	3.091 (2)	172 (3)
Symmetry codes: (i) −x+1, −y+2, −z+1; (ii) x, y−1, z.				
IVA-HBr-ACA				
N1—H1N···O2^{i}	0.90 (2)	1.97 (4)	2.793 (5)	153 (6)
N2—H2N···Br01^{i}	0.86 (2)	2.57 (2)	3.415 (4)	169 (4)
O1—H1O···O2	0.87 (3)	1.79 (5)	2.585 (5)	151 (10)
O3—H3O···Br01	0.85 (3)	2.43 (3)	3.253 (4)	162 (7)
O5—H5O···Br01	0.87 (3)	2.42 (4)	3.258 (6)	161 (7)
Symmetry code: (i) −*x*+3/2, *y*+1/2, *z*−1/2.				
IVA-ACA				
O3—H3O···O2^{i}	0.86 (2)	2.25 (2)	3.007 (2)	147 (3)
O3—H3O···O5^{i}	0.86 (2)	2.56 (3)	3.097 (3)	121 (3)
N1—H1N···O5^{ii}	0.93 (3)	1.91 (3)	2.819 (3)	169 (2)
N2—H2N···O1	0.92 (3)	1.84 (3)	2.646 (2)	145 (2)
O4—H4O···O2	0.92 (2)	1.81 (2)	2.705 (2)	164 (4)
Symmetry codes: (i) −*x*+1, *y*, −*z*+3/2; (ii) −*x*+1, −*y*+1, −*z*+1.				
IVA-DACA				
O3—H1O···O5^{i}	0.86 (3)	1.91 (3)	2.752 (2)	166 (3)
N1—H1N···O7^{ii}	0.84 (2)	1.93 (2)	2.737 (2)	158 (2)
N2—H2N···O1	0.78 (3)	1.98 (3)	2.679 (2)	149 (2)
O4—H2O···O2	0.89 (3)	1.75 (3)	2.635 (2)	173 (3)
O6—H3O···O1	0.84 (4)	1.81 (4)	2.648 (2)	171 (3)
Symmetry codes: (i) *x*, *y*−1, *z*; (ii) −*x*+1/2, *y*+1/2, −*z*+1/2.				
IVA-ETA				
N1—H1N···O4^{i}	0.841 (19)	1.918 (19)	2.7582 (16)	176.6 (17)
N2—H2N···O1	0.822 (19)	1.984 (18)	2.6883 (14)	143.3 (17)
O3—H3O···N3	0.81 (2)	1.94 (2)	2.710 (2)	159 (2)
N3—H4N···O1^{ii}	0.86 (1)	2.47 (2)	3.1555 (19)	138 (1)
O4—H4O···O2^{iii}	0.87 (3)	1.90 (3)	2.7400 (16)	164 (3)
Symmetry codes: (i) −*x*+1, −*y*+2, −*z*+1; (ii) *x*−1, *y*+1, *z*; (iii) *x*−1, *y*, *z*.				
IVA-EGL				
N1—H1N···O4^{i}	0.897 (18)	1.841 (19)	2.7323 (18)	171.7 (17)

N2—H2N···O1	0.855 (17)	1.895 (17)	2.6606 (17)	148.2 (15)
O3—H3O···O5	0.90	1.83	2.7018 (18)	162
O4—H4O···O2^{ii}	0.87 (2)	1.88 (2)	2.7290 (17)	163 (2)
O5—H5O···O1^{iii}	0.84 (2)	1.94 (2)	2.7803 (17)	177 (2)
Symmetry codes: (i) −*x*+1, −*y*+1, −*z*+1; (ii) *x*+1, *y*, *z*; (iii) *x*+1, *y*−1, *z*.				

Table S2. Torsion angles of IVA in the prepared multicomponent systems.

Solid forms	Torsions τ (°)				
	∠C1-C2-C4-O2	∠O2-C4-C2-C3	∠C6-N1-C4-O2	∠C5-C6-N1-C4	∠C7-C6-N1-C4
IVA Form-B	-5.48	177.60	8.81	-24.95	153.22
IVA-2H_2O	-6.35	172.77	-1.27	65.90	-113.86
IVA-GER	5.61	-179.33	-6.29	63.27	-119.77
IVA-HCl-EA	-174.07	3.35	0.29	-63.82	117.24
IVA-HBr-ACA	154.71	-19.93	0.5	74.32	-105.24
IVA-ACA	-3.00	174.23	-6.36	52.49	-128.74
IVA-DACA	-3.80	177.99	-0.62	55.80	-124.82
IVA-ETA	-6.28	173.87	3.76	47.72	-133.59
IVA-EGL	-0.10	176.28	-6.47	53.81	-127.20

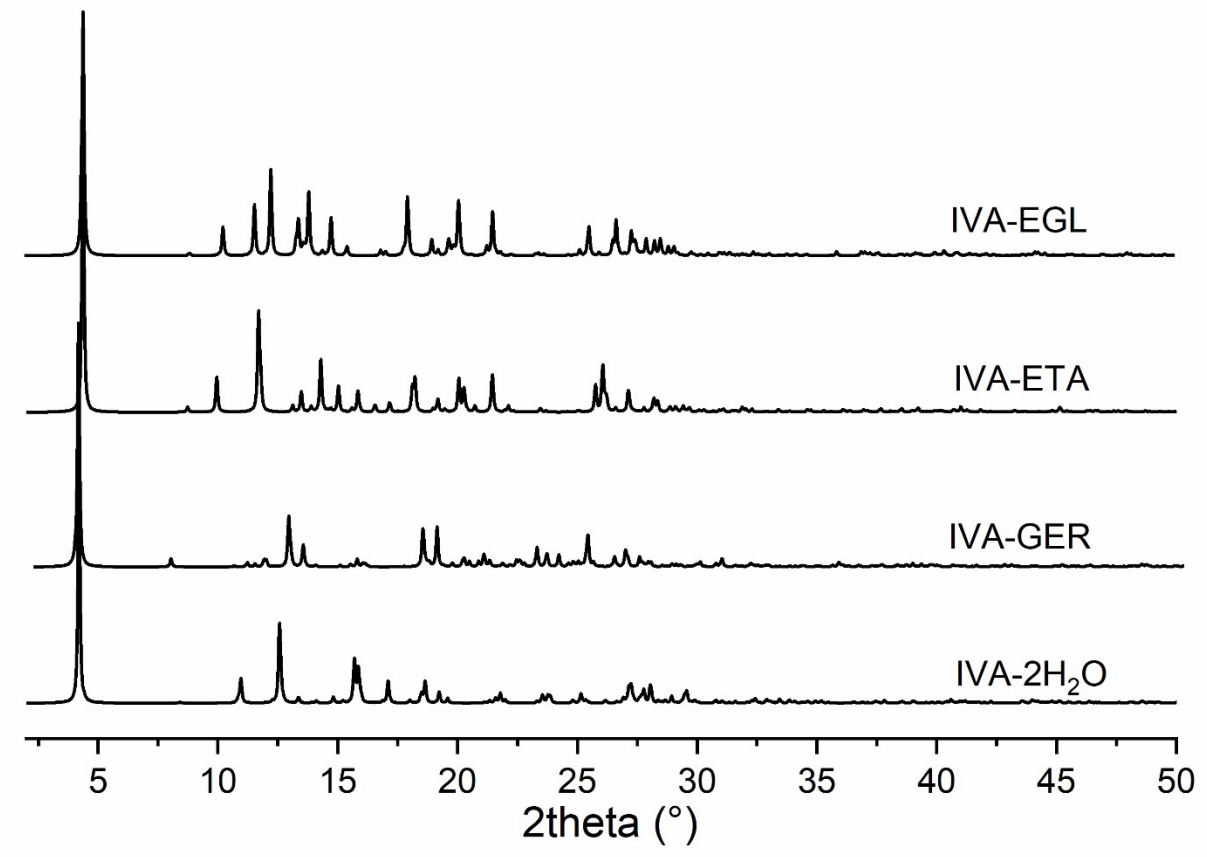


Figure S7. PXRD plot of IVA closely packed crystal structures. IVA-ETA and IVA-EGL show similar powder patterns with most of the peaks overlaying, while IVA-2H_2O and IVA-GER show only a few 2θ peaks overlaying each other.

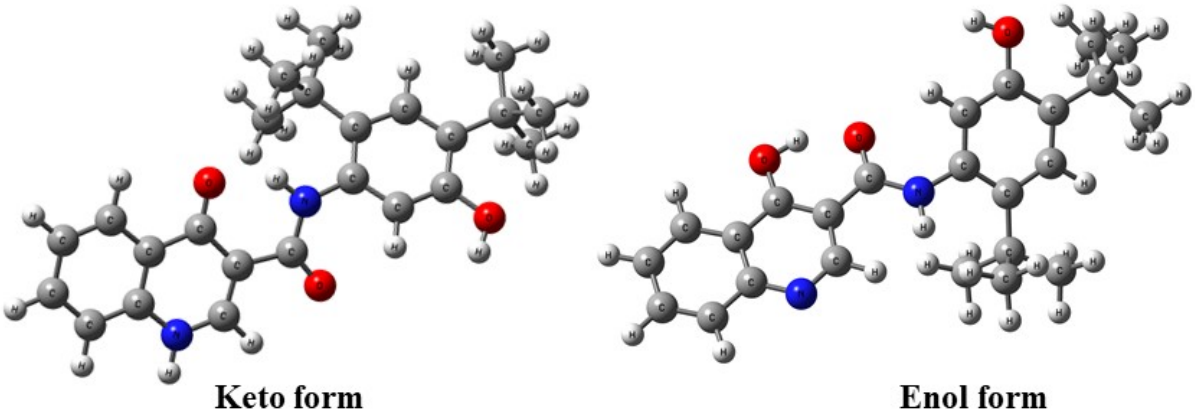


Figure S8. The optimised structure of keto and enol forms of IVA in the multicomponent solids was drawn using the Gaussian software.

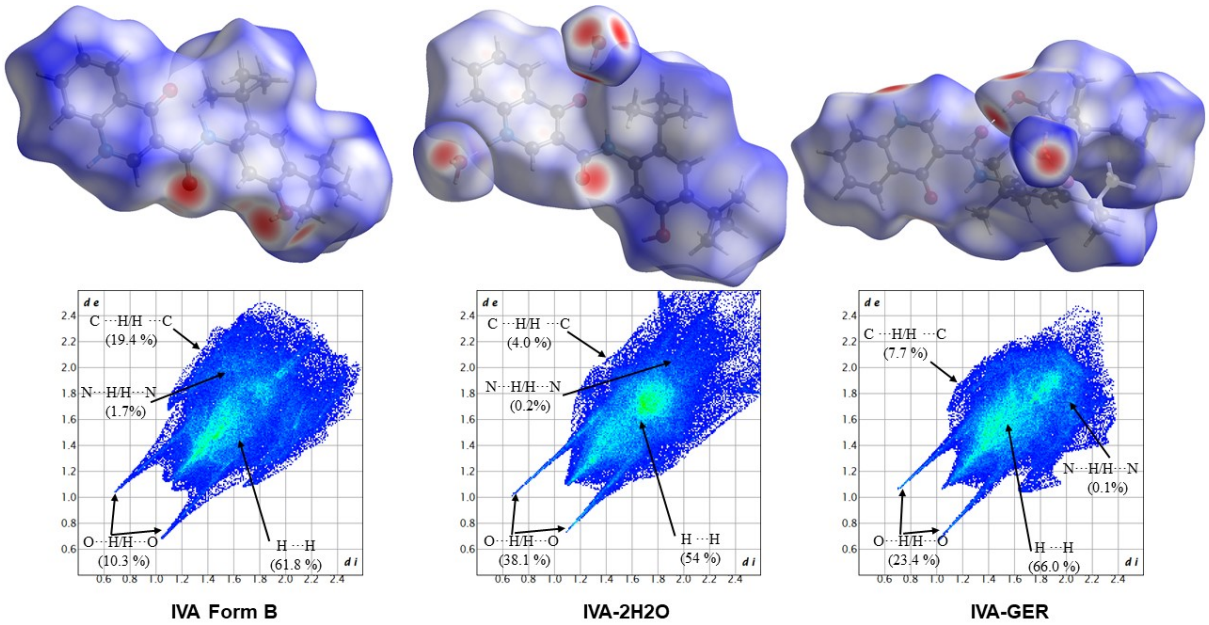


Figure S9. Hirschfeld surface map and 2D plot of IVA FORM B, IVA-2H_2O and IVA-GER.

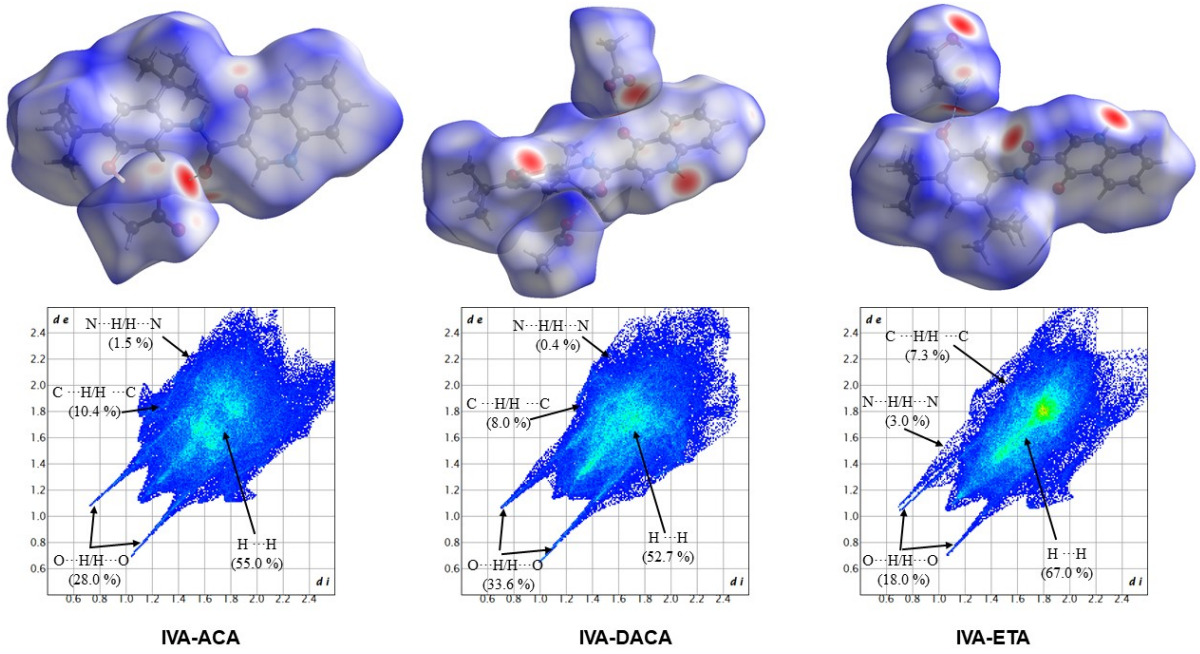


Figure 10. Hirschfeld surface map and 2D plot of IVA-ACA, IVA-DACA, and IVA-ETA.

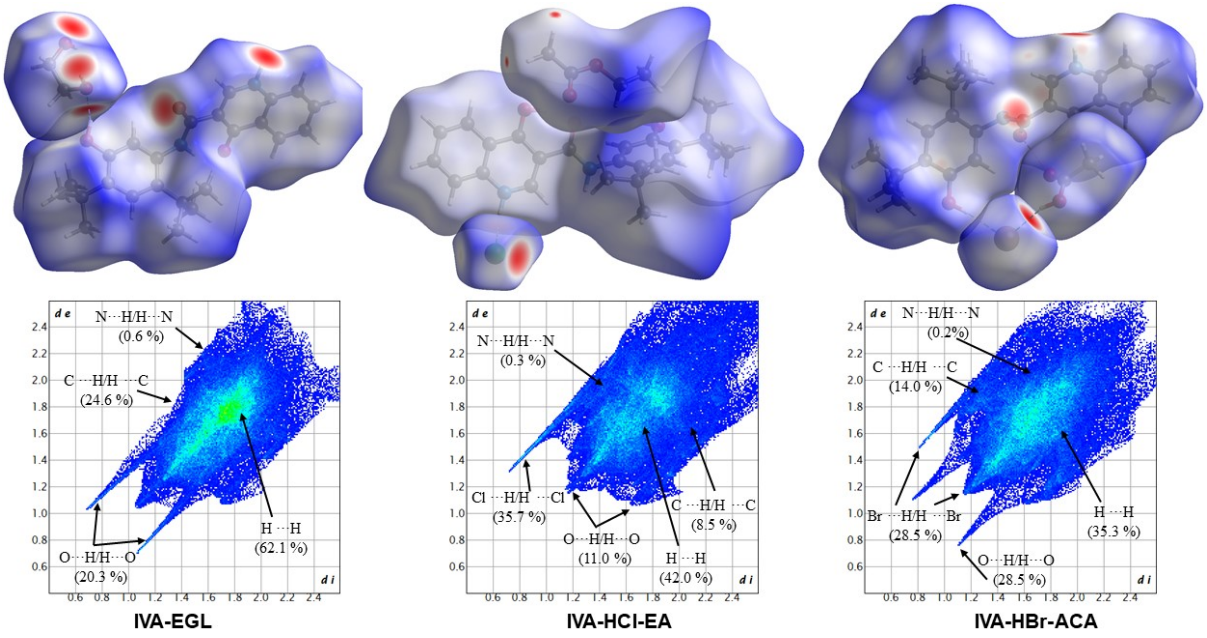
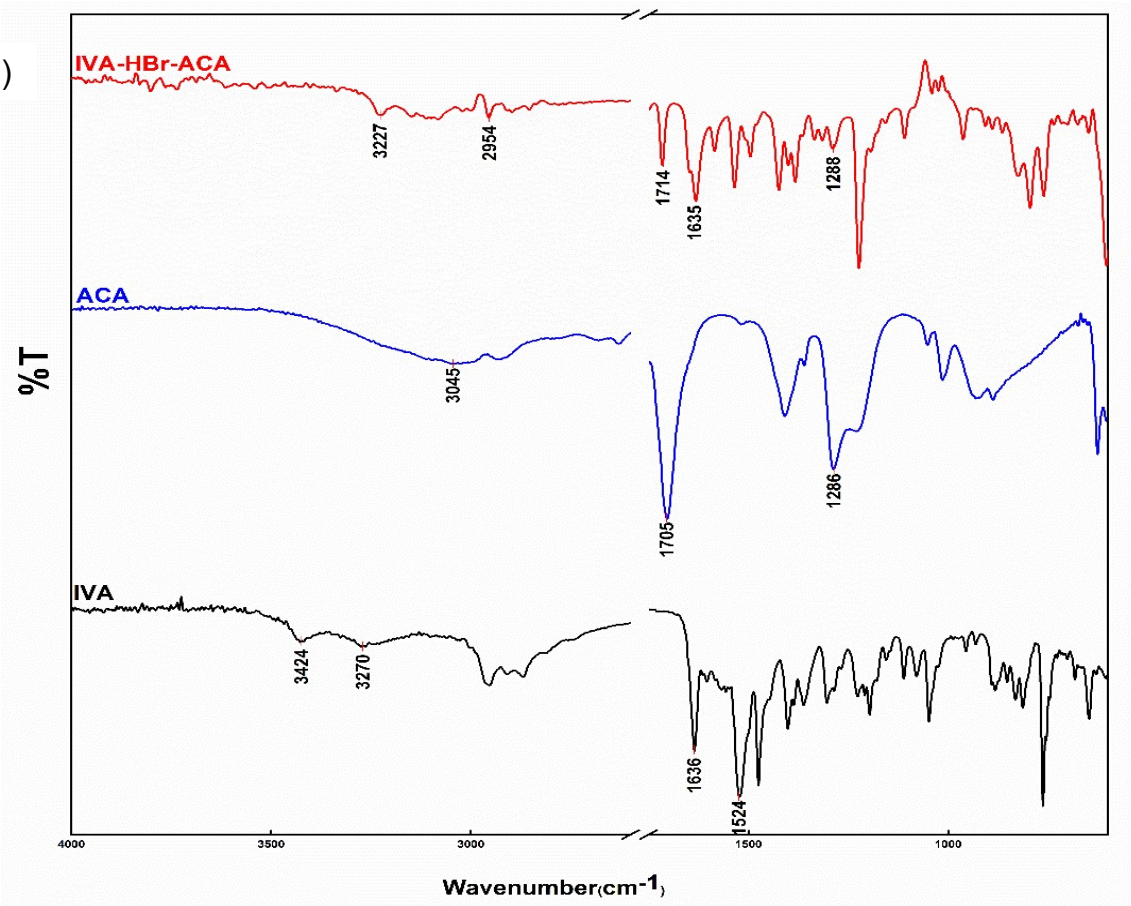
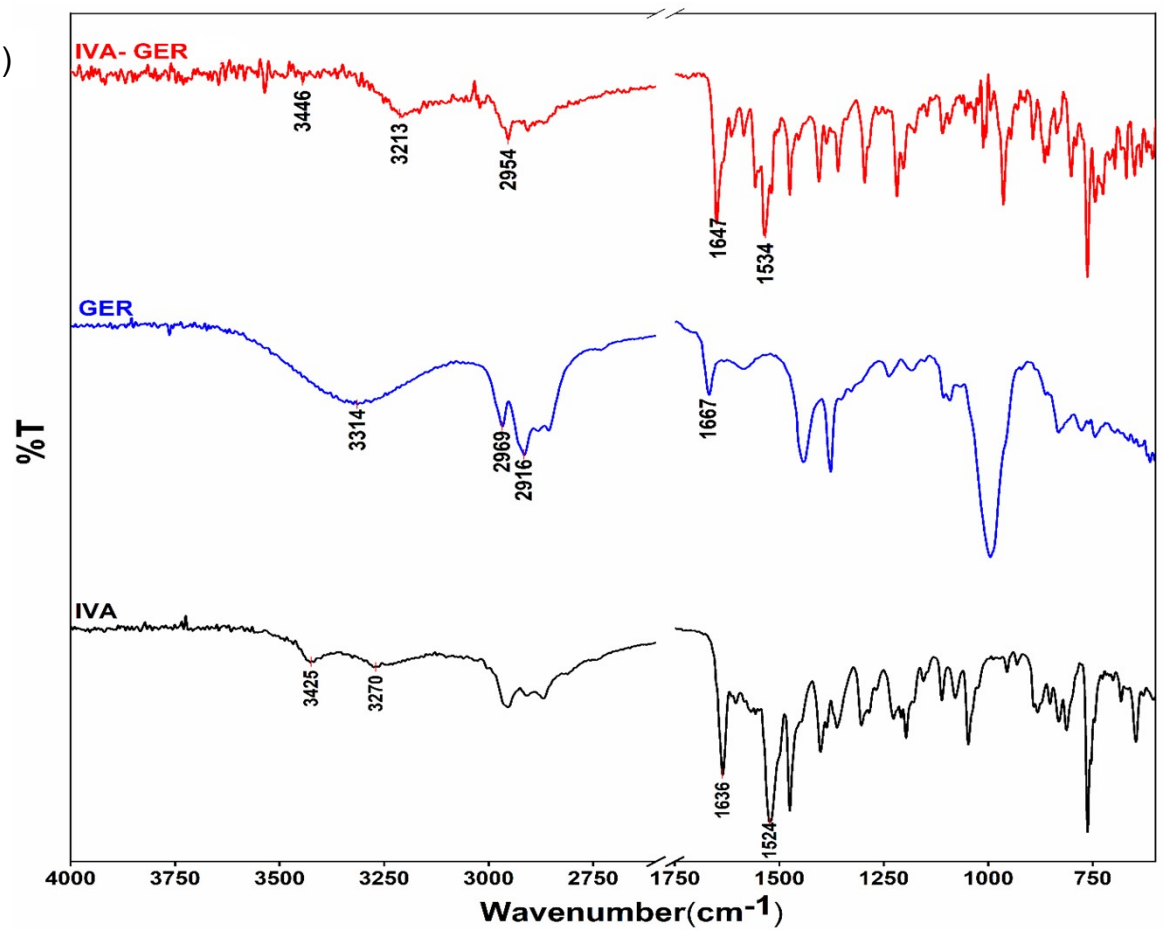


Figure S11. Hirschfeld surface map and 2D fingerprint plot of IVA-EGL, IVA-HCl-EA, and IVA-HBr-ACA.

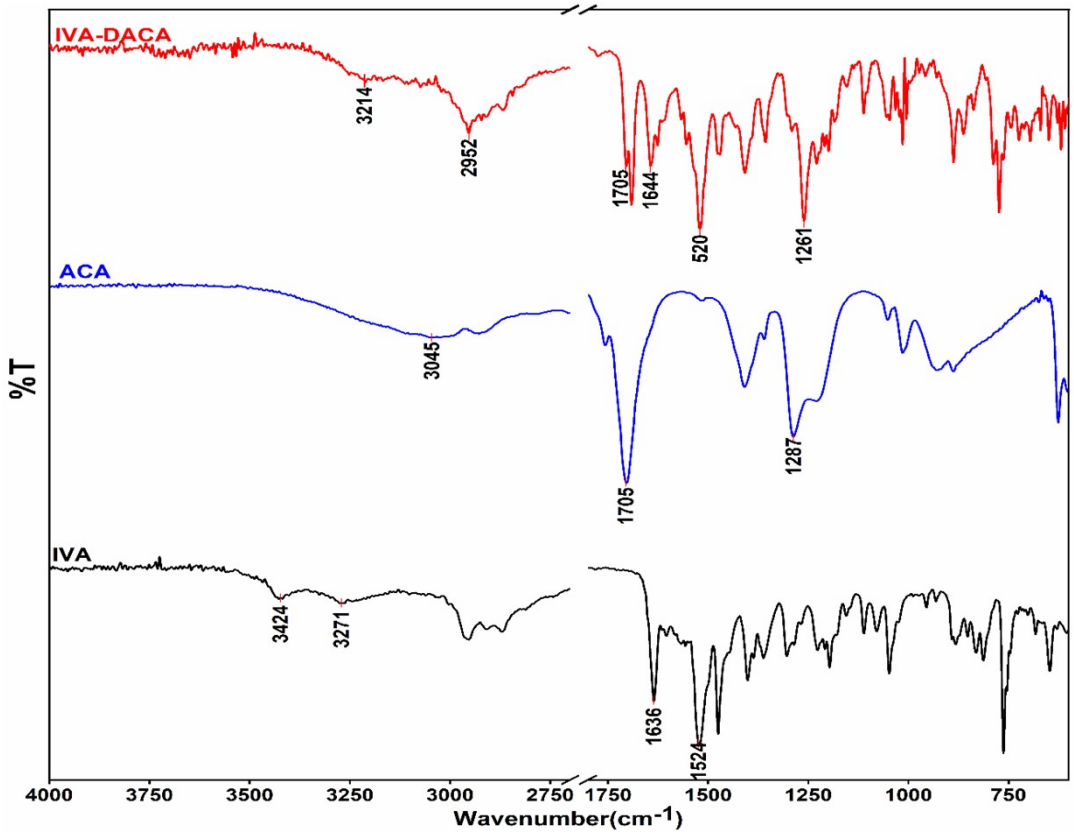
a)


IVA-HBr-ACA
3227
2954
1714
1635
1288
ACA
3045
1705
1286
IVA
3424
3270
1636
1524
%T
4000
3500
3000
1500
1000
Wavenumber(cm-1)

b)


IVA- GER
3446
3213
2954
1647
1534
GER
3314
2969
2916
1667
IVA
3425
3270
1636
1524
%T
4000
3750
3500
3250
3000
2750
1750
1500
1250
1000
750
Wavenumber(cm-1)

c)


IVA-DACA
3214
2952
1705
1644
520
1261
ACA
3045
1705
1287
IVA
3424
3271
1636
1524
%T
4000
3750
3500
3250
3000
2750
1750
1500
1250
1000
750
Wavenumber(cm-1)

d)

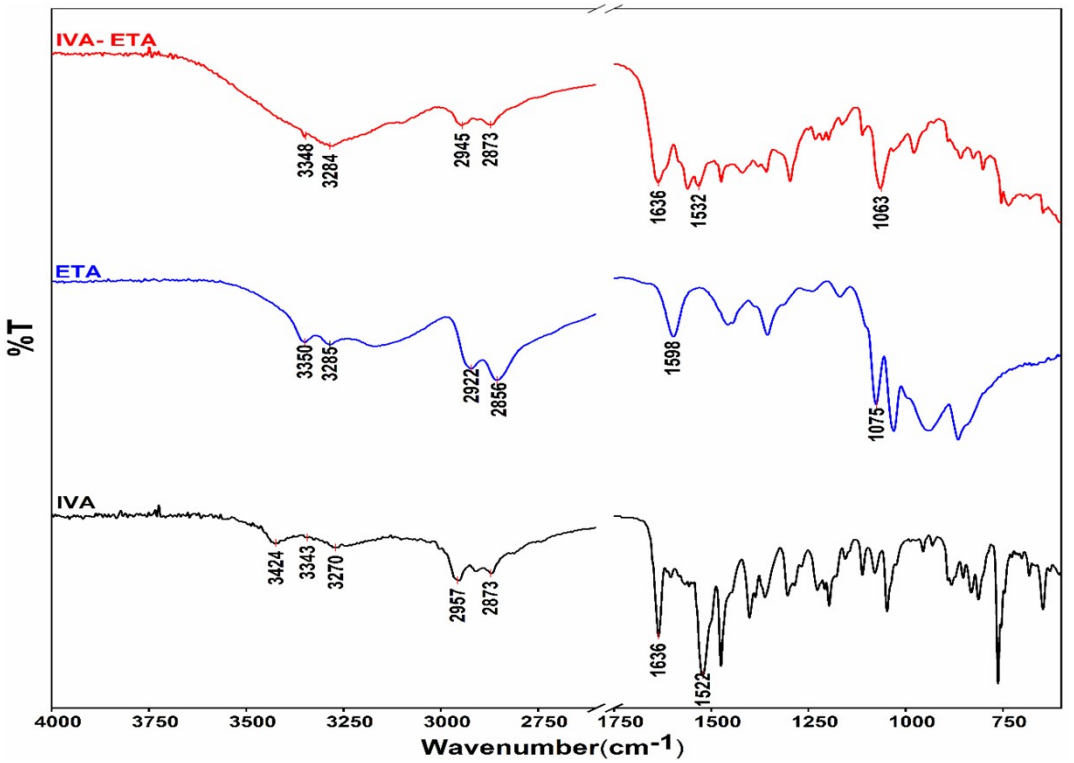


Figure S12. FT-IR Comparison of prepared IVA multicomponent solids with the coformer and IVA molecules (a: IVA-HBr-ACA, b: IVA-GER, c: IVA-DACA, d: IVA-ETA).

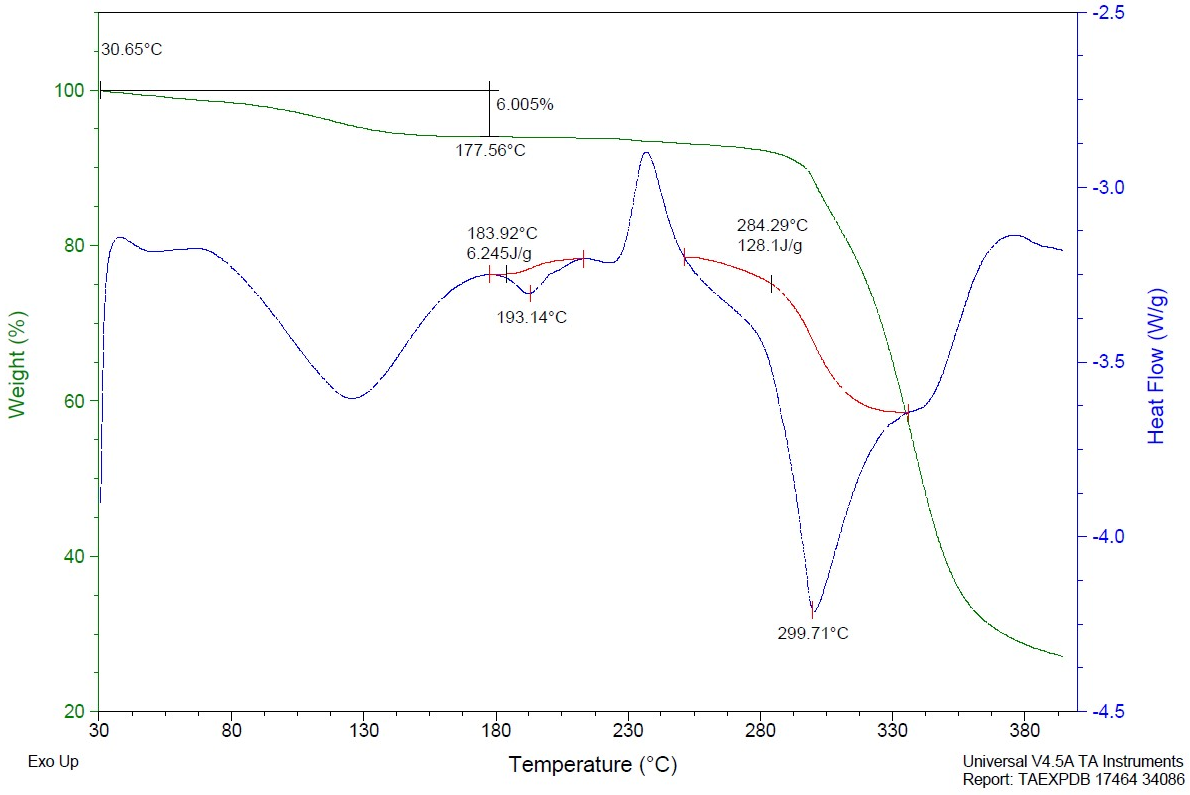


Figure S13. DSC-TGA plot of IVA-HBr-ACA after solubility in 1.2 pH buffer.

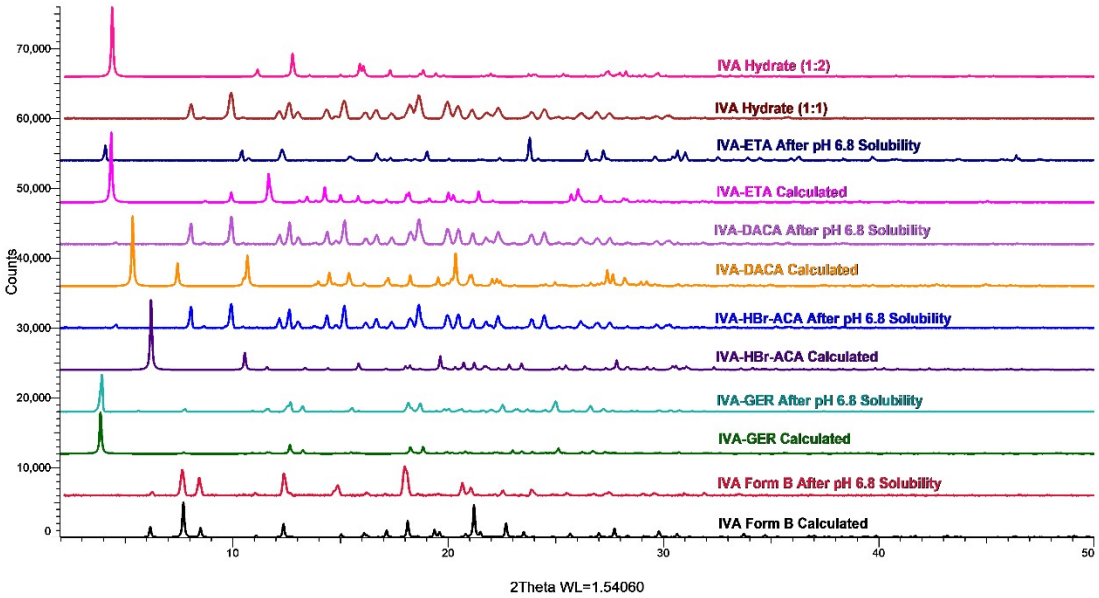


Figure S14. PXRD of residues after pH 6.8 solubility.

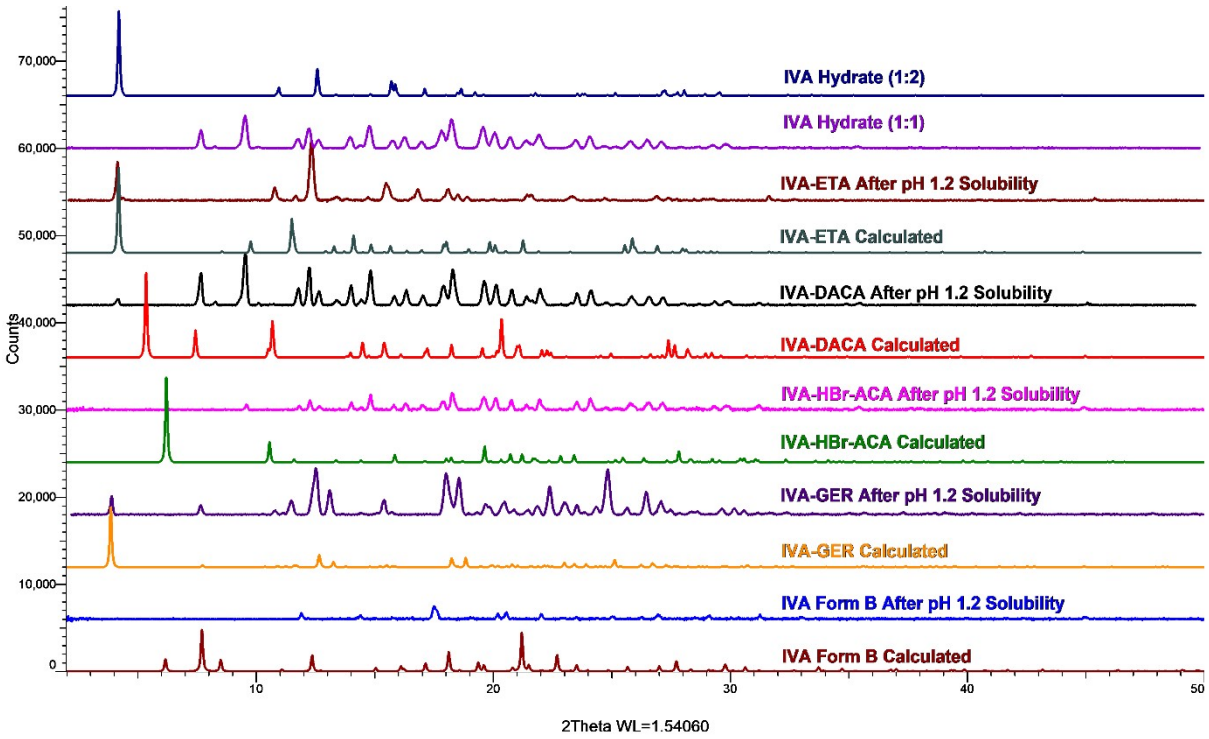


Figure S15. PXRD of residues after pH 1.2 solubility.