Baloxavir marboxil polymorphs: Investigating the influence of molecule packing on the dissolution properties

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Table S1 Screening of BXM crystal form (Part of the experimental process)

Solution evaporation studies			
Starting form	Solvent sysytem	Evaporation temp. (℃)	PXRD analysis
Form I	ethyl acetate	25, under reduced pressure	I
Form I	Tetrahydrofuran	25, under reduced pressure	I+II
Form I	Acetonitrile	25 , under reduced pressure	II
Form I	Dichloromethane	25, under reduced pressure	I+II
Form I	ethyl acetate- cyclohexane	25 , under reduced pressure	III
Form I	acetone	25 , under reduced pressure	I
Form I	ethyl acetate	25	I+II
Cooling crystallization studies			
Starting form	Solvent system	crystallization temp. (℃)	PXRD analysis
Form I	ethyl acetate	-20	III
Form I	ethyl acetate	0	III
Form I	methanol	-10	I
Form I	methanol	25	I
Form I	ethanol	25	I
Form I	acetone	25	I
Form I	n-propanol	25	I
Form I	propan-2-ol	25	I
Form I	Methanol-water（1:1）	25	I
Form I	1-Butanol	25	I
Form I	2-Butanol	25	I
Form I	Methyl isobutyl ketone	25	I
Form I	Acetonitrile-n-heptane(3:7)	25	II
Form I	acetone-water（1:1）	25	I
Form I	dimethylbenzene	25	I
Solvent /anti-solvent precipitation studies			
Starting form	Solvent /anti-solvent	temp. (℃)	PXRD analysis
Form I	Acetonitrile / water	25	I
Form I	Acetic Acid / methyl tert-butyl ether	25	I
Form I	Acetic Acid / water	25	I

Form I	ethyl acetate/ cyclohexane	25	I
Form I	Acetonitrile / n-heptane	0	II
Form I	1,4-Dioxane/ water	25	I
Form I	Acetic Acid / n-heptane	25	I
Form I	Tetrahydrofuran / n-heptane	0	II
Equilibration studies			
Starting form	Solvent system	Equilibration temp. (℃)	PXRD analysis
Form I	water	25	I
Form II	water	25	II
Form III	water	25	I

Table S2 Hydrogen Bonds geometry (Å, °) for Form I.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C7—H7B···O4[1]	0.97	2.50	3.077(3)	118
C11—H11···F1[2]	0.93	2.52	3.207(3)	130

[1]-1+X,+Y,-1+Z; [2]1+X,+Y,1+Z

Table S3 Hydrogen-bond geometry (Å, °) for Form II

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C4*A*—H4*A*···S1*A*^{i}	0.95	2.80	3.716 (7)	162
C11*A*—H11*A*···F1*A*^{ii}	0.95	2.51	3.091 (8)	120
C4*B*—H4*B*···S1*B*^{i}	0.95	2.79	3.717 (7)	164
C11*B*—H11*B*···F1*B*^{iii}	0.95	2.41	3.116 (8)	131
C27*B*—H27*E*···O5*A*^{iii}	0.98	2.51	3.339 (14)	142

Symmetry codes: (i) *x*+1, *y*, *z*; (ii) *x*, *y*, *z*−1; (iii) *x*+1, *y*, *z*+1.

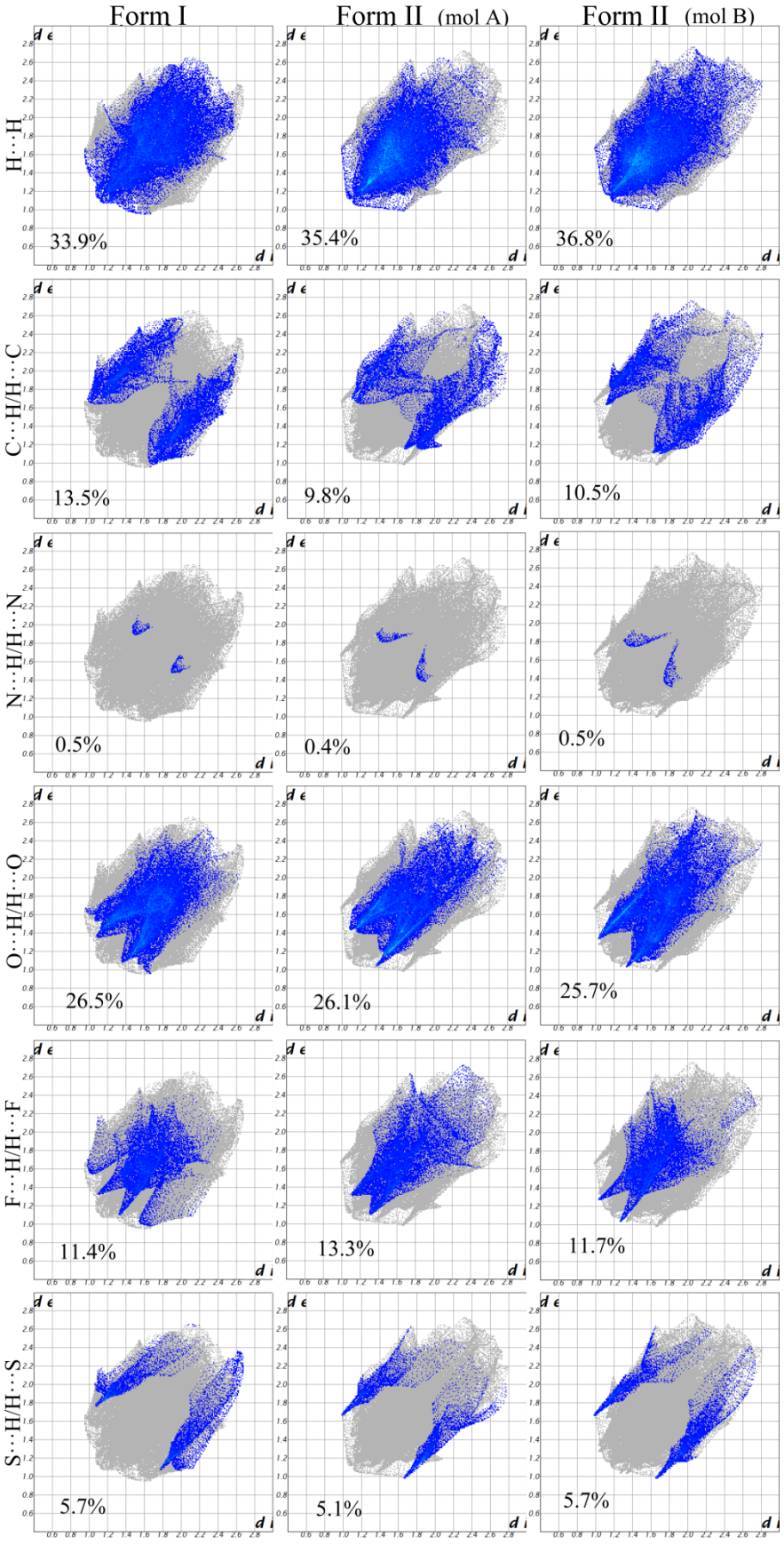

Figure S1 2D fingerprint plots of the Hirshfeld surfaces for components of BXM Form I and II.

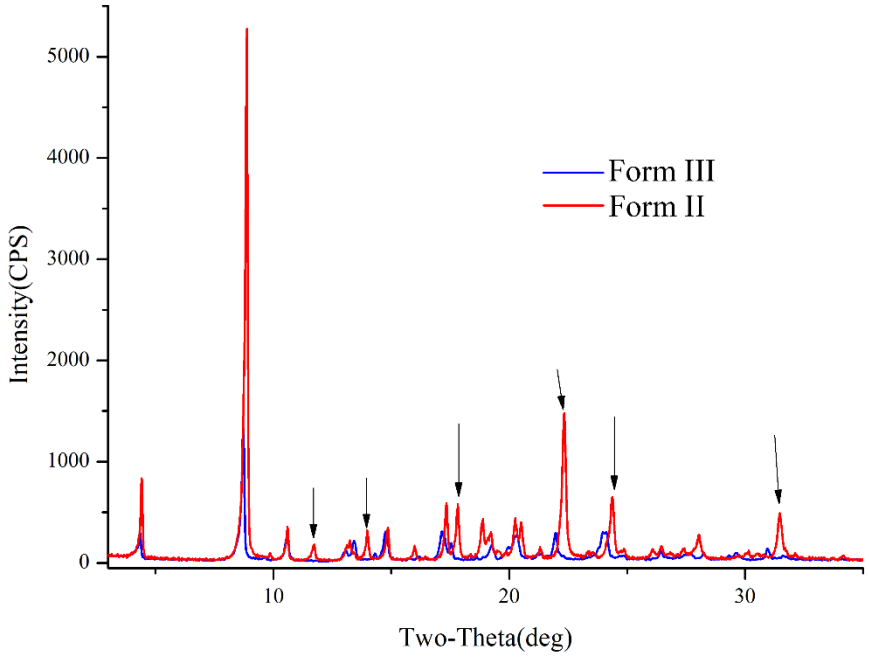

Figure S2 Showing the comparison of observed PXRD patterns of Form II and III. The variations in peak positions across the polymorphs are pointed by the arrows.

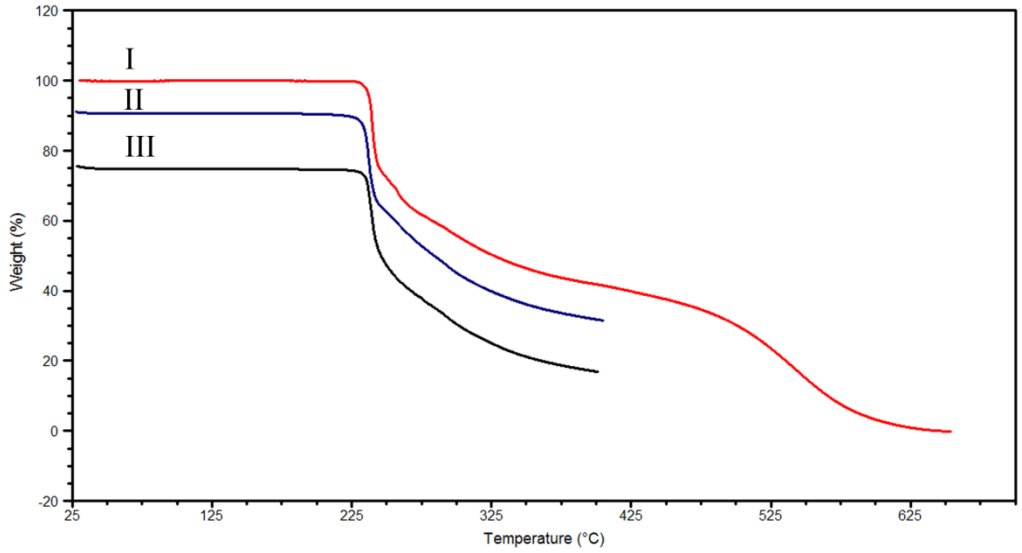

Figure S3 TG curves of BXM in I, II and III at a 10℃/min heating rate.

Table S4. Morphology Predictions for Form I and II by Means of BFDH and GM Calculations.

	BFDH Morphology			Growth Morphology	
h k l	**Multiplicity**	**D (hkl)**	**% Total area**	**Eatt (Total)**	**% Total area**
Form I					
0 -2 0	1	10.098	32.5	−47.906	35. 2
0 0 1	2	8.969	16.8	−51.462	21.0

0 -1 1	2	8.197	17.7	−59.884	12.1
1 0 0	2	6.727	9.4	−69.820	16.0
1 0 -1	2	6.493	7.5	−68.486	14.4
1 -1 0	2	6.382	9.1	-	
1 -1-1	2	6.181	7.0	−78.515	1.4
Aspect ratio		1.778		1.835	
		Form II			
0 -20	1	19.655	54.1	−31.244	61.9
0 0 1	2	9.133	11.6	−89.143	13.8
0 -11	2	8.896	11.8	−92.006	5.2
1 0 0	2	6.630	5.8	−122.566	5.9
1 0-1	2	6.605	5.6	−117.703	9.5
1 -10	2	6.538	5.7	−124.306	3.1
1-1-1	2	6.514	5.5	−120.936	0.6
Aspect ratio		3.254		4.270	

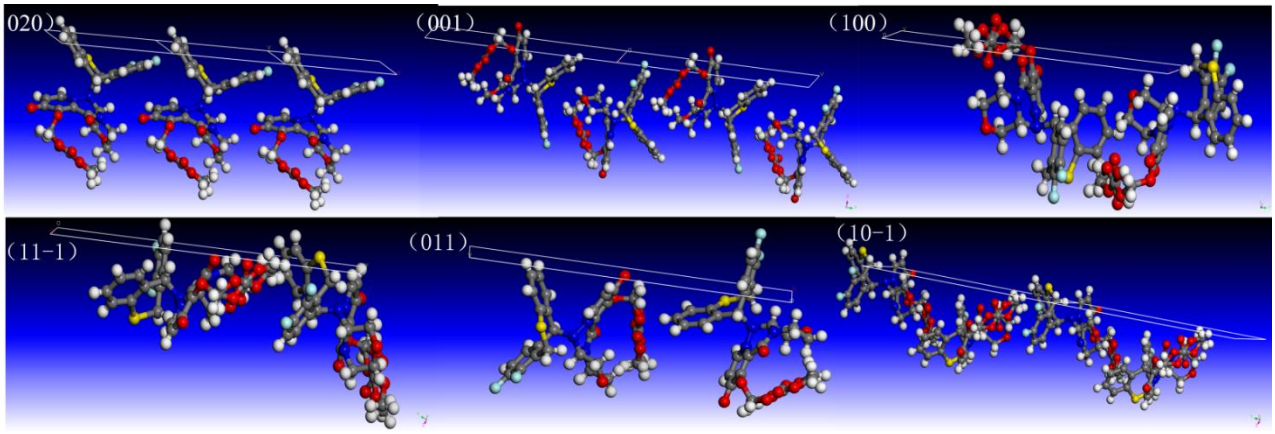

Figure S4. Crystal slices of different facets of BXM Form I expressing the presence of functional groups. The most dominant facet (020) is covered by 1 phenyl, and second dominant facet (001) is covered by 1 carbonyl.

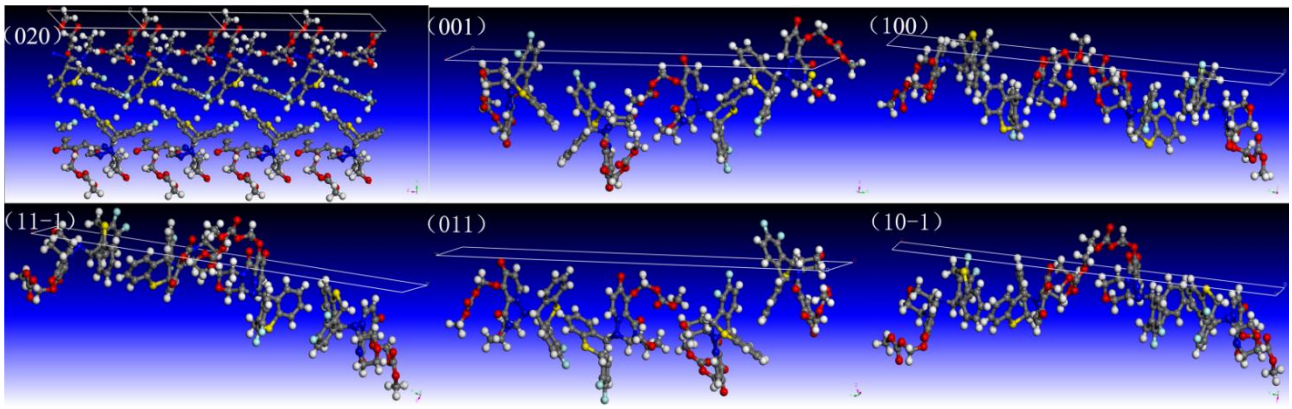

Figure S5. Crystal slices of different facets of BXM Form II expressing the presence of functional groups. The most dominant facet (020) is covered by 1 methoxyl, and second dominant facet (001) is covered by 2 fluorines, 2 carbonyl and 1 methymethyl carbonate chain.

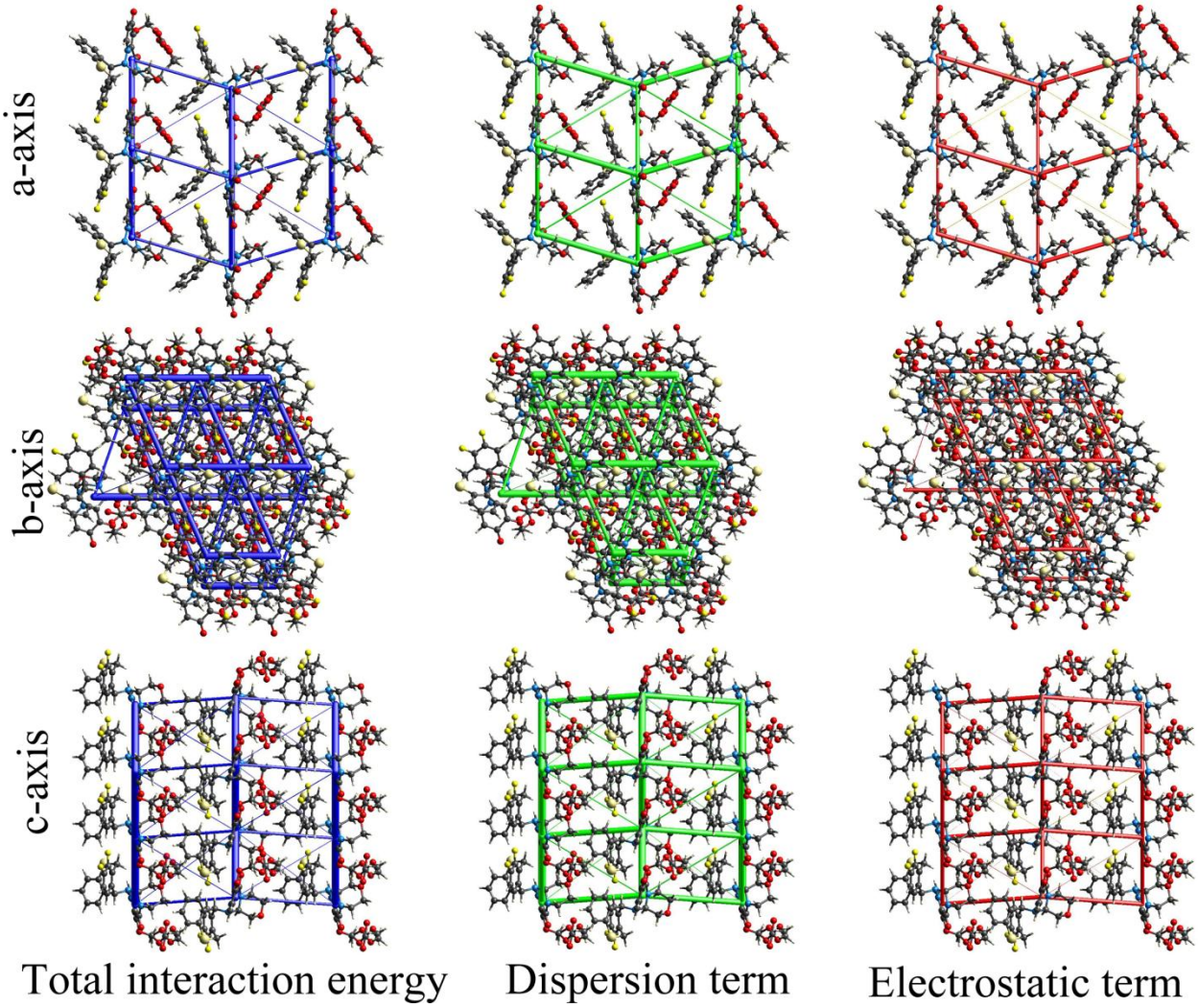

Figure S6. Energy frameworks corresponding to the different energy components and the total interaction energy in BXM Form I.

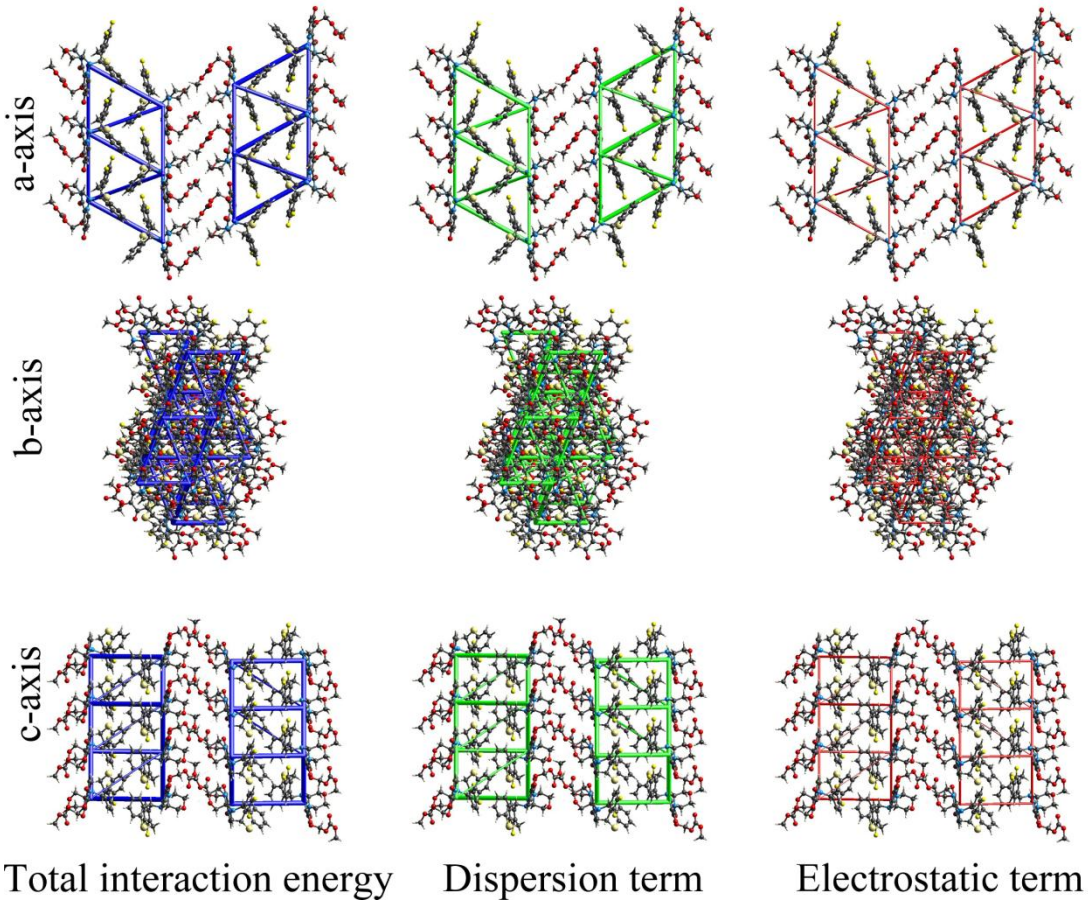

Figure S7. Energy frameworks corresponding to the different energy components and the total interaction energy in BXM Form II.

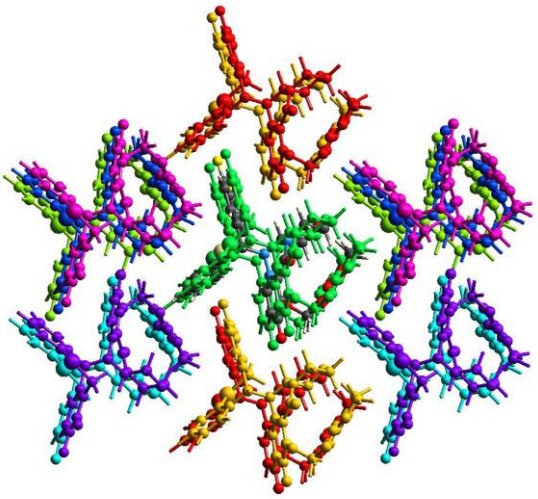

Figure S8 Color coding for the neighboring molecules around molecule of BXM Form I. The molecule is shown with atom type color.

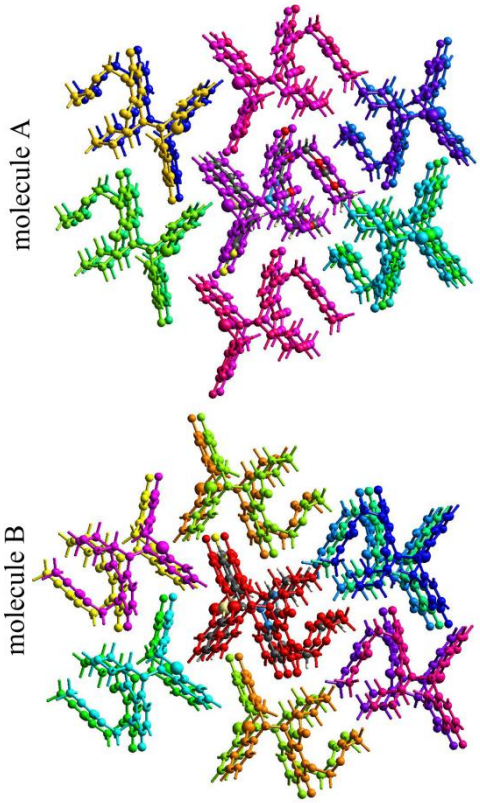

Figure S9: Color coding for the neighboring molecules around molecule A (top) and molecule B (bottom) of BXM Form II. The molecules are shown with atom type color.

Table S5 Molecular pairs and the interaction energies (kJ/mole) obtained from energy framework calculation for BXM Form I.

Interaction Energies (kJ/mol)
R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	2	x, y, z	9.49	B3LYP/6-31G(d,p)	-5.4	-3.6	-35.2	21.3	-25.9
	2	x, y, z	9.83	B3LYP/6-31G(d,p)	-29.3	-7.3	-51.7	33.9	-60.5
	2	-x, y+1/2, -z	12.27	B3LYP/6-31G(d,p)	-1.1	-0.3	-6.0	0.2	-6.5
	2	x, y, z	7.12	B3LYP/6-31G(d,p)	-35.7	-10.8	-87.9	77.3	-74.6
	2	-x, y+1/2, -z	12.04	B3LYP/6-31G(d,p)	3.6	-1.7	-15.6	6.1	-7.3
	2	-x, y+1/2, -z	10.52	B3LYP/6-31G(d,p)	-40.6	-10.7	-66.5	130.7	-28.0
	2	-x, y+1/2, -z	12.73	B3LYP/6-31G(d,p)	3.8	-1.1	-14.0	4.3	-6.4
	2	-x, y+1/2, -z	13.11	B3LYP/6-31G(d,p)	-3.3	-0.7	-4.5	0.7	-7.6

Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Table S6 Molecular pairs and the interaction energies (kJ/mole) obtained from energy framework calculation for BXM Form II.

molecule A

Interaction Energies (kJ/mol)
R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	0	x, y, z	7.10	B3LYP/6-31G(d,p)	-29.3	-10.0	-70.9	52.2	-67.9
	0	x, y, z	9.82	B3LYP/6-31G(d,p)	-22.7	-7.0	-46.9	30.4	-51.3
	1	-	11.93	B3LYP/6-31G(d,p)	0.0	0.0	0.0	0.0	0.0
	0	x, y, z	9.78	B3LYP/6-31G(d,p)	0.0	0.0	0.0	0.0	0.0
	1	-	13.04	B3LYP/6-31G(d,p)	-9.3	-4.9	-31.2	23.4	-26.2
	1	-	10.34	B3LYP/6-31G(d,p)	-0.0	-0.0	-0.0	0.0	-0.1
	1	-	10.38	B3LYP/6-31G(d,p)	-22.7	-7.0	-46.9	30.4	-51.3
	1	-	12.28	B3LYP/6-31G(d,p)	-0.0	-0.0	-0.0	0.0	-0.0
	1	-	12.81	B3LYP/6-31G(d,p)	-0.1	-0.0	-0.1	0.0	-0.1
	1	-	12.31	B3LYP/6-31G(d,p)	-0.1	-0.0	-0.1	0.0	-0.1
	1	-	11.39	B3LYP/6-31G(d,p)	-29.3	-10.0	-70.9	52.2	-67.9
	1	-	12.61	B3LYP/6-31G(d,p)	-0.1	-0.0	-0.1	0.0	-0.2
	2	x, y, z	7.10	B3LYP/6-31G(d,p)	-29.3	-10.0	-70.9	52.2	-67.9
	2	x, y, z	9.82	B3LYP/6-31G(d,p)	-22.7	-7.0	-46.9	30.4	-51.3
	2	x, y, z	9.78	B3LYP/6-31G(d,p)	-9.3	-4.9	-31.2	23.4	-26.2

Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
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molecule B

Interaction Energies (kJ/mol)
R is the distance between molecular centroids (mean atomic position) in Å.

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	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
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	1	-	11.93	B3LYP/6-31G(d,p)	0.0	0.0	0.0	0.0	0.0
	2	x, y, z	9.78	B3LYP/6-31G(d,p)	0.0	0.0	0.0	0.0	0.0
	1	-	13.04	B3LYP/6-31G(d,p)	-9.3	-4.9	-31.2	23.4	-26.2
	1	-	10.34	B3LYP/6-31G(d,p)	-0.0	-0.0	-0.0	0.0	-0.1
	1	-	10.38	B3LYP/6-31G(d,p)	-22.7	-7.0	-46.9	30.4	-51.3
	1	-	12.28	B3LYP/6-31G(d,p)	-0.0	-0.0	-0.0	0.0	-0.0
	1	-	12.81	B3LYP/6-31G(d,p)	-0.1	-0.0	-0.1	0.0	-0.1
	1	-	12.31	B3LYP/6-31G(d,p)	-0.1	-0.0	-0.1	0.0	-0.1
	1	-	11.39	B3LYP/6-31G(d,p)	-29.3	-10.0	-70.9	52.2	-67.9
	1	-	12.61	B3LYP/6-31G(d,p)	-0.1	-0.0	-0.1	0.0	-0.2

Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Overall Energy Profile

Interaction Energies (kJ/mol)
R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the four energy components, scaled appropriately (see the scale factor table below)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	0	x, y, z	7.10	B3LYP/6-31G(d,p)	-29.3	-10.0	-70.9	52.2	-67.9
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	1	-	11.93	B3LYP/6-31G(d,p)	0.0	0.0	0.0	0.0	0.0
	0	x, y, z	9.78	B3LYP/6-31G(d,p)	0.0	0.0	0.0	0.0	0.0
	1	-	13.04	B3LYP/6-31G(d,p)	-9.3	-4.9	-31.2	23.4	-26.2
	1	-	10.34	B3LYP/6-31G(d,p)	-0.0	-0.0	-0.0	0.0	-0.1
	1	-	10.38	B3LYP/6-31G(d,p)	-22.7	-7.0	-46.9	30.4	-51.3
	1	-	12.28	B3LYP/6-31G(d,p)	-0.0	-0.0	-0.0	0.0	-0.0
	1	-	12.81	B3LYP/6-31G(d,p)	-0.1	-0.0	-0.1	0.0	-0.1
	1	-	12.31	B3LYP/6-31G(d,p)	-0.1	-0.0	-0.1	0.0	-0.1
	1	-	11.39	B3LYP/6-31G(d,p)	-29.3	-10.0	-70.9	52.2	-67.9
	1	-	12.61	B3LYP/6-31G(d,p)	-0.1	-0.0	-0.1	0.0	-0.2
	2	x, y, z	7.10	B3LYP/6-31G(d,p)	-29.3	-10.0	-70.9	52.2	-67.9
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	2	x, y, z	9.78	B3LYP/6-31G(d,p)	-9.3	-4.9	-31.2	23.4	-26.2

Scale factors for benchmarked energy models
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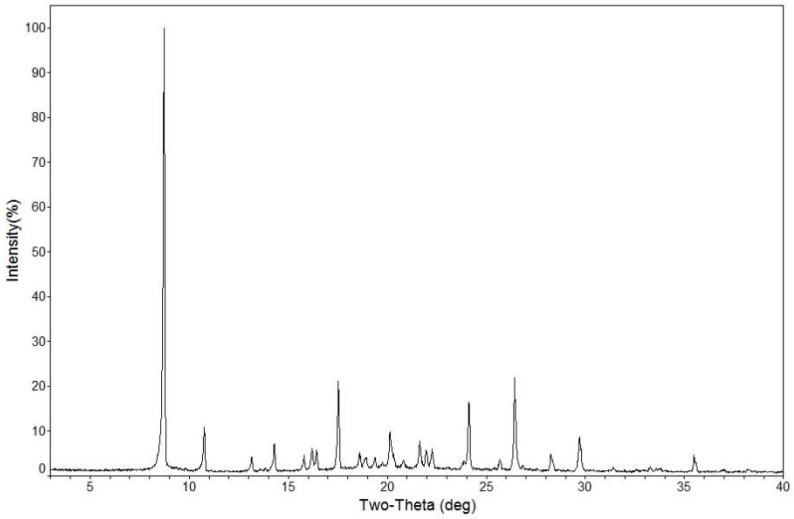

Figure S10 The PXRD pattern of the source BXM

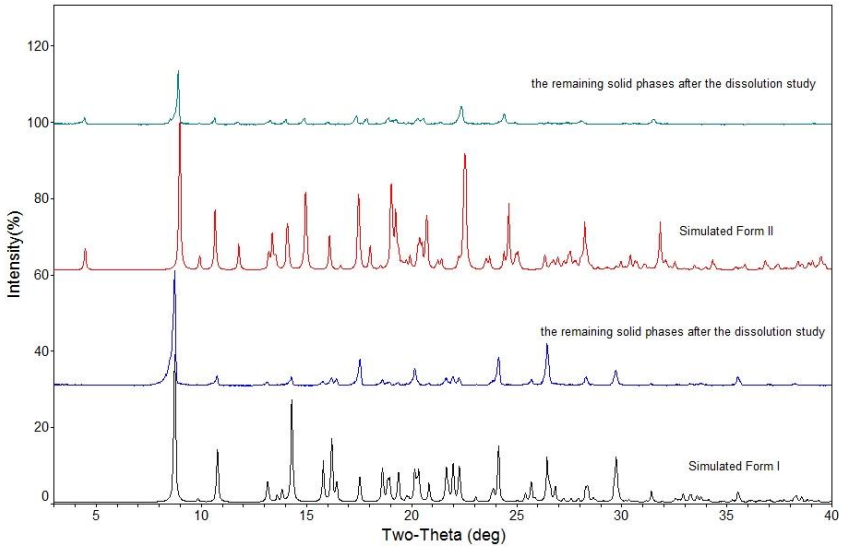

Figure S10 The PXRD pattern of the remaining solid phases after the dissolution study and the simulated PXRD patterns of the BXM Form I and II.

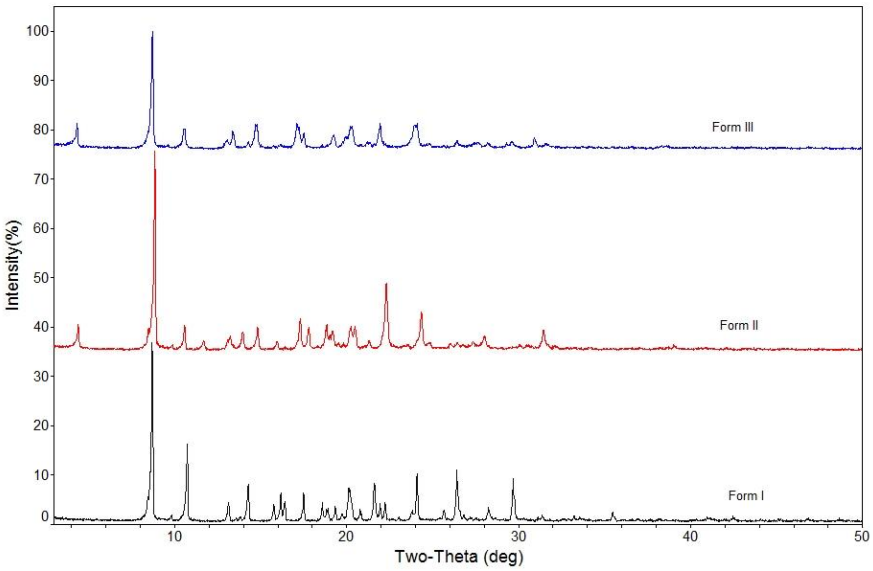

Figure S11 Stability of Form I, Form II and Form III after storage of 12 months at 25°C±2°C and 60% RH±5% R shown in the PXRD pattern.