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SUPPLEMENTARY INFORMATION

Polymorphism in cocrystals of metronidazole benzoate

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Table S1. Crystal data and refinement parameters of BZMDSLC polymorphs I and II.

Parameter	**Polymorph I**	**Polymorph II**
CCDC	1890433	1892488
Empirical formula	$C_{20}H_{19}N_3O_7$	$C_{20}H_{19}N_3O_7$
Formula weight	413.38	413.38
Temperature/K	301.34	295.85
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a/Å	9.5055 (6)	10.645 (3)
b/Å	31.2239 (19)	21.957 (8)
c/Å	6.8578 (4)	8.674 (3)
β/°	102.628 (2)	91.131 (11)
Volume/Å^3	1986.2 (2)	2027.0 (12)
Z	4	4
ρ_{calc}g/cm^3	1.382	1.355
μ/mm^{-1}	0.106	0.104
F (000)	864.0	864.0
Crystal size/mm^3	0.678 × 0.244 × 0.16	0.285 × 0.181 × 0.08
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.884 to 55.016	5.05 to 52.034
Index ranges	-12 ≤ h ≤ 12, -40 ≤ k ≤ 40, -8 ≤ l ≤ 8	-13 ≤ h ≤ 12, -27 ≤ k ≤ 27, -10 ≤ l ≤ 10
Reflections collected	69959	16752
Independent reflections	4553 [R_{int} = 0.0348]	3980 [R_{int} = 0.1226]
Data/restraints/parameters	4553/0/277	3980/0/274
Goodness-of-fit on F^2	1.048	1.001
Final R indexes [I>=2σ (I)]	R_1 = 0.0429, wR_2 = 0.1111	R_1 = 0.0634, wR_2 = 0.1191
Final R indexes [all data]	R_1 = 0.0496, wR_2 = 0.1182	R_1 = 0.1677, wR_2 = 0.1633
Largest diff. peak/hole / e Å^{-3}	0.16/-0.20	0.17/-0.24

Table S2. Hydrogen-bonds of polymorphs I and II of BZMDSLC.

BZMDSLC-I					
Donor – H ⋯ Acceptor	D – H (Å)	H ⋯ A (Å)	D ⋯ A (Å)	D – H ⋯ A (º)	Type
O1A–H1A⋯N2	0.89	1.85	2.6610 (18)	170	*i*
C4A–H4AA⋯O1	0.93	2.43	3.270 (2)	151	*ii*
C2–H2⋯O3A	0.93	2.55	3.4504 (19)	163	*ii*
C10–H10⋯O2	0.93	2.58	3.486 (2)	164	*iii*
O3A–H3A⋯O2A	0.82	1.90	2.6218(18)	145	Intra
C7A–H7A⋯O1A	0.93	2.40	2.721 (2)	100	Intra
C5–H5A⋯O2	0.97	2.46	2.8282 (2)	102	Intra
C6–H6B⋯O2	0.97	2.43	3.0062(19)	118	Intra
BZMDSLC-II					
Donor – H ⋯ Acceptor	D – H (Å)	H ⋯ A (Å)	D ⋯ A (Å)	D – H ⋯ A (º)	Type
O1A–H1A⋯N2	0.82	1.82	2.632 (4)	170	*i*
O3A–H3A⋯O4	0.82	2.60	3.171 (4)	128	*ii*
C5–H5B⋯O4	0.97	2.36	3.251 (4)	152	*iv*
C6–H6B⋯O2A	0.97	2.40	3.206 (4)	140	*ii*
C9–H9⋯O1	0.93	2.58	3.288 (5)	134	*ii*
O3A–H3A⋯O2A	0.82	1.87	2.588 (4)	145	Intra
C5–H5A⋯O2	0.97	2.50	2.864 (4)	102	Intra
C6–H6B⋯O2	0.97	2.46	3.078 (4)	121	Intra
(*i*) x,y,z ; (*ii*) 1-x,1-y,1-z; (*iii*) -1+x,3/2-y,1/2+z; (*iv*) x,1/2-y,1/2+z					

Table S3. Centroid distances of π-π stacking on polymorphs I and II of BZMDSLC.

Polymorph I								
Cg(I)	Cg(J)	Cg-Cg	Alpha	Beta	Gamma	CgI_Perp	CgJ_Perp	Slippage
Cg3	Cg3	3.5952(9)	0.00(7)	12	12	3.5170(6)	3.5169(6)	0.746
Cg1	Cg3	3.6280(9)	5.22(7)	21.3	19.9	-3.4113(6)	-3.3813(6)	1.315
Cg3	Cg1	3.6280(9)	5.22(7)	19.9	21.3	-3.3813(6)	-3.4113(6)	1.235
Cg2	Cg2	4.0737(10)	11.25(8)	38.7	27.7	3.6084(7)	-3.1773(7)	2.549
Cg2	Cg2	4.0737(10)	11.25(8)	27.7	38.7	-3.1773(7)	3.6084(7)	1.891
Cg1	Cg2	4.9729(10)	67.37(8)	12.5	72.4	1.5051(6)	4.8557(7)	
Polymorph II								
Cg(I)	Cg(J)	Cg-Cg	Alpha	Beta	Gamma	CgI_Perp	CgJ_Perp	Slippage
Cg1	Cg1	3.846(2)	0.00(19)	30.9	30.9	-3.3013(14)	-3.3013(14)	1.973
Cg1	Cg3	4.010(3)	3.3(2)	29.5	32.5	3.3812(14)	3.4898(18)	1.975
Cg3	Cg1	4.010(3)	3.3(2)	32.5	29.5	3.4896(18)	3.3812(14)	2.155
Cg2	Cg3	4.581(3)	53.8(2)	50.3	10.2	-4.5089(18)	2.929(2)	
Cg3	Cg2	4.581(3)	53.8(2)	10.2	50.3	2.929(2)	-4.5091(18)	
Cg2	Cg2	5.439(3)	79.7(2)	16.6	88.1	0.1764(18)	-5.2130(18)	
Cg2	Cg3	5.729(4)	75.4(2)	31.9	72.7	-1.7031(18)	-4.864(2)	

Cg1 -> imidazole; Cg2 -> phenyl; Cg3 -> salicylic

Table S4. Crystal data and refinement parameters of BZMDFMA polymorphs I and II.

Parameter	**Polymorph I**	**Polymorph II**
CCDC	1890426	1892489
Empirical formula	$C_{15}H_{15}N_3O_6$	$C_{15}H_{15}N_3O_6$
Formula weight	333.30	333.30
Temperature/K	273.15	273.15
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/c$	Pbca
a/Å	9.0358 (5)	7.2928 (5)
b/Å	26.6419 (14)	17.0257 (9)
c/Å	6.8796 (3)	25.6078 (16)
β/°	102.419 (2)	
Volume/$Å^3$	1617.38 (14)	3179.6 (3)
Z	4	4
$\rho_{calc}g/cm^3$	1.369	1.393
μ/mm^{-1}	0.108	0.110
F (000)	696.0	1392.0
Crystal size/mm^3	0.632 × 0.172 × 0.168	0.228 × 0.198 × 0.105
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.538 to 55.056	5.042 to 54.19
Index ranges	$-11 \le h \le 11$, $-34 \le k \le 34$, $-8 \le l \le 8$	$-9 \le h \le 9$, $-21 \le k \le 21$, $-32 \le l \le 32$
Reflections collected	46849	60358
Independent reflections	3705 [R_{int} = 0.0658]	3511 [R_{int} = 0.1521]
Data/restraints/parameters	3705/0/219	3511/0/218
Goodness-of-fit on F^2	1.044	1.007
Final R indexes [I>=2σ (I)]	R_1 = 0.0542, wR_2 = 0.1330	R_1 = 0.0575, wR_2 = 0.1285
Final R indexes [all data]	R_1 = 0.0783, wR_2 = 0.1544	R_1 = 0.1387, wR_2 = 0.1771
Largest diff. peak/hole / e $Å^{-3}$	0.37/-0.32	0.20/-0.30

Table S5. Hydrogen-bonds of polymorphs I and II of BZMDFMA.

BZMDFMA-I					
Donor – H ⋯ Acceptor	D – H (Å)	H ⋯ A (Å)	D ⋯ A (Å)	D – H ⋯ A (º)	Type
O1A–H1A⋯N2	0.82	1.84	2.655 (3)	172	*i*
C2A–H2A⋯O1	0.93	2.45	3.286 (3)	149	*ii*
C4–H4A⋯O2A	0.96	2.58	3.440 (3)	149	*iii*
C2–H2⋯O2A	0.93	2.57	3.496 (3)	176	*ii*
C2A–H2A⋯O1A	0.93	2.41	2.745 (3)	101	Intra
C5–H5A⋯O2	0.97	2.39	2.831 (3)	107	Intra
BZMDFMA-II					
Donor – H ⋯ Acceptor	D – H (Å)	H ⋯ A (Å)	D ⋯ A (Å)	D – H ⋯ A (º)	Type
O1A–H1A⋯N2	0.82	1.89	2.661 (3)	156	*i*
C2–H2⋯O2A	0.93	2.20	3.101 (5)	163	*iv*
C9–H9⋯O3	0.93	2.41	2.729 (5)	100	Intra
C5–H5A⋯O2	0.97	2.39	2.851 (4)	108	Intra
(*i*) x,y,z ; (*ii*) 1-x,1-y,-z; (*iii*) x,y,1+z; (*iv*) -1/2+x,3/2-y,1-z					

Table S6. Centroid distances of π-π stacking on polymorphs I and II of BZMDFMA.

Polymorph I								
Cg(I)	Cg(J)	Cg-Cg	Alpha	Beta	Gamma	CgI_Perp	CgJ_Perp	Slippage
Cg2	Cg2	4.0001(14)	6.34(11)	28.6	34.7	3.2869(10)	3.5128(10)	1.914
Cg2	Cg2	4.0002(14)	6.34(11)	34.7	28.6	3.5128(10)	3.2870(10)	2.280
Cg1	Cg1	4.6885(12)	0.02(12)	49.4	49.4	3.0500(8)	3.0501(8)	3.561
Cg1	Cg2	4.9059(14)	64.94(12)	19.4	70.0	1.6748(9)	4.6275(10)	
Polymorph II								
Cg(I)	Cg(J)	Cg-Cg	Alpha	Beta	Gamma	CgI_Perp	CgJ_Perp	Slippage
Cg2	Cg2	4.0684(19)	11.70(15)	37.3	27.7	3.6026(13)	3.2348(13)	2.467
Cg2	Cg2	4.0684(19)	11.70(15)	27.7	37.3	3.2348(13)	3.6026(13)	1.890
Cg1	Cg2	5.6299(18)	78.67(16)	26.4	75.7	1.3868(13)	5.0439(14)	

Cg1 → imidazole; Cg2 → phenyl.

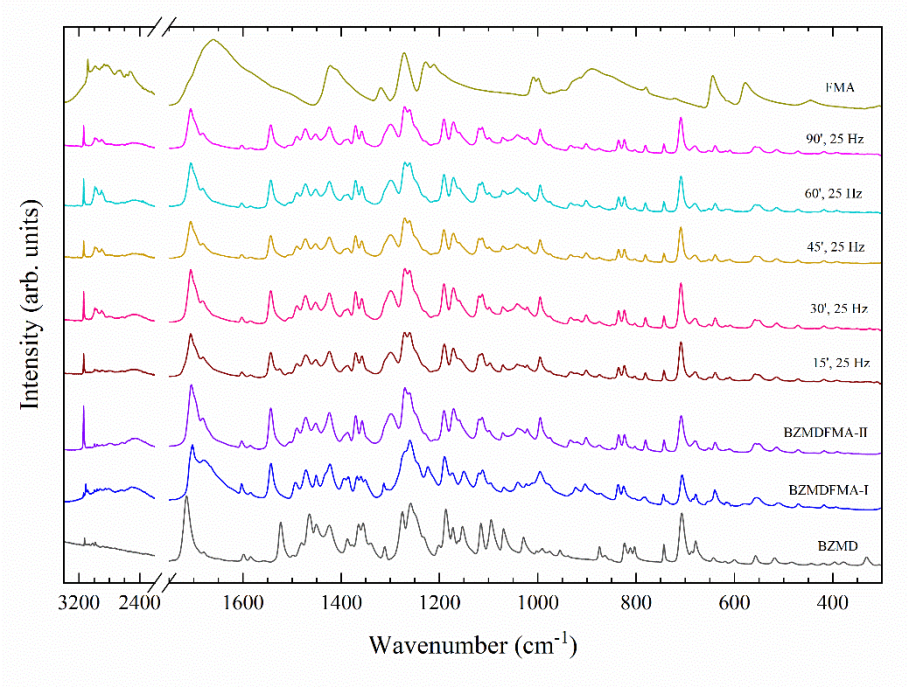

Figure S1. FT-IR spectra of the physical mixture of BZMD and FMA as a function of the neat grinding time compared to the BZMD and BZMDFMA polymorphs spectra.

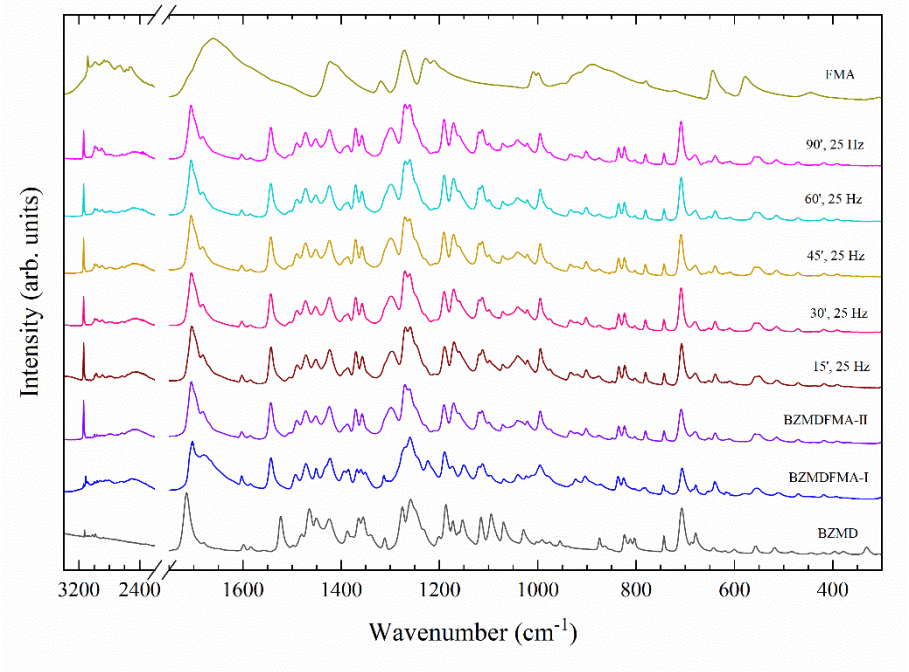

Figure S2. FT-IR spectra of the physical mixture of BZMD and FMA as a function of ethanol-assisted grinding time compared to the BZMD and BZMDFMA polymorphs spectra.

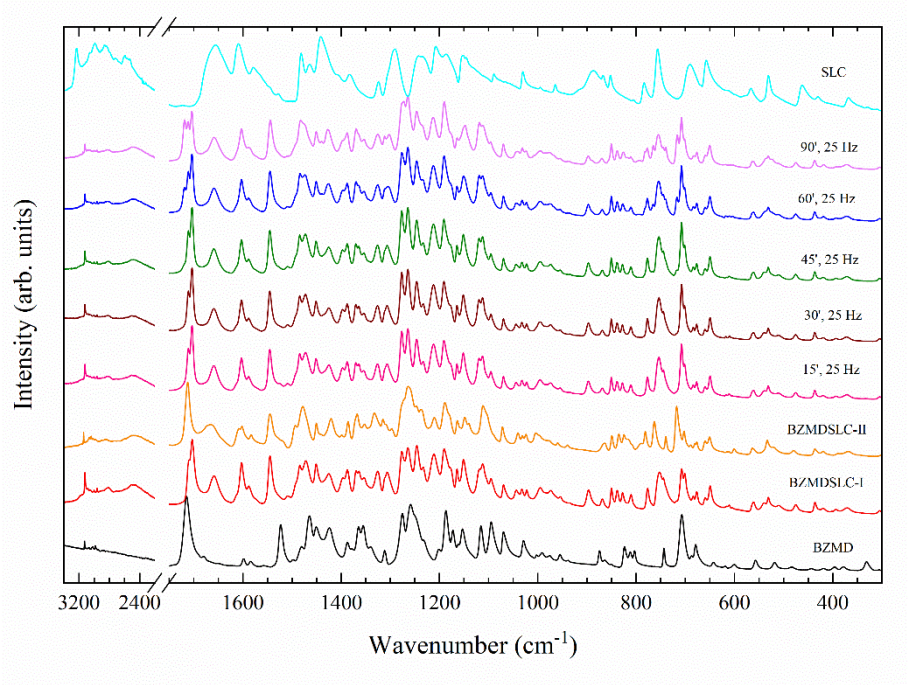

Figure S3. FT-IR spectra of the physical mixture of BZMD and SLC as a function of the neat grinding time compared to the BZMD and BZMDSLC polymorphs spectra.

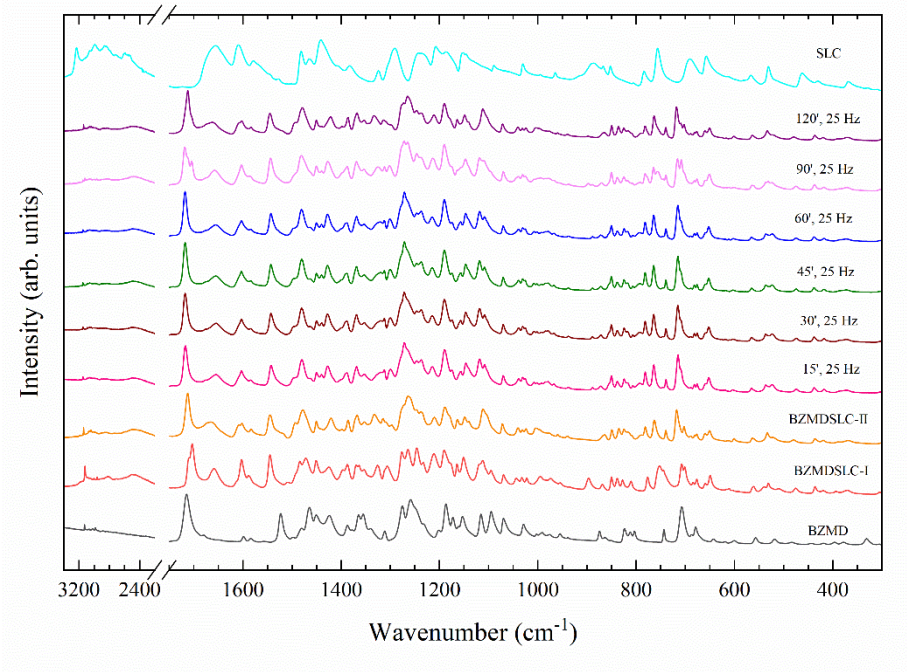

Figure S4. FT-IR spectra of the physical mixture of BZMD and SLC as a function of the ethanol-assisted grinding time compared to the BZMD and BZMDSLC polymorphs spectra.

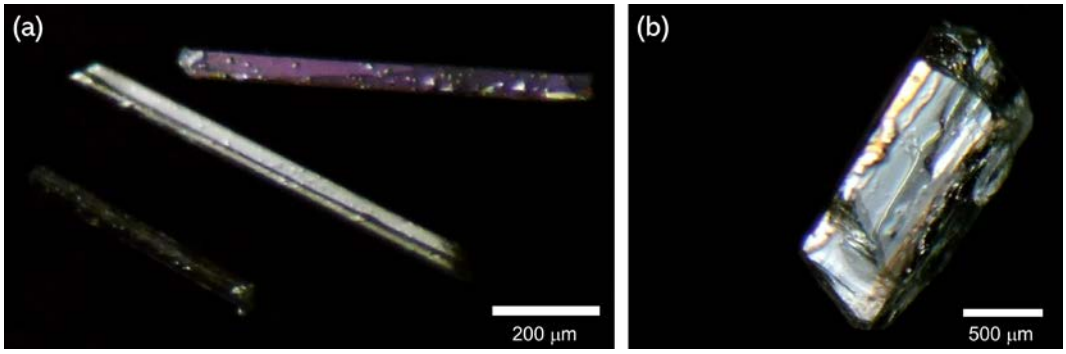

Figure S5 - Crystalline habits of the BZMDSLC polymorphs: (a) form I and (b) form II.

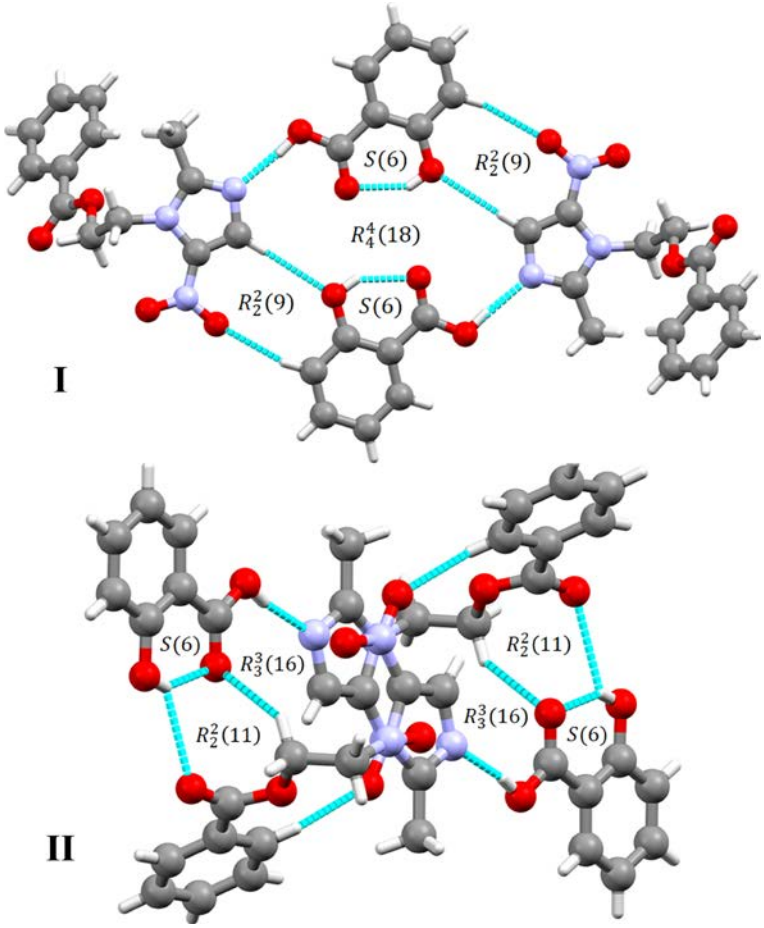

Figure S6. Synthons and graph sets of polymorphs I and II of BZMDSLC.

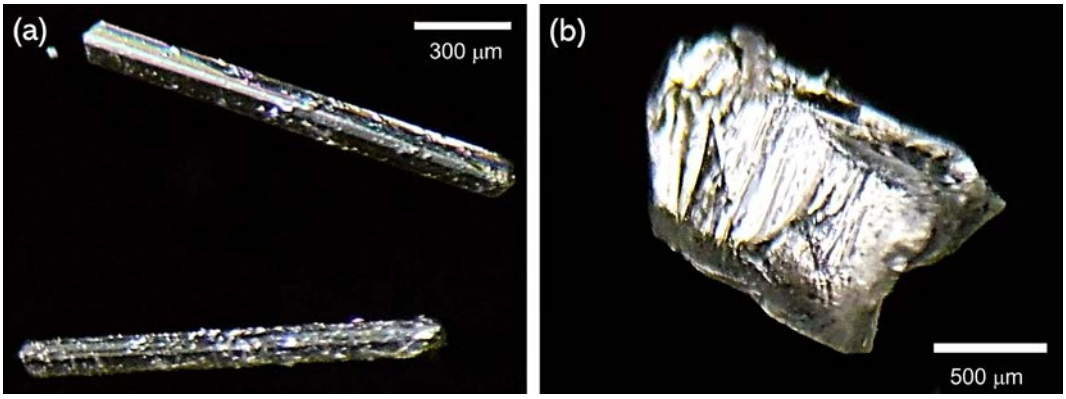

Figure S7. Crystalline habits of polymorphs of cocrystals BZMDFMA. a) form I b) form II.

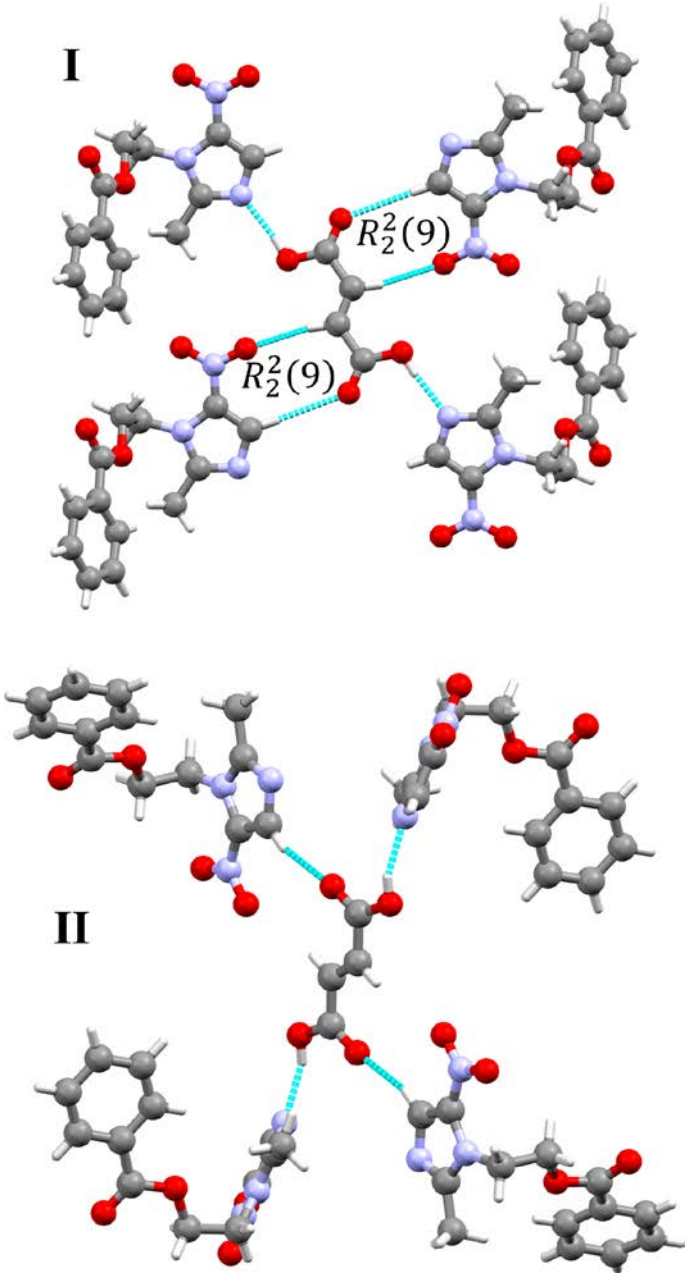

Figure S8. Synthons and graph sets of polymorphs I and II of BZMDFMA.

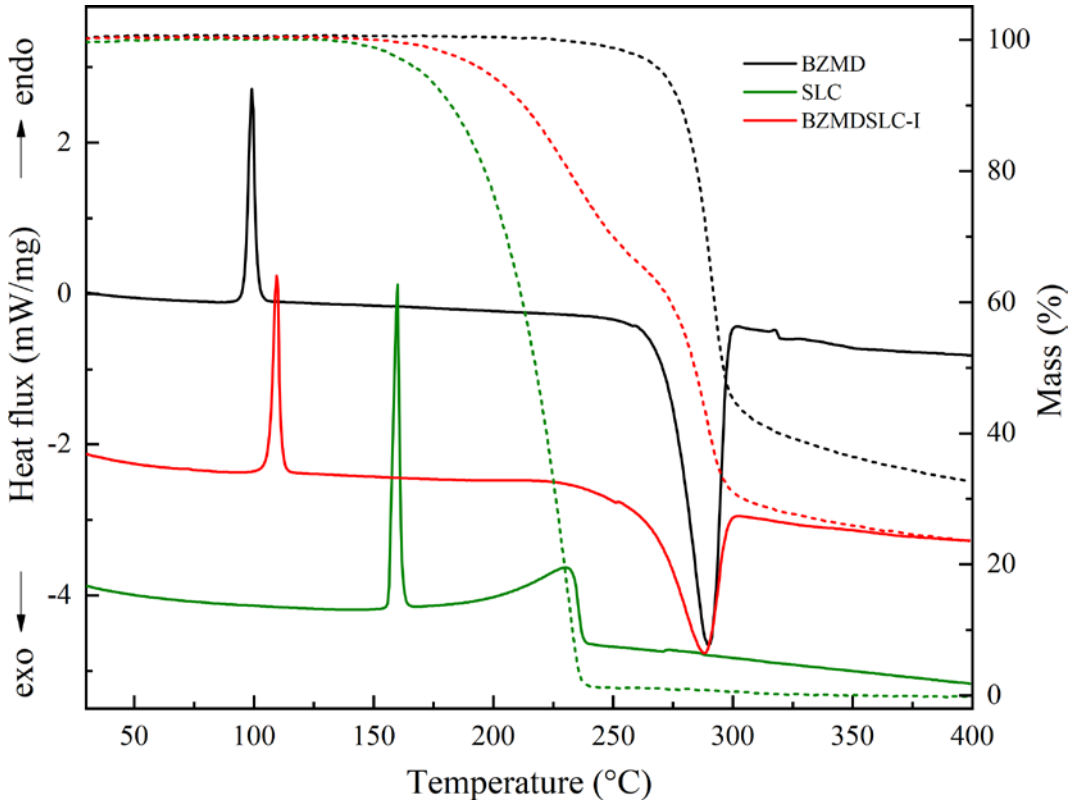

Figure S9. Simultaneous thermogravimetry and differential scanning calorimetry of BZMDSLC-I, BZMD and SLC.

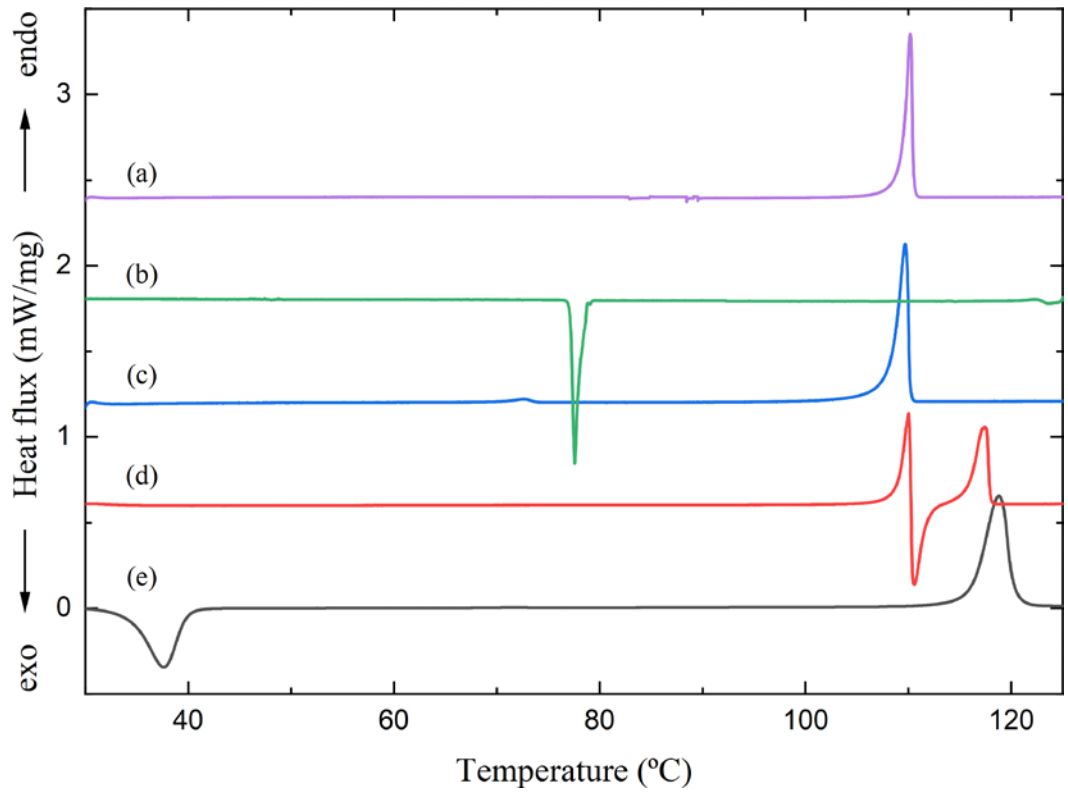

Figure S10. Representative DSC curves of BZMDSLC. (a)-(c) form I heating/cooling/heating cycles. (d) heating exhibiting the melting of form I recrystallizing into form II. (e) amorphous sample recrystallizing into form II.

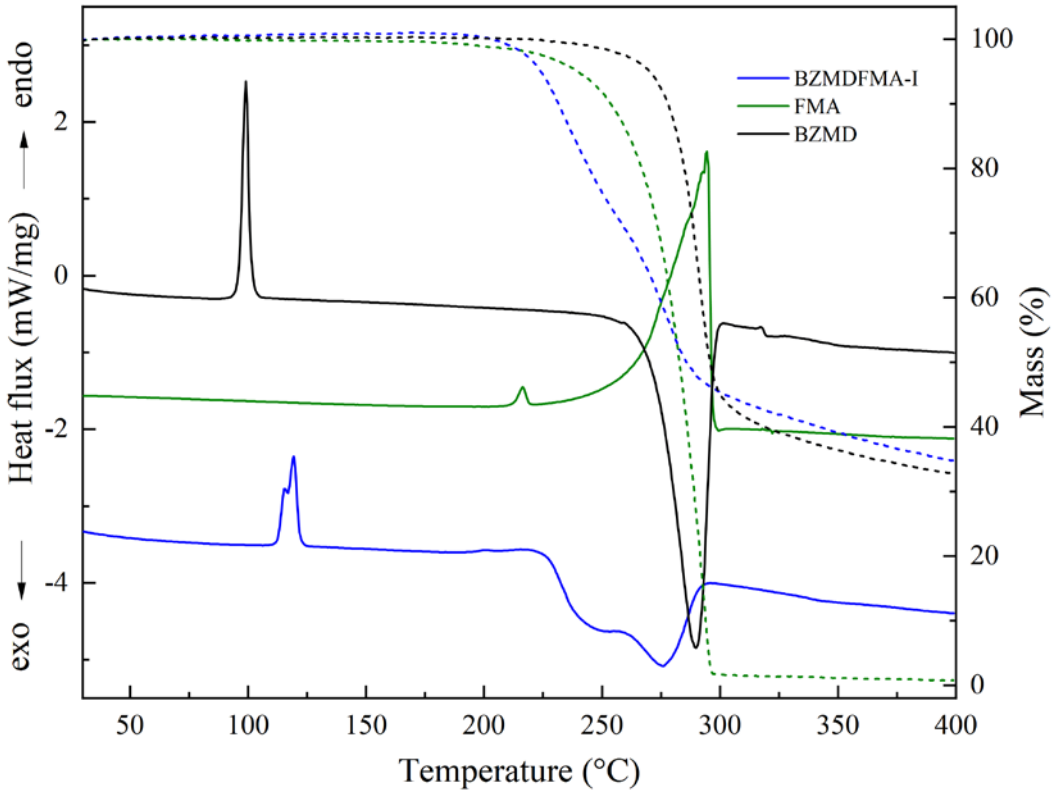

Figure S11. Simultaneous thermogravimetry and differential scanning calorimetry of BZMDFMA-I, BZMD, and FMA.