

# Cocrystal and salt forms of furosemide: solubility and diffusion variations

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## Supporting Information

### Contents

Description	Page No.
<b>Table S1.</b> Neutron normalized hydrogen bond geometrical parameters	S2-S3
<b>Table S2.</b> Melting points of salt/cocrystal/coformer/API	S4
<b>Table S3.</b> pH variation after solubility experiments.	S4
<b>Figure S1.</b> ORTEP diagrams of FSM-TOL-MeOH, FSM-TOL-MeNO <sub>2</sub> and FSM-toluene	S5
<b>Figure S2.</b> Powder x-ray diffraction patterns of new solid forms of FSM	S6-S10
<b>Figure S3.</b> DSC and TGA of FSM and its salt/cocrystals	S11-S14
<b>Figure S4.</b> FT-IR spectra of FSM and its salt/cocrystals	S14-S17
<b>Figure S5.</b> Overlay diagrams of FSM conformations.	S18

**Table S1.** Neutron normalized hydrogen bond geometrical parameters (intermolecular O–H, N–H and C–H distances).

Compound	Interaction	D–H/ Å	H···A/ Å	D···A/ Å	∠D–···A/ °	Symmetry
FSM-TMPZ	O(1)–H(1O)···N(3)	0.98	1.73	2.670(5)	159	
	N(2)–H(2A)···O(5)	1.01	2.43	3.152(6)	128	x,1+y,z
	N(2)–H(2B)···O(5)	1.01	2.05	2.973(7)	152	1-x,1/2+y,1/2-z
	C(15)–(15A)···O(1)	1.08	2.28	3.198(7)	141	
	C(16)H(16B)···O(2)	1.08	2.28	3.353(7)	170	
FSM-ANT	N(1)–H(1A)···O(3)	1.01	2.28	2.965(4)	124	-1/2+x,1/2+y,z
	O(1)–H(1O)···O(6)	0.98	1.59	2.557(4)	166	1/2+x,1/2+y,z
	N(2)–H(2A)···N(3)	1.01	2.08	3.086(5)	172	
	N(2)–H(2B)···O(5)	1.01	2.25	3.123(4)	145	1/2+x,-1/2+y,z
	N(3)–H(3A)···O(4)	1.01	2.02	3.004(4)	164	2-x,y,1/2-z
	N(4)–H(4A)···O(2)	1.01	1.98	2.967(5)	165	-1/2+x,-1/2+y,z
	C(8)–H(8A)···O(3)	1.08	2.44	3.149(4)	122	-1/2+x,1/2+y,z
FSM-PPZ (1:1)	N(2)–H(2A)···O(1)	1.01	1.82	2.822(3)	171	1-x,1-y,-z
	N(2)–H(2B)···O(1)	1.01	2.11	2.909(3)	134	x,-1+y,z
	N(4)–H(4A)···O(2)	1.01	1.68	2.666(3)	166	1-x,2-y,-z
	N(4)–H(4B)···N(3)	1.01	1.82	2.806(3)	163	1/2-x,1/2+y,-1/2-z
	C(8)–H(8B)···O(5)	1.08	2.36	3.337(4)	149	1/2-x,1/2+y,1/2-z
	C(12)–H(12)···O(1)	1.08	2.31	3.395(4)	178	1/2+x,3/2y,1/2+z
	C(16)–(16A)···O(4)	1.08	2.36	3.176(3)	131	
FSM-PCM hydrate	N(1)–H(1A)···O(3)	1.01	2.09	3.031(8)	154	
	N(1)H(1B)···N(2)	1.01	2.21	3.108(10)	148	-3-x,1-y,1-z
	O(2)–H(1O)···O(1)	0.98	1.57	2.551(7)	173	
	C(3)–H(3)···O(100)	1.08	2.42	3.24(3)	131	-2-x,-y,1-z
	C(4)–H(4)···O(6)	1.08	2.42	3.306(14)	138	-3-x,-y,1-z
	C(4)–H(4)···O(6')	1.08	2.19	3.270(13)	177	-3-x,-y,1-z
FSM-TOL- EtOH	O(1)–H(1O)···O(6)	0.98	1.59	2.563(3)	172	
	N(2)–H(2A)···O(5)	1.01	1.96	2.956(3)	167	-x,-1/2+y,3/2-z
	N(2)–H(2B)···O(7)	1.01	1.84	2.800(4)	159	
	N(3)–H(3A)···O(2)	1.01	1.93	2.899(3)	161	
	N(3)–H(3B)···N(2)	1.01	2.37	3.284(3)	151	x,1/2-y,-1/2+z
	O(7)–H(7O)···O(4)	0.98	1.87	2.825(3)	163	-x,1/2+y,3/2-z
	C(10)–H(10)···O(4)	1.08	2.46	3.423(3)	148	-x,1-y,1-z
C(12)–H(12)···O(6)	1.08	2.31	3.229(3)	142	1+x,y,z	

	C(15)–H(15)···O(5)	1.08	2.51	3.433(3)	143	$x, 1/2-y, -1/2+z$
FSM-TOL- MeOH	O(1)–H(10)···O(6)	0.98	1.57	2.542(2)	171	
	N(2)–(2A)···O(10)	1.01	1.83	2.746(13)	149	$2-x, -1/2+y, 1/2-z$
	N(2)–H(2B)···O(4)	1.01	1.57	2.941(2)	157	$2-x, 1/2+y, 1/2-z$
	N(3)–H(3A)···O(2)	1.01	1.93	2.893(3)	159	
	N(3)–H(3B)···N(2)	1.01	2.42	3.352(3)	154	$x, 1/2-y, -1/2+z$
	O(10)–(10A)···O(5)	0.98	1.95	2.852(5)	152	
	C(10)–H(10)···O(5)	1.08	2.47	3.490(3)	156	$2-x, -y, -z$
	C(12)–H(12)···O(6)	1.08	2.35	3.175(3)	132	$1+x, y, z$
	C(21)–(21B)···O(1)	1.08	2.50	3.522(4)	157	
FSM-TOL- MeNO <sub>2</sub>	O(1)–H(10)···O(6)	0.98	1.61	2.579(5)	166	$1-x, -y, -z$
	N(2)–H(2A)···O(4)	1.01	1.91	2.918(7)	174	$2-x, -1/2+y, 1/2-z$
	N(2)–H(2B)···O(8)	1.01	2.20	3.070(7)	143	$1-x, -1/2+y, 1/2-z$
	N(3)–H(3A)···N(2)	1.01	2.37	3.338(6)	160	$1-x, 1/2+y, 1/2-z$
	N(3)–H(3B)···O(2)	1.01	1.93	2.929(5)	170	$1-x, -y, -z$
FSM- toluene	N(2)–H(1B)···O(5)	1.01	2.12	3.066(5)	154	$1-x, 2-y, -z$
	O(1)–H(10)···O(2)	0.98	1.64	2.612(4)	168	$2-x, 1-y, -z$
	N(2)–H(2B)···O(4)	1.01	2.04	2.989(5)	156	$-x, 2-y, -z$
FSM-PPZ (2:1)	N(2)–H(2B)···O(1)	1.01	1.96	2.852(4)	146	$-1/2+x, 1/2-y, -1/2+z$
	N(3)–H(3A)···O(1)	1.01	1.72	2.715(3)	167	$-1/2+x, 1/2-y, -1/2+z$
	N(3)–H(3B)···O(2)	1.01	1.73	2.688(3)	157	$5/2-x, -1/2+y, 3/2-z$
	C(12)–H(12)···O(4)	1.08	2.40	3.282(5)	137	$5/2-x, 1/2+y, 3/2-z$
	C(15)– H(15A)···O(5)	1.08	2.24	3.155(4)	141	$2-x, -y, 1-z$

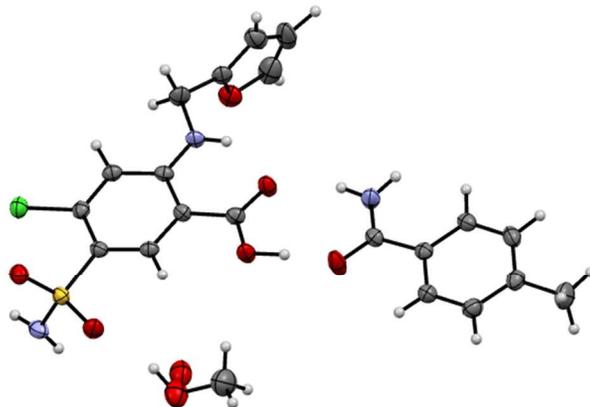
**Table S2.** Melting points of salt/cocrystal/coformer/API.

Cocrystal/salts	Coformer MP (°C)	API/Coformer water solubility	Cocrystal MP (°C)
FSM	206	<0.1 mg/ml	206
FSM-PCM sesquihydrate	105	Soluble	~120
FSM-TOL-EtOH	161-163	~0.5 mg/mL	~175
FSM-ANT	109-111	Sparingly soluble	144
FSM-TMPZ	77-80	4 mg/mL	170
FSM-PPZ (1:1)	109-112	1000 mg/mL	225
FSM-THP	273	7.36 mg/mL	201
FSM-CAF	238	21.6 mg/mL	225
FSM-ADN	360	1.03 mg/mL	218
FSM-CYT	320	8 mg/mL	232
FSM-PPZ (2:1)	109-112	1000 mg/mL	235

**Table S3.** pH variation after solubility experiments.

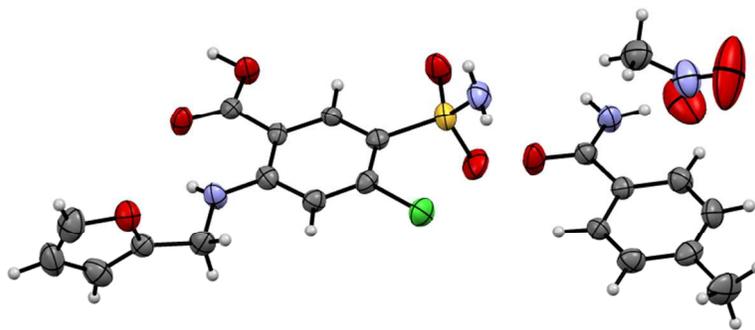
Cocrystals/salts	pH (after 1h)
FSM	6.4
FSM-PPZ(1:1)	8.2
FSM-PPZ (2:1)	6.9
FSM-TMPZ	6.5
FSM-ANT	6.3
FSM-CYT	6.9
FSM-CAF	6.9
FSM-ADE	6.6
FSM-THP	6.4
FSM-PCM-sesquihydrate	6.3
FSM-TOL-EtOH	6.3

ORTEP diagram of FSM-TOL-MeOH



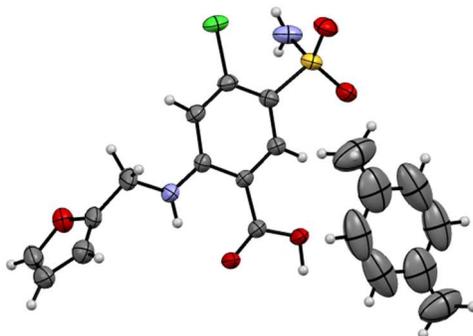
(a)

ORTEP diagram of FSM-TOL-MeNO<sub>2</sub>



(b)

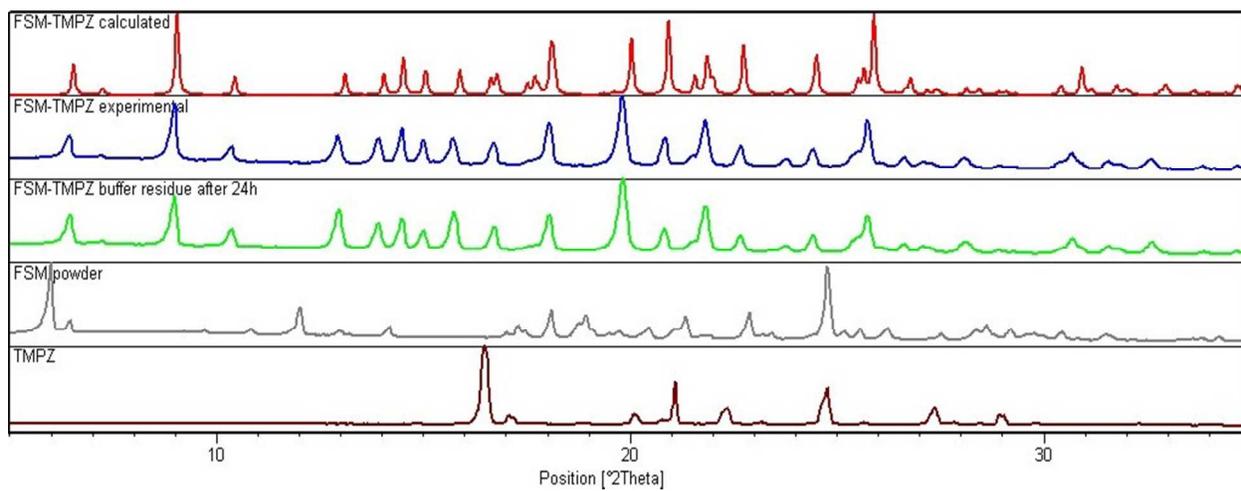
ORTEP diagram of FSM-Toluene



(c)

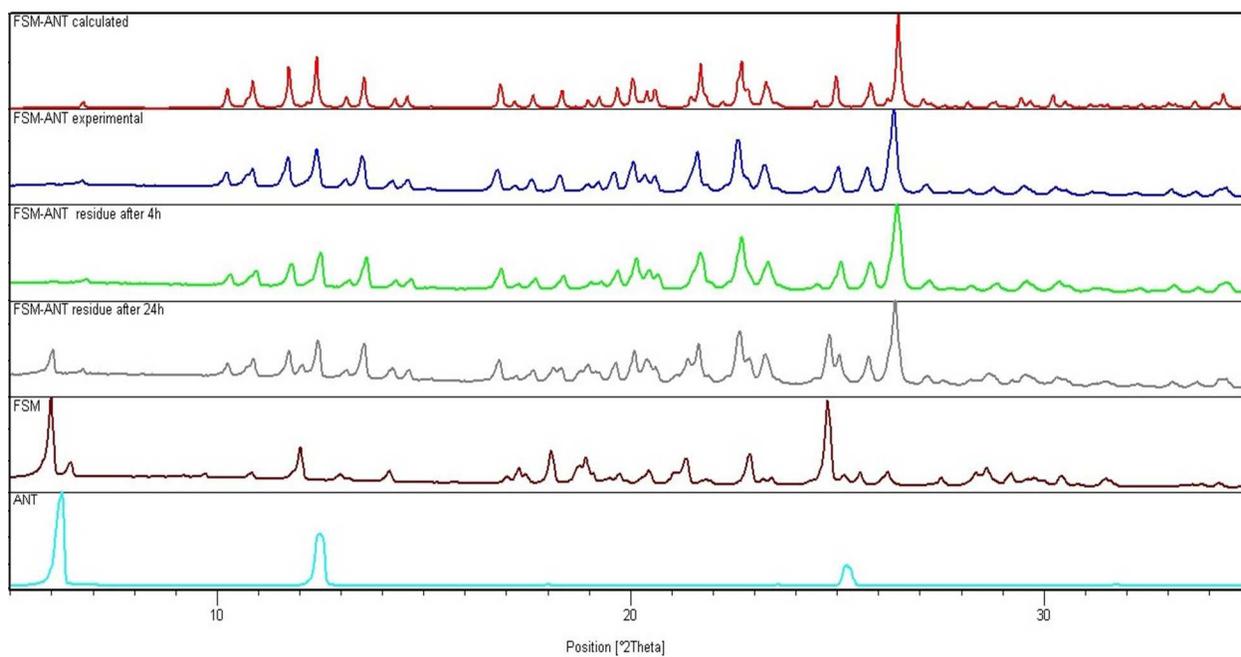
**Figure S1.** ORTEP diagrams of FSM-TOL-MeOH, FSM-TOL-MeNO<sub>2</sub> and FSM-toluene.

## FSM-TMPZ



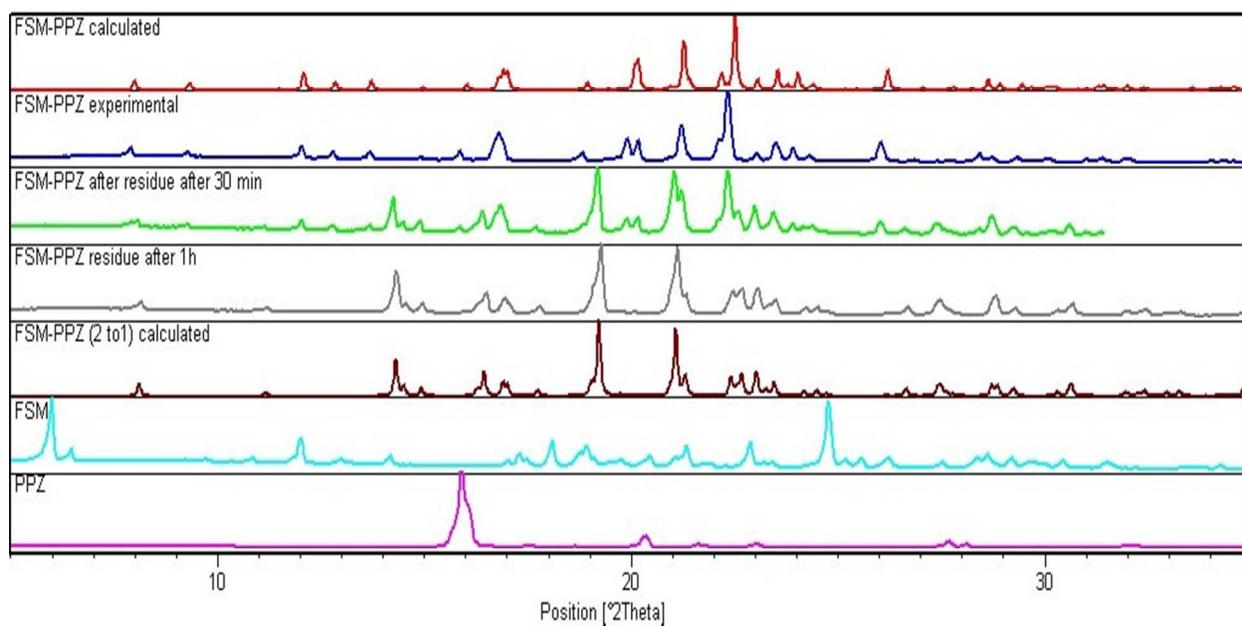
(a)

## FSM-ANT



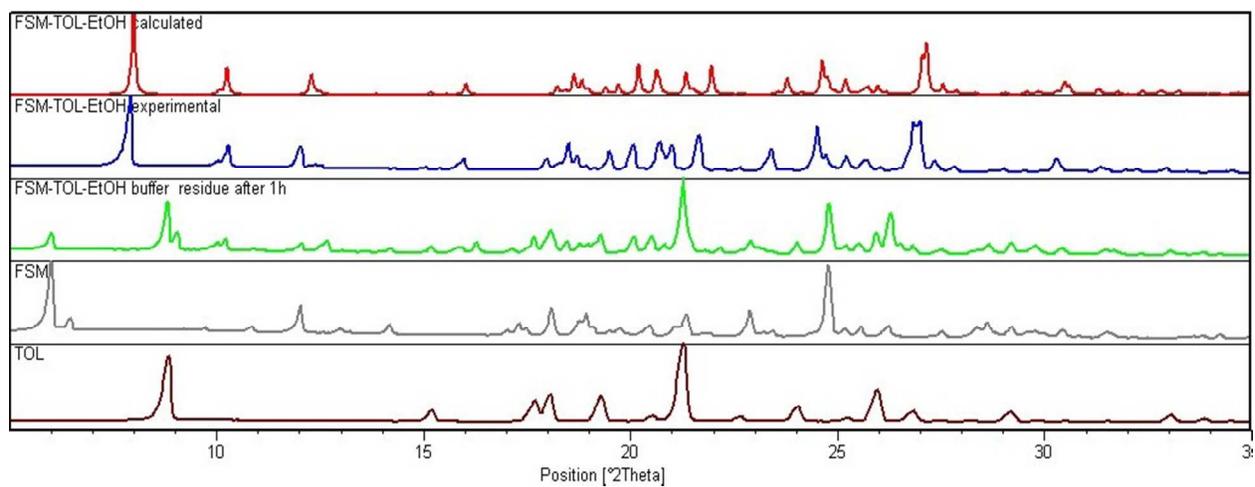
(b)

### FSM-PPZ (1:1)



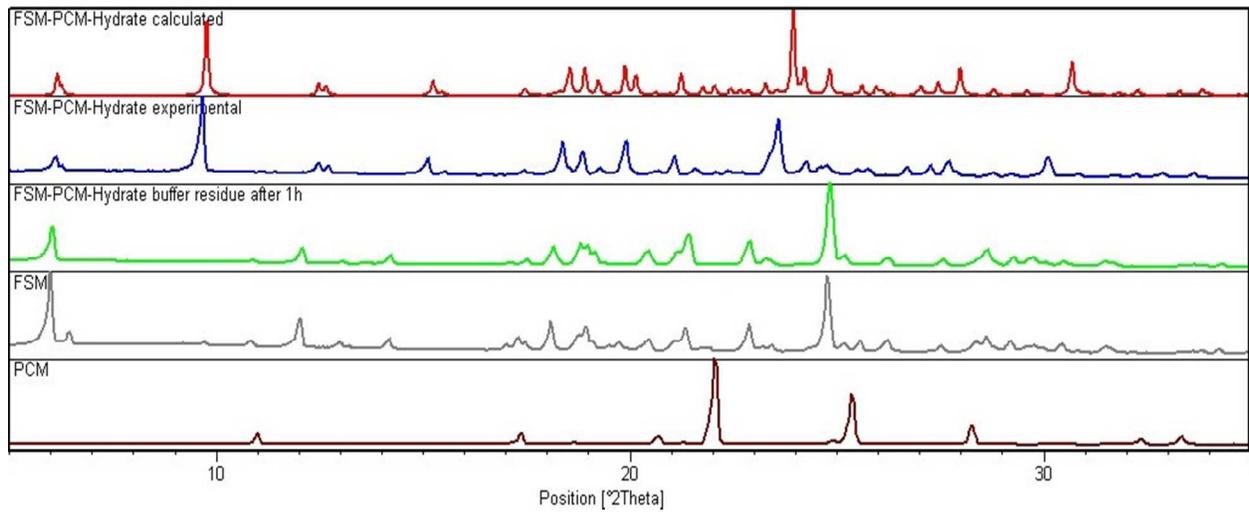
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### FSM-TOL-EtOH



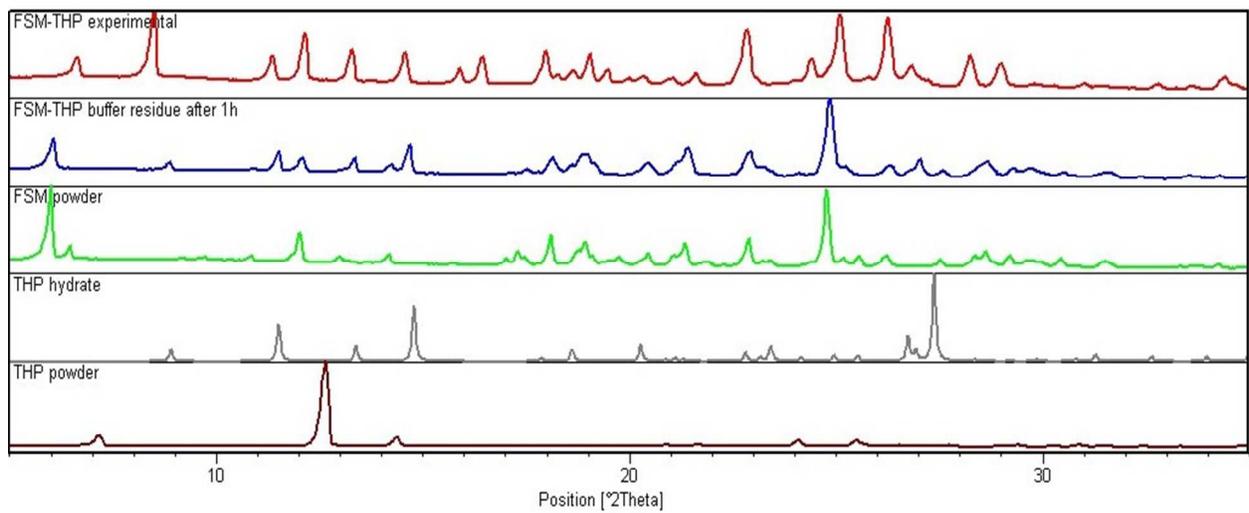
(d)

## FSM-PCM hydrate



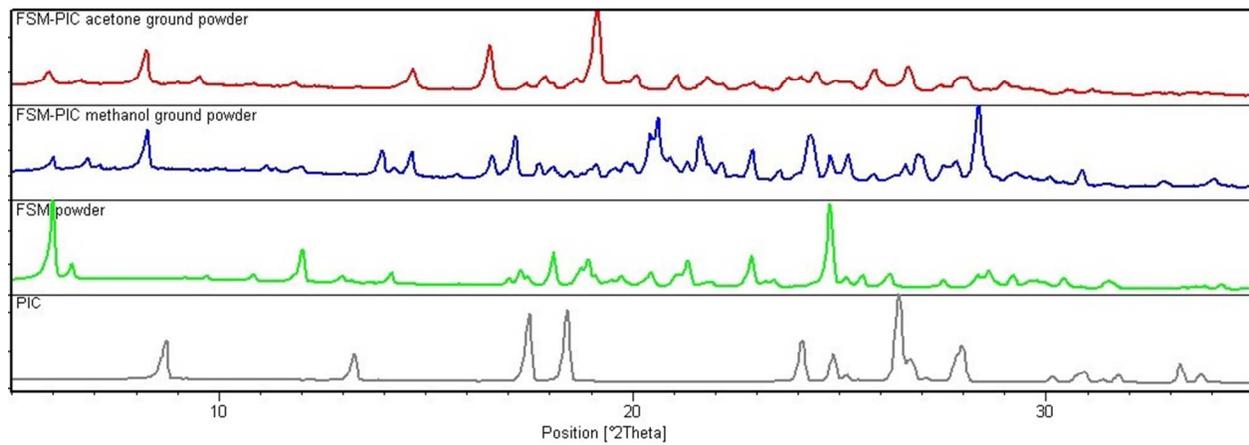
(e)

## FSM-THP



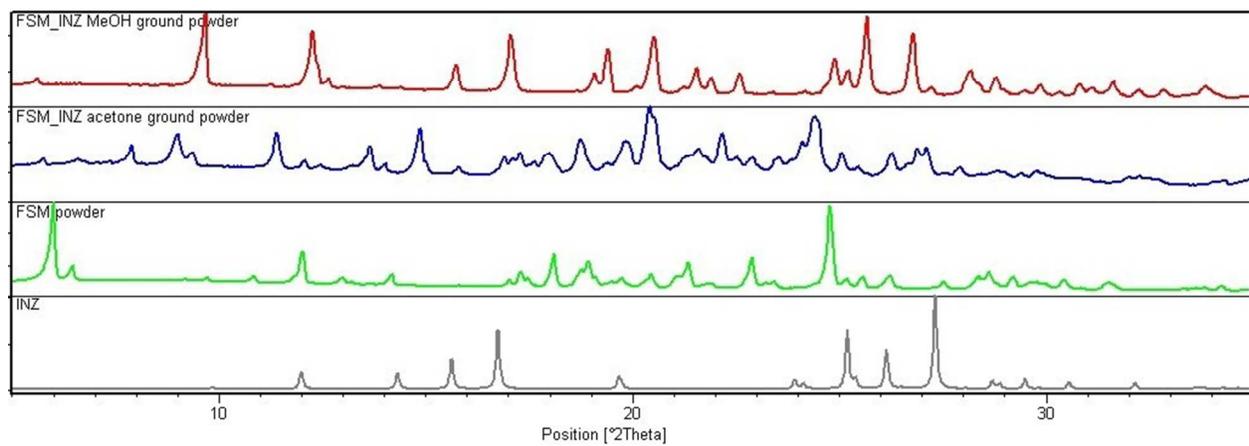
(f)

## FSM-PIC



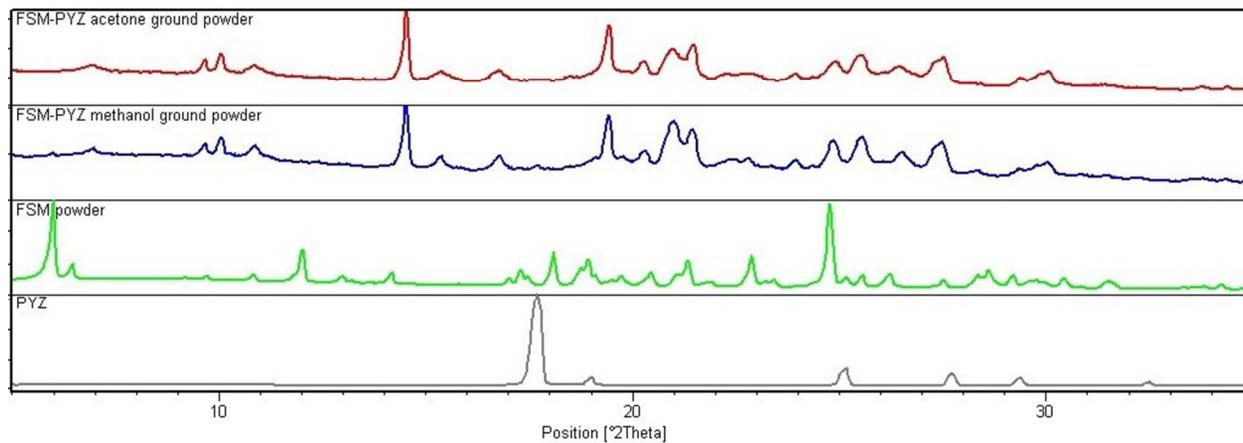
(g)

## FSM-INZ



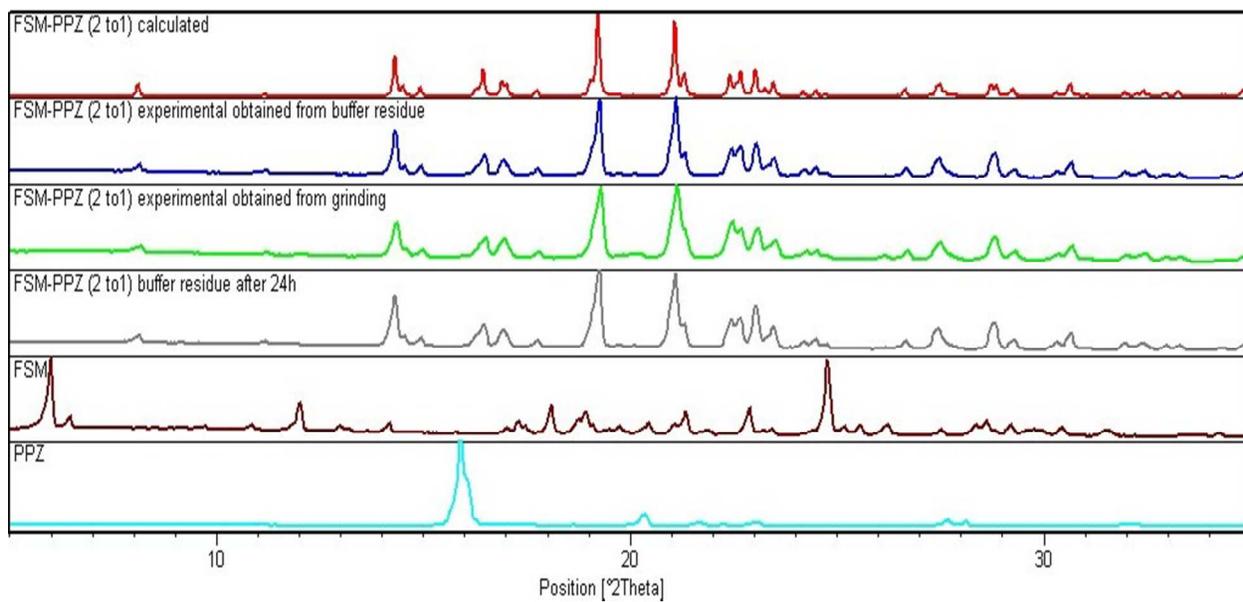
(h)

## FSM-PYZ



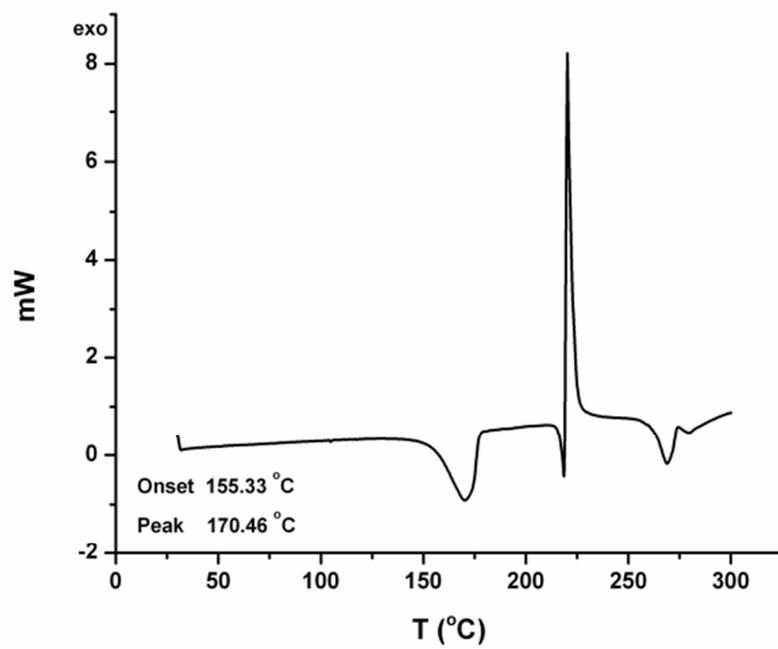
(i)

## FSM-PPZ (2:1)



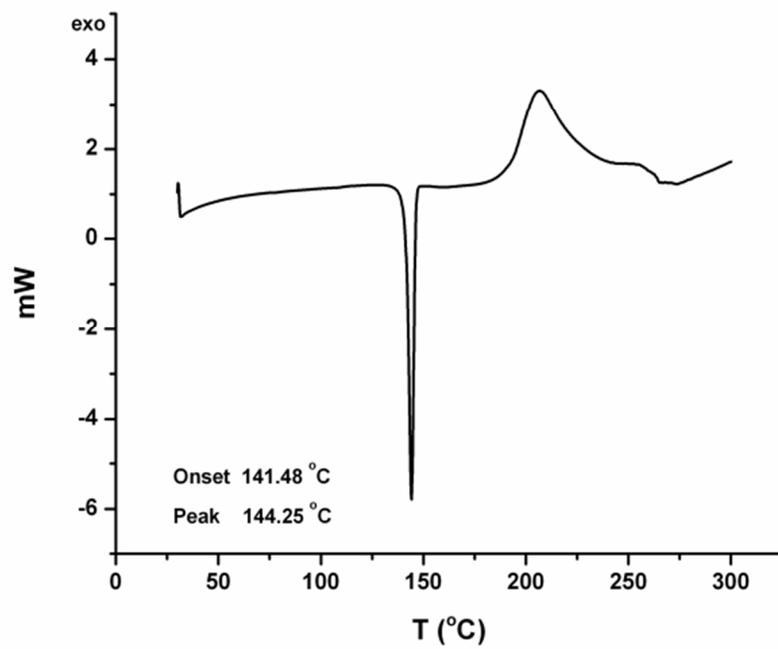
**Figure S2.** Powder x-ray diffraction patterns of new solid forms of FSM.

## FSM-TMPZ



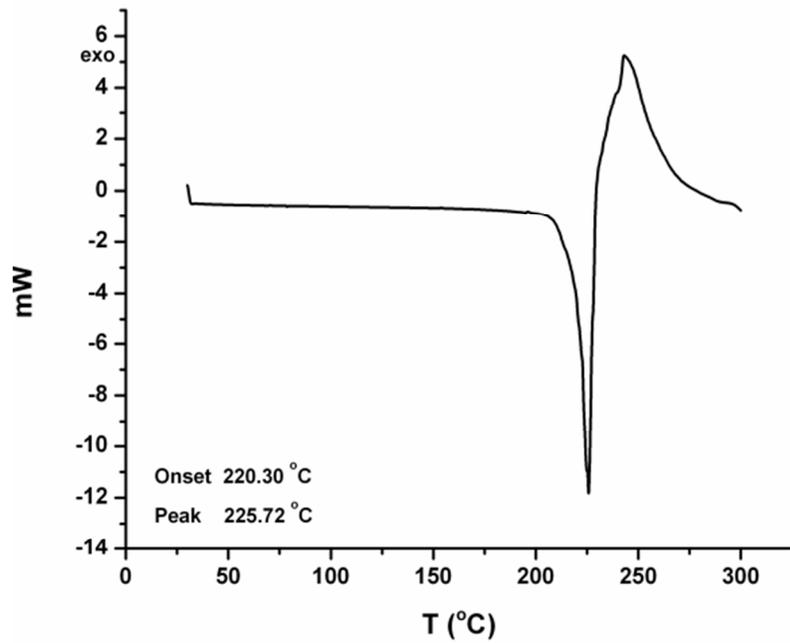
(a)

## FSM-ANT



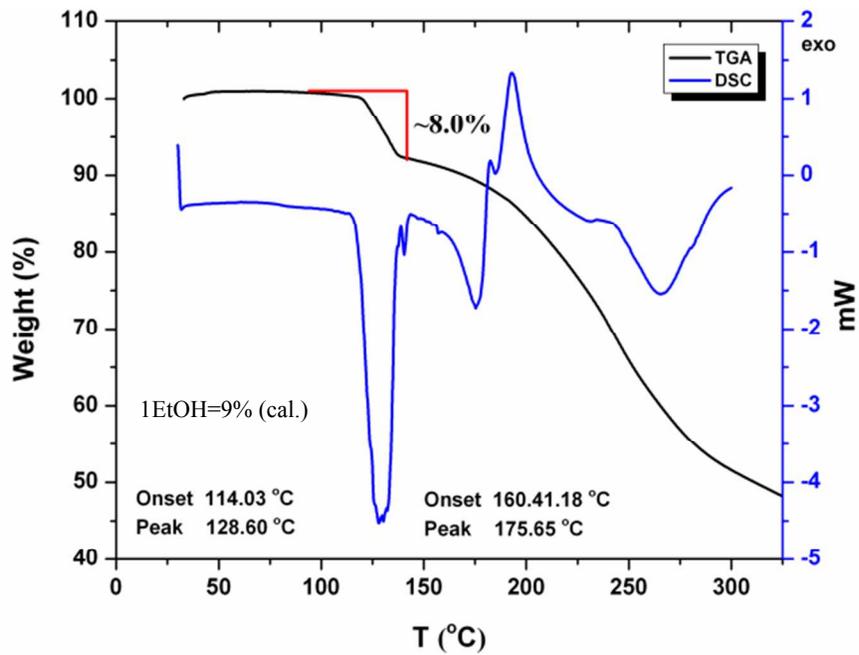
(b)

### FSM-PPZ



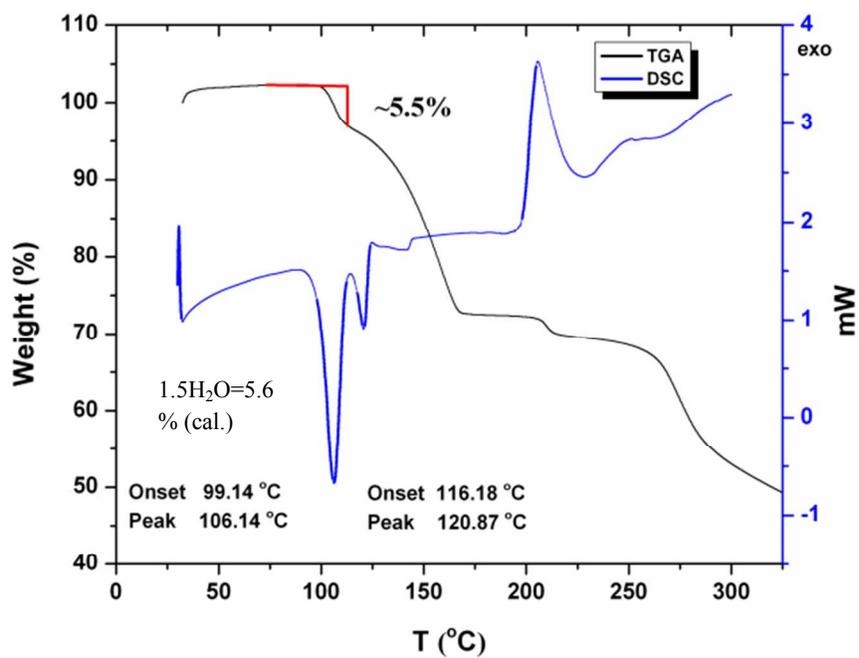
(c)

### FSM-TOL-EtOH



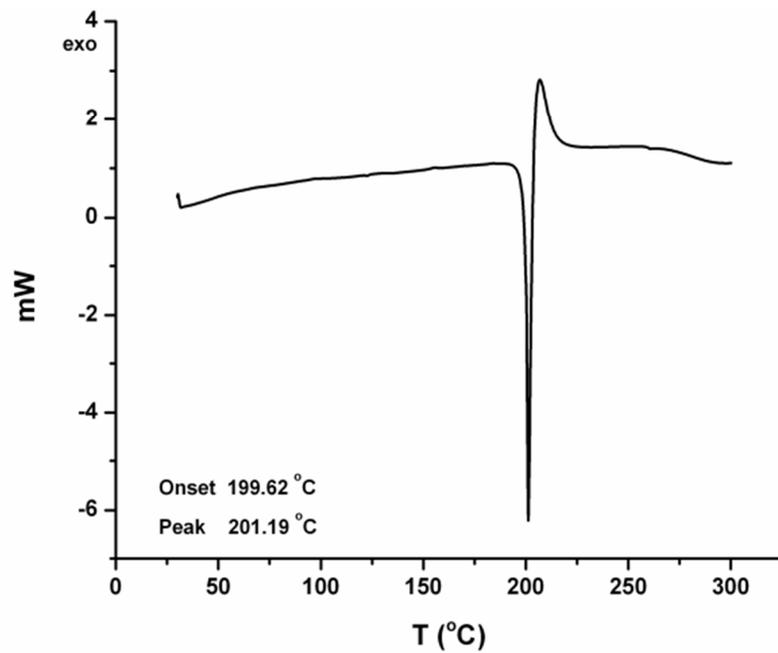
(d)

### FSM-PCM sesquihydrate



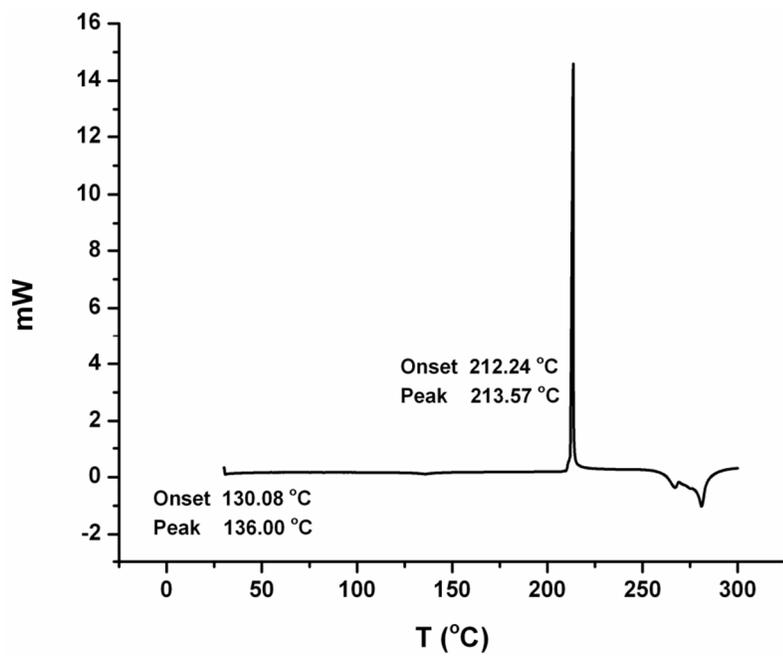
(e)

### FSM-THP



(f)

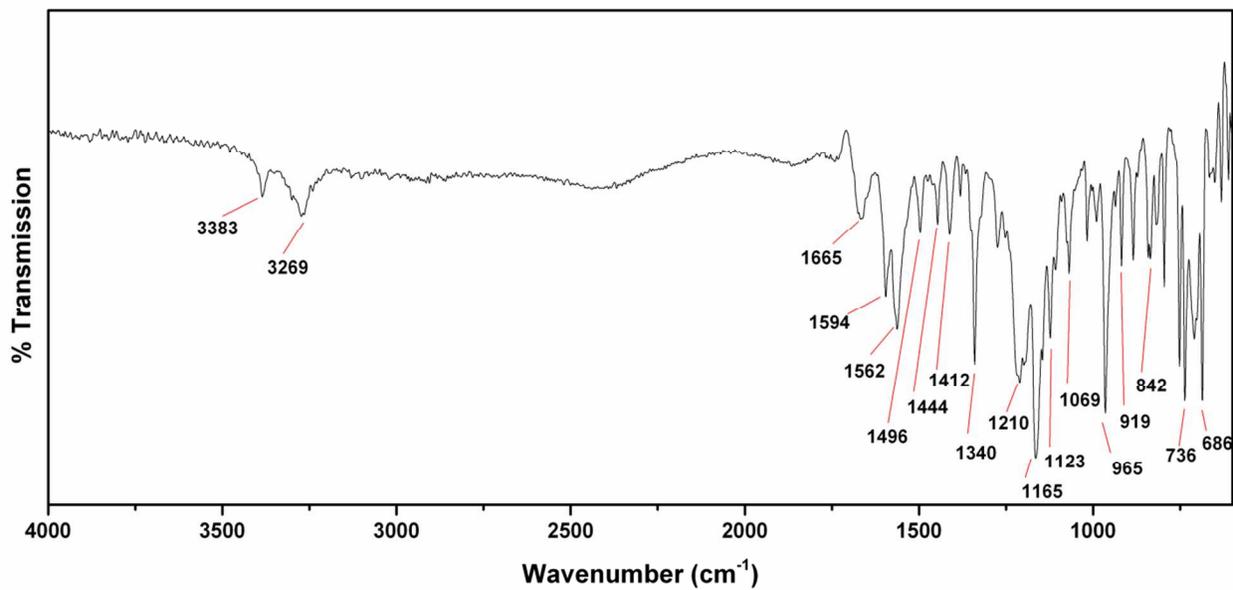
## FSM



(g)

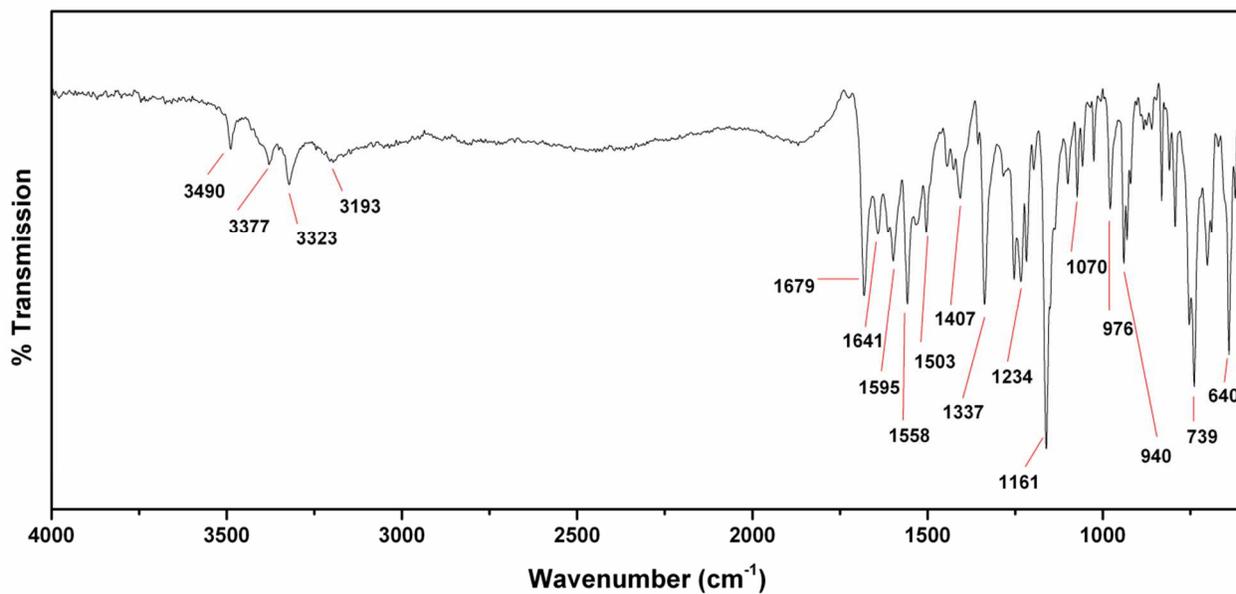
Figure S3. DSC and TGA of FSM and its salt/cocrystals.

## FSM-TMPZ



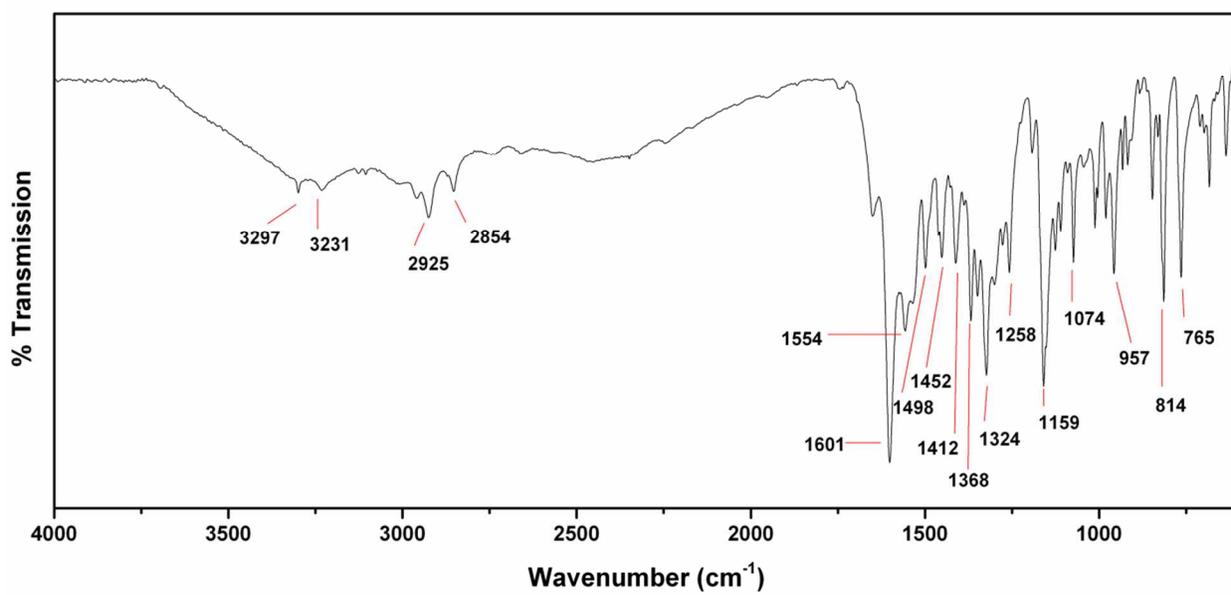
(a)

### FSM-ANT



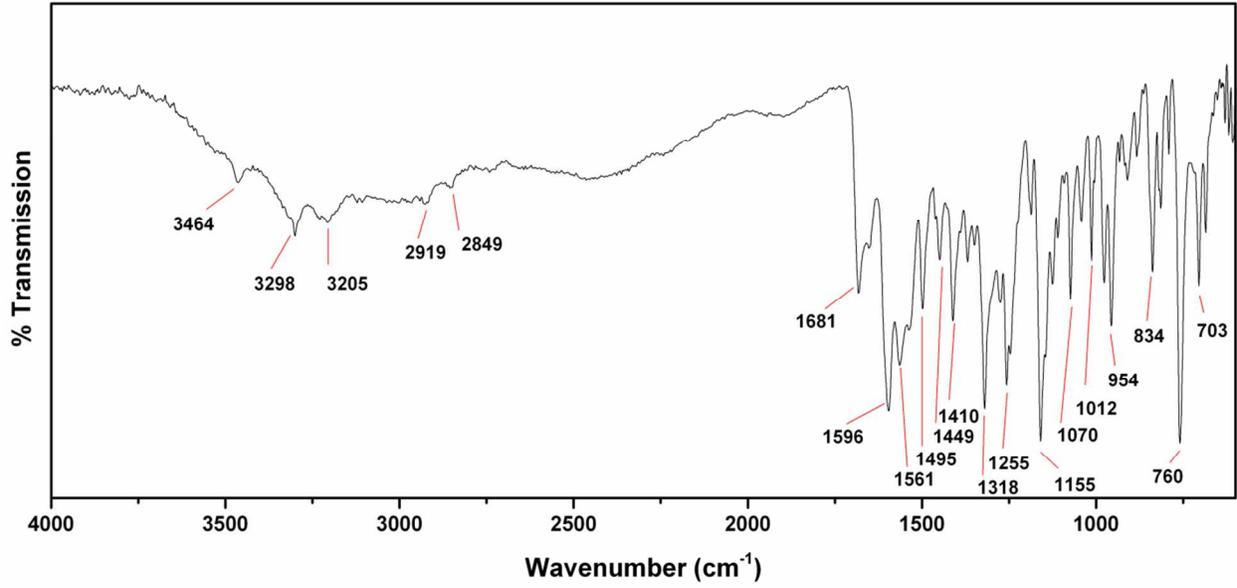
(b)

### FSM-PPZ



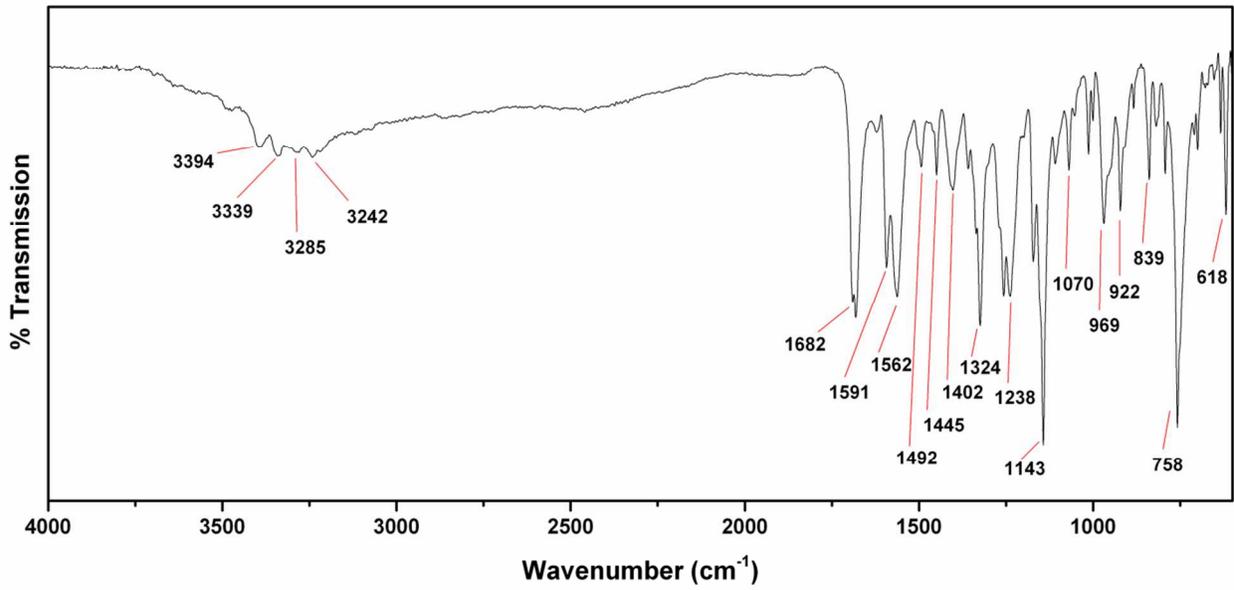
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### FSM-TOL-EtOH



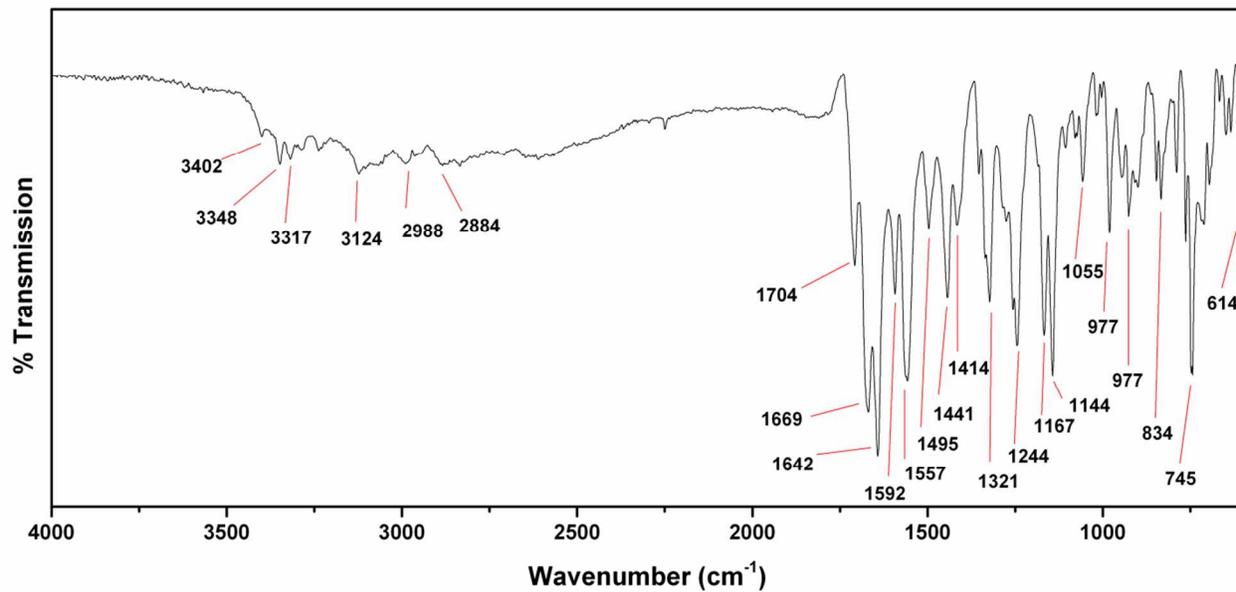
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### FSM-PCM sesquihydrate



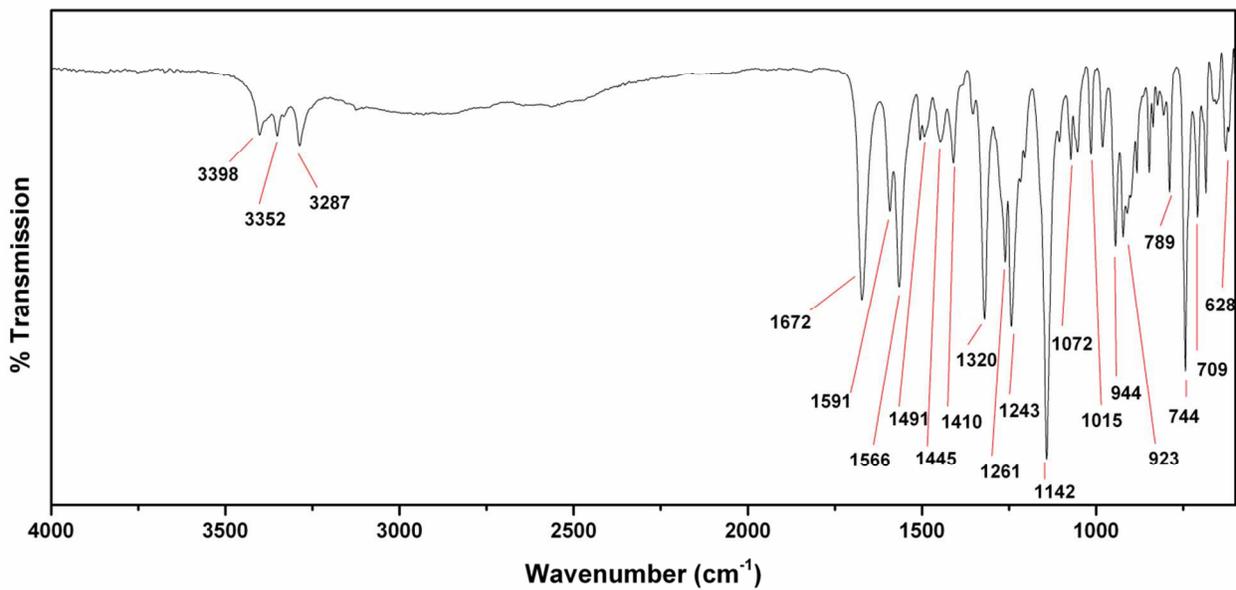
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## FSM-THP



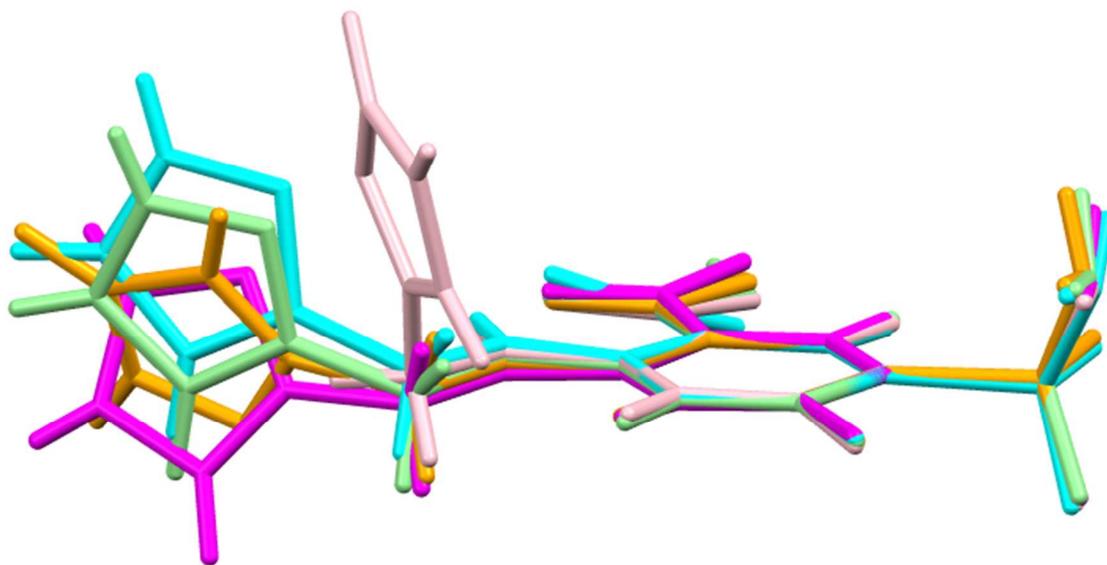
(f)

## FSM



(g)

Figure S4. FT-IR spectra of FSM and its salt/cocrystals.



**Figure S5.** Overlay diagrams of FSM conformations. (Pink: FSM-ANT, orange: FSM-TMPZ, light green: FSM-TOL-EtOH, cyan: FSM-PPZ (1:1) and magenta: FSM-PPZ (2:1); FSM-PCM-sesquihydrate is not included due to disorder).