Hydrates and Solvates of Acotiamide Hydrochloride: Crystallization, Structure, Stability and Solubility

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Supporting Information

Table 1. Recrystallization experiments of AH in different mixed solvents

V(ml)/V(ml)	2/0	2/0.01	2/0.02	2/0.04	2/0.08	1.8/0.2	1.6/0.4	1.0/1.0
Methanol -water	3	3	3	4/5	4/5	4	4	2
Ethanol -water	6	1	1	7	7	2	2	2
n-propanol -water	8	1	1	1	2	2	2	2
Acetone-water	1	1	1	1	2	2	2	2

Note: 1, 2, 3, 4, 5, 6, 7 and 8 represent 1AH-1W-I, 1AH-3W, 1AH-1M, 1AH-1W-1M-I, 1AH-1W-1M-II, 1AH-1E, 1AH-1W-1E, 1AH-1P, respectively.

Table 2. Crystal form transformation of 1AH-3W was investigated in the acetone-water solvent

$V_{acetone}$(ml)/V_{water}(ml)	2/0	2/0.01	2/0.02	2/0.04	2/0.08	1.8/0.2	1.6/0.4
2h	1	1	1	2	2	2	2
4h	1	1	1	2	2	2	2
6h	1	1	1	2	2	2	2
8h	1	1	1	1	2	2	2
12h	1	1	1	1	2	2	2
24h	1	1	1	1	2	2	2

Note: 1 and 2 represent 1AH-1W-I, 1AH-3W, respectively.

Table 3. Crystal form transformation of 1AH-1W-I was investigated in the acetone-water solvent

$V_{acetone}$(ml)/V_{water}(ml)	2/0	2/0.01	2/0.02	2/0.04	2/0.08	1.8/0.2	1.6/0.4
2h	1	1	1	1	1	2	2
4h	1	1	1	1	1	2	2
6h	1	1	1	1	1	2	2
8h	1	1	1	1	1	2	2
12h	1	1	1	1	1	2	2
24h	1	1	1	1	2	2	2

Note: 1 and 2 represent 1AH-1W-I, 1AH-3W, respectively.

Table 4. Hydrogen-bond geometry (A°) of AH hydrates and solvates

	H bond	D-H /Å	D…A/Å	D-H…A/°	symmetry code
1AH-1W-I	N1-H1B…O6	0.79(2)	2.944(2)	163(2)	

	N3-H3A…Cl1	0.74(3)	3.428(2)	135(3)	
	N4-H4A…Cl1	0.90(2)	3.098(2)	173(2)	
	O1-H1A…O4	0.91(3)	2.563(2)	154(3)	
	O6-H6A…Cl1	0.88(4)	3.204(2)	173(3)	
	O6-H6B…O1	0.83(4)	2.981(3)	149(3)	-x+1, -y+1, -z+1
1AH-3W	N1-H1A…O6	0.86(2)	2.884(2)	168(2)	
	N3-H3A…Cl1	0.84(2)	3.259(2)	141(2)	
	N4-H4A…Cl1	0.93(2)	3.155(2)	177(2)	
	O1-H1B…O4	0.87(2)	2.543(2)	152(2)	
	O6-H6A…Cl1	0.84(2)	3.268(2)	163(2)	
	O6-H6B…O7	0.83(2)	2.823(2)	163(3)	-x, y, -z-1/2
	O7-H7A…O8	0.87(2)	2.842(2)	175(2)	-x, y-1, -z-1/2
	O7-H7B…O1	0.88(2)	2.933(2)	173(2)	
	O8-H8A…O5	0.83(2)	2.866(2)	170(2)	
	O8-H8B…Cl1	0.82(2)	3.293(2)	172(2)	x, -y+1, z-1/2
1AH-1M	N1-H1B…O6	0.83(4)	2.946(3)	160(3)	
	N3-H3A…Cl1	0.90(3)	3.367(2)	129(2)	
	N4-H4A…Cl1	1.01(3)	3.098(2)	169(2)	
	O1-H1A…O4	0.92(4)	2.552(3)	152(4)	
	O6-H6A…Cl1	0.94(4)	3.152(2)	162(4)	
1AH-1W-1M-I	N1-H2A…O6	0.79 (2)	2.795 (2)	168(2)	-x+1, -y+1, -z+2
	N3-H3A…Cl1	0.76(2)	3.263(2)	137(2)	-x+1, -y+1, -z+2
	N4-H4A…Cl1	0.95(2)	3.145(2)	178(2)	-x+1, -y+1, -z+2
	O1-H1A…O4	0.90(3)	2.560(2)	149(3)	
	O6-H6A…Cl1	0.72(3)	3.173(2)	166(3)	
	O6-H6B…Cl1	0.94(2)	3.178(2)	177(3)	-x+1, -y+1, -z+2
	O7-H7A…O5	1.04(6)	2.723(3)	174(5)	-x+1, -y+2, -z+1
1AH-1W-1M-II	N1-H1B…O7	0.82 (2)	2.928 (2)	171(2)	
	N3-H3A…Cl1	0.78(2)	3.309(2)	141(2)	
	N4-H4A…Cl1	0.90(2)	3.136(2)	174(2)	
	O1-H1A…O4	1.00(4)	2.559(2)	142(3)	
	O6-H6A…O5	0.84(3)	2.975(2)	163(5)	-x+1/2, -y+3/2, -z
	O6-H6B…Cl1	0.83(1)	3.541(4)	165(4)	-x+1/2, y+1/2, -z+1/2
	O7-H7A…Cl1	0.66(3)	3.156(2)	174(4)	
1AH-1E	N1-H1B…O6	0.80(3)	2.915(4)	166(3)	
	N3-H3A…Cl1	0.77(3)	3.380(2)	137(3)	
	N4-H4A…Cl1	0.91(3)	3.084(2)	175(3)	
	O1-H1A…O4	0.84(4)	2.579(3)	147(3)	
	O6-H6A…Cl1	0.81(5)	3.147(3)	160(5)	
1AH-1W-1E	N1-H1B…O6	0.77(2)	2.798(2)	172(2)	-x, -y+1, -z+1
	N3-H3A…Cl1	0.77(3)	3.251(2)	135(3)	-x, -y+1, -z+1
	N4-H4A…Cl1	0.89(2)	3.154(2)	179(2)	-x, -y+1, -z+1
	O1-H1A…O4	0.84(2)	2.562(2)	146(2)	
	O6-H6A…Cl1	0.88(4)	3.175(2)	175(2)	-x, -y, -z+1
	O6-H6B…Cl1	0.78(4)	3.202(2)	161(2)	
	O7-H7A…O5	0.84(3)	2.766(2)	169(2)	-x, -y+2, -z+2
1AH-1P	N1-H1A…O6	0.81(2)	2.907(2)	163(2)	
	N3-H3A…Cl1	0.74(3)	3.388(2)	138(2)	
	N4-H4A…Cl1	0.84(2)	3.117(2)	176(2)	
	O1-H1B…O4	0.84(3)	2.591(2)	151(3)	
	O6-H6A…Cl1	0.85(3)	3.155(2)	170(3)	

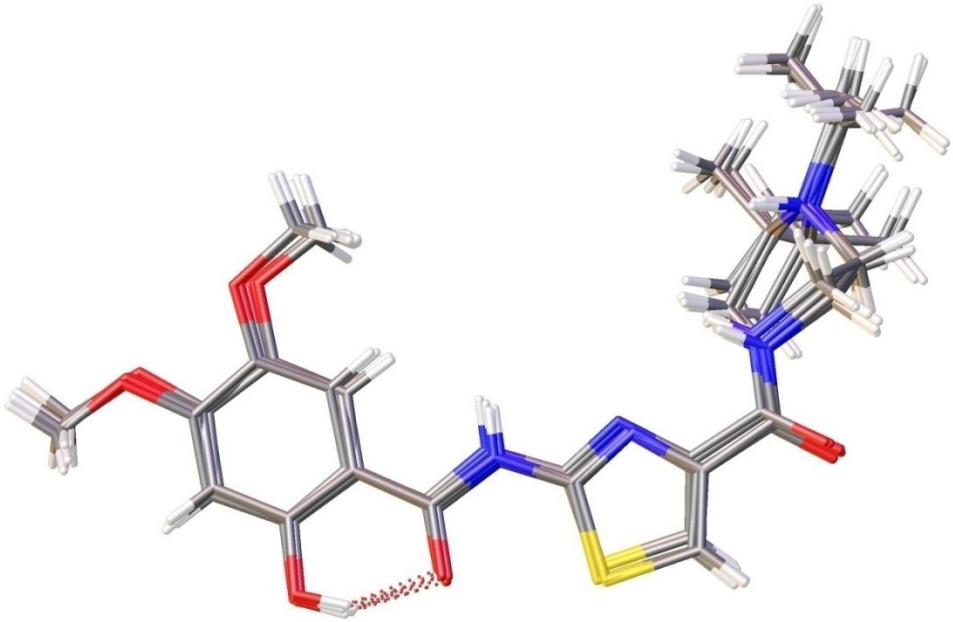

Figure 1. The overlap picture of acotiamide cations in the structures of eight crystals.

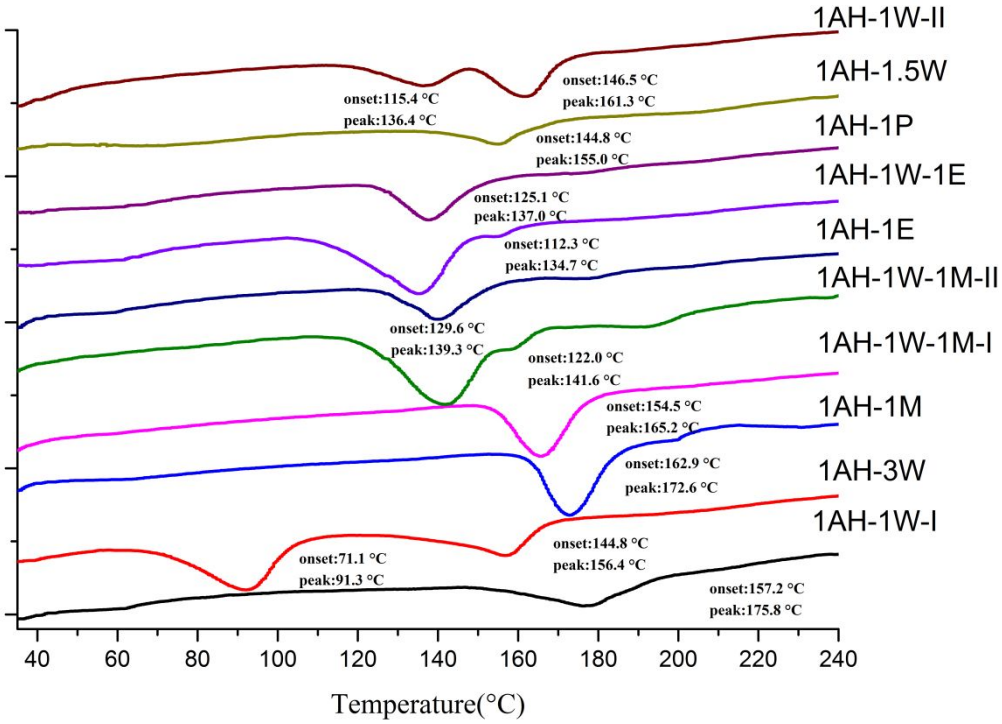

Figure 2. DSC profiles of ten kinds of solid phase forms

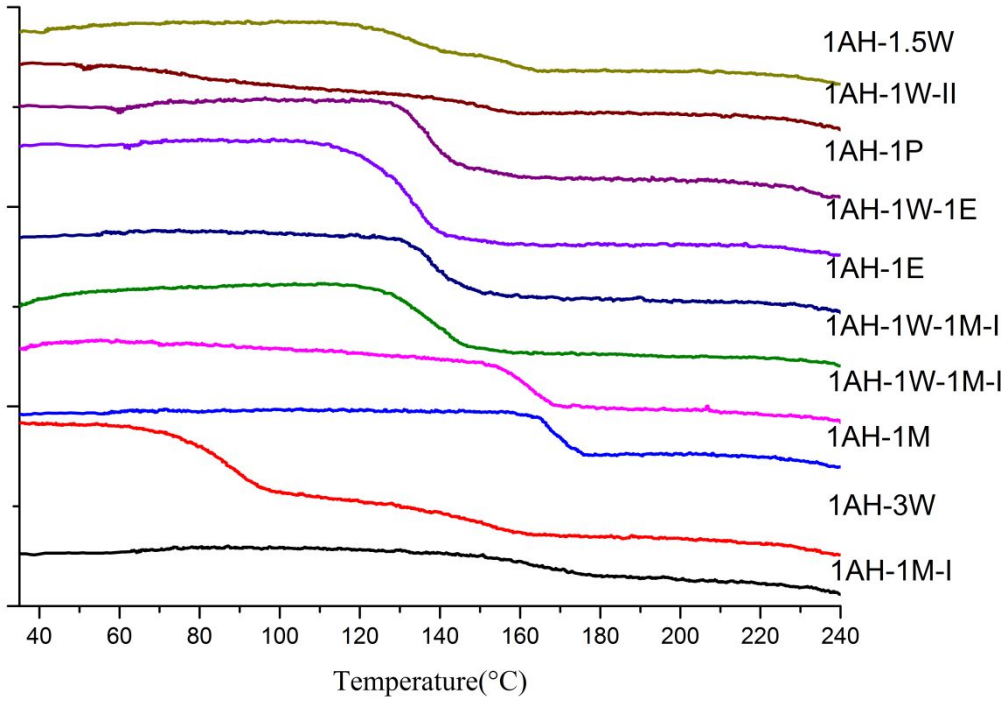

Figure 3. TG profiles of ten kinds of solid phase forms

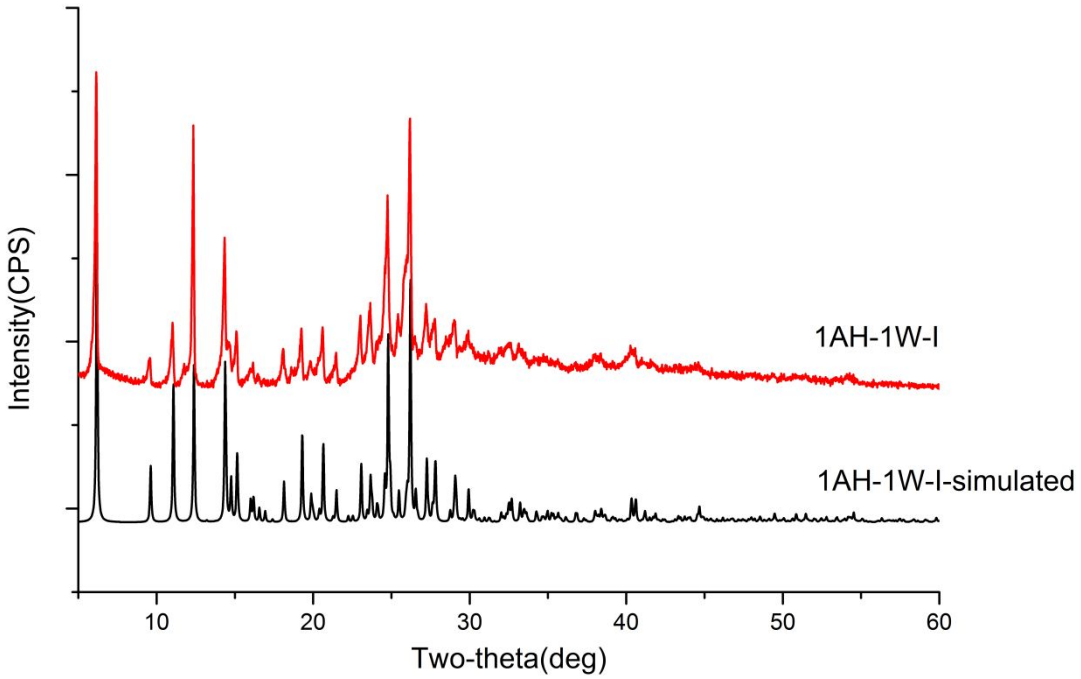

Figure 4. The experiment and calculated XPRD patterns of 1AH-1W-I

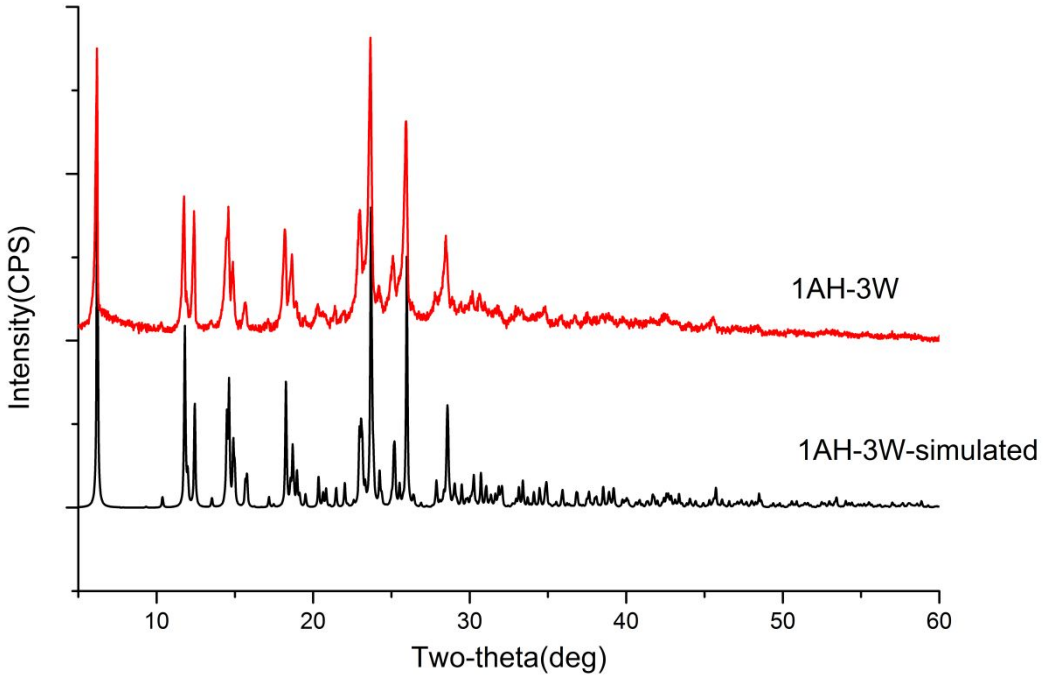

Figure 5. The experiment and calculated XPRD patterns of 1AH-3W

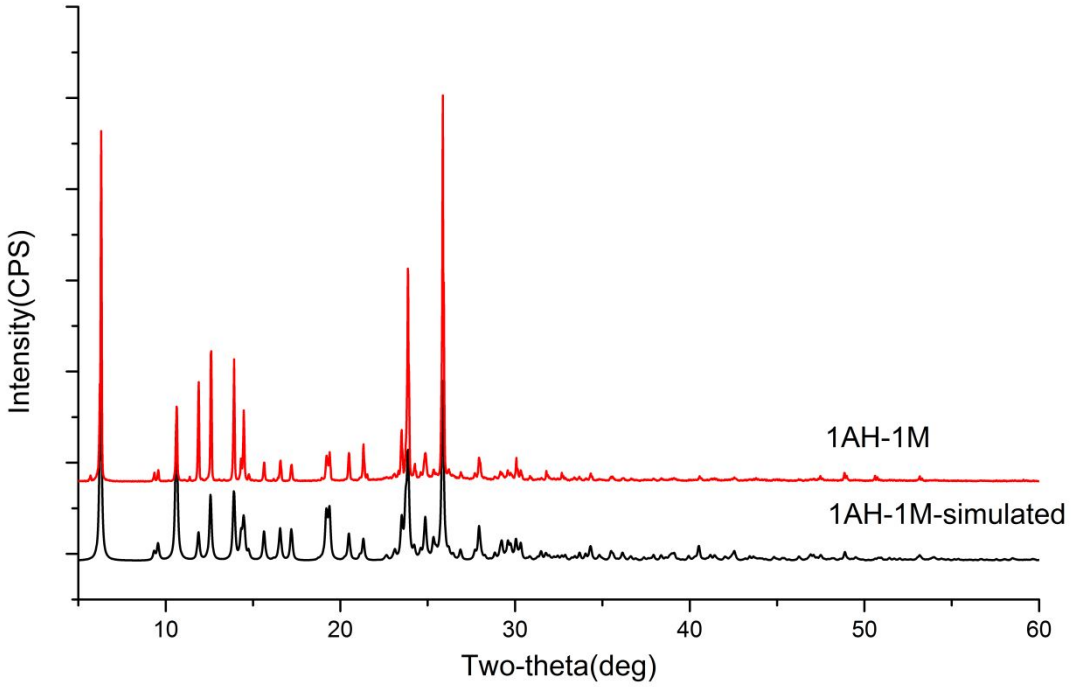

Figure 6. The experiment and calculated XPRD patterns of 1AH-1M

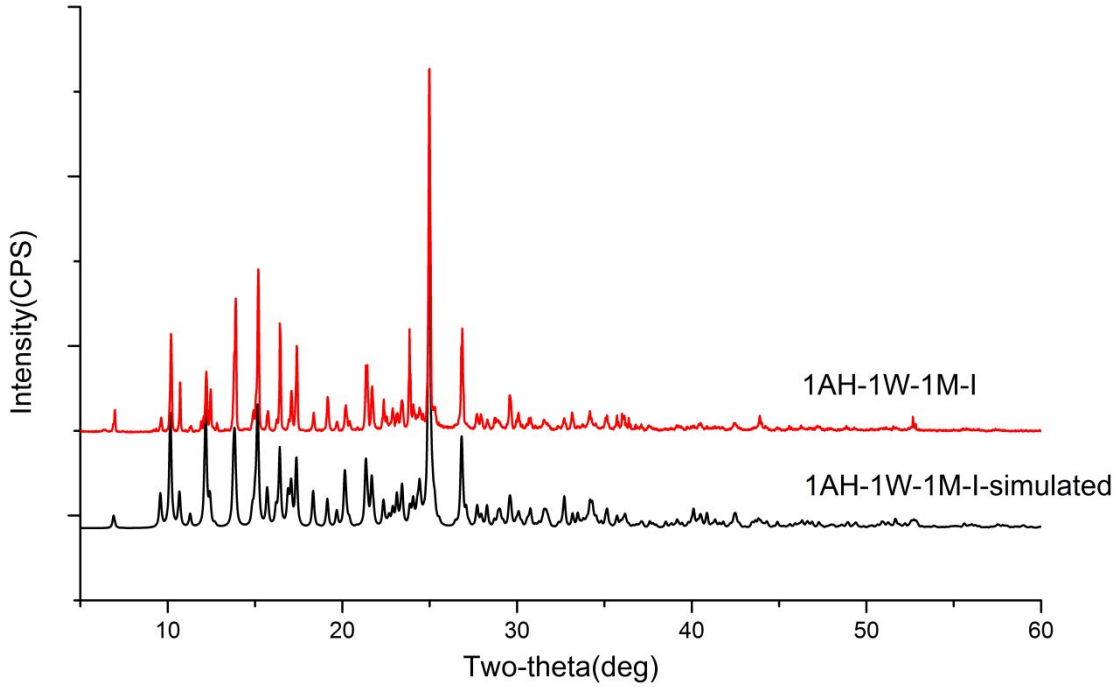

Figure 7. The experiment and calculated XPRD patterns of 1AH-1W-1M-I

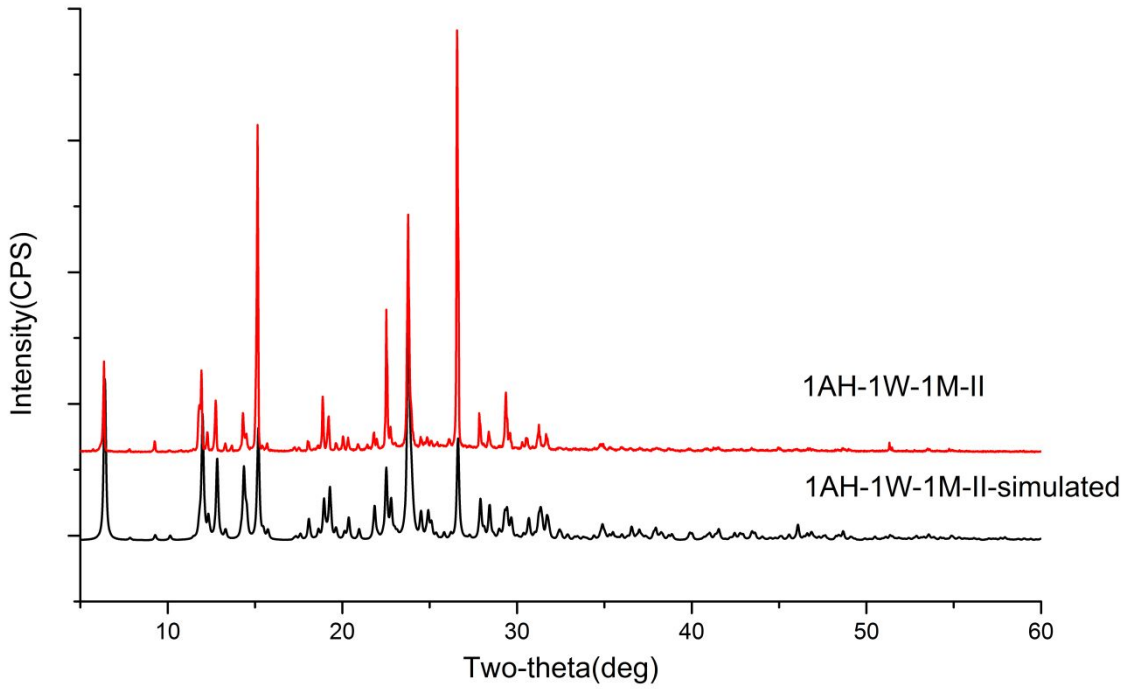

Figure 8. The experiment and calculated XPRD patterns of 1AH-1W-1M-II

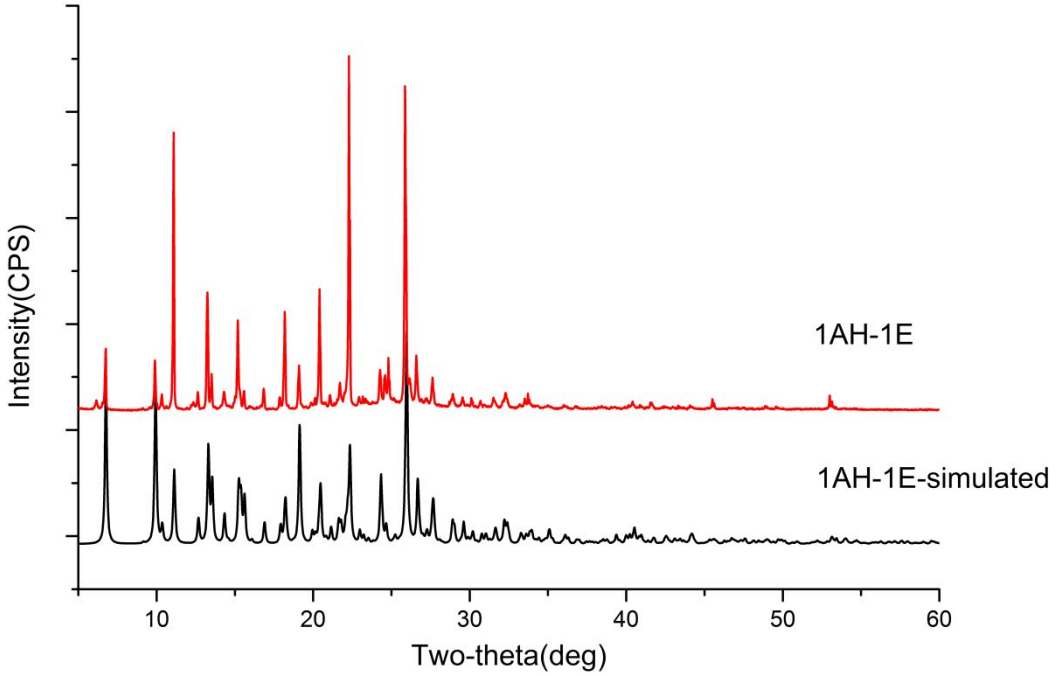

Figure 9. The experiment and calculated XPRD patterns of 1AH-1E

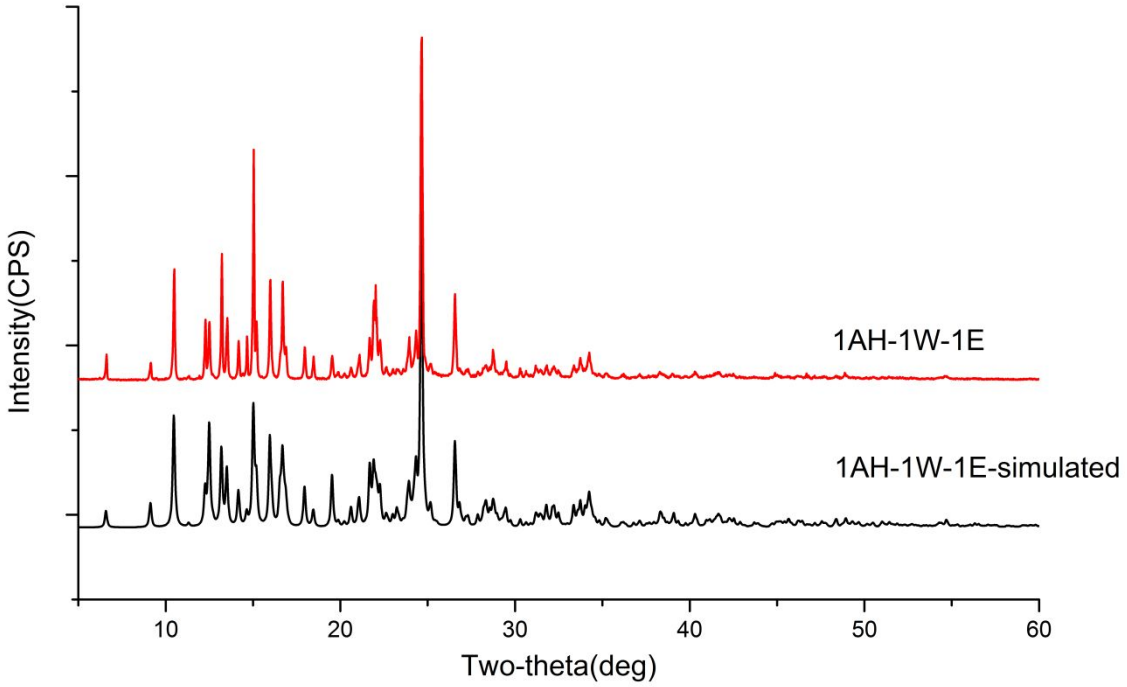

Figure 10. The experiment and calculated XPRD patterns of 1AH-1W-1E

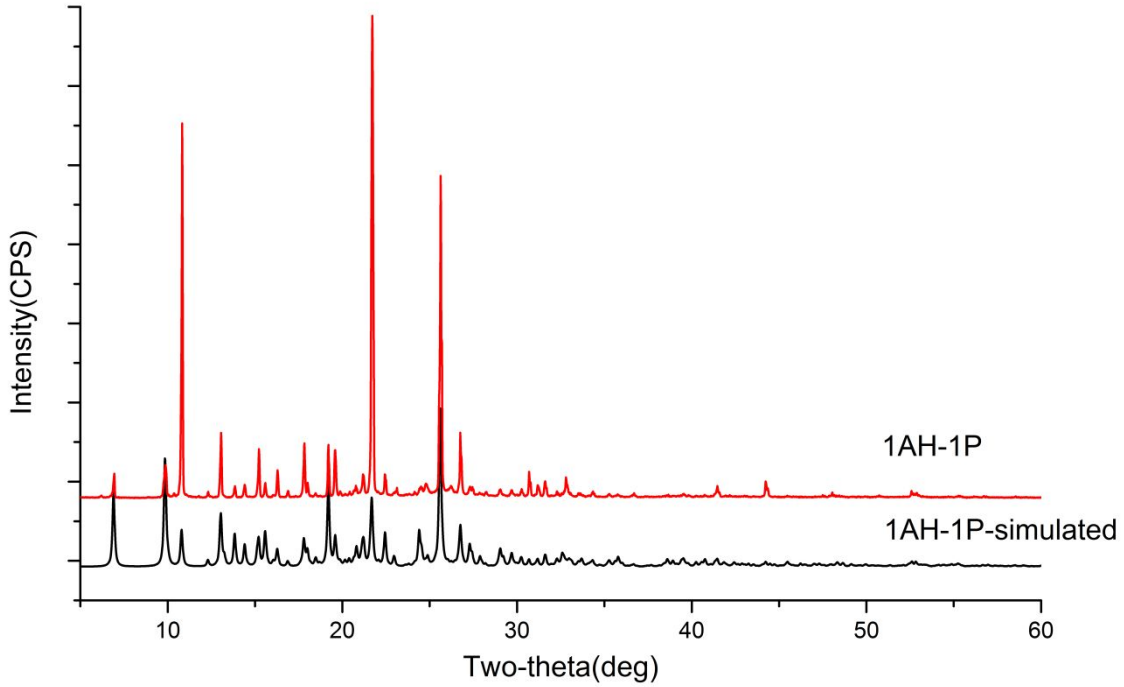

Figure 11. The experiment and calculated XPRD patterns of 1AH-1P

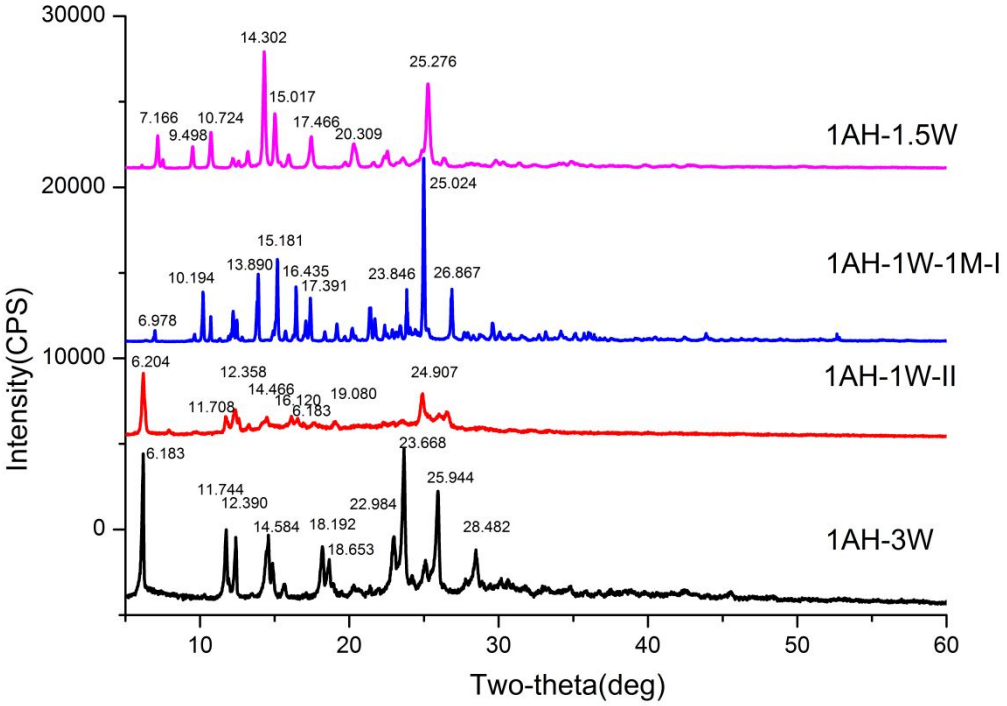

Figure 12. The experiment patterns of 1AH-1.5W, H-1W-II, 1AH-1W-1M-I and1AH-3W

with marked main peaks

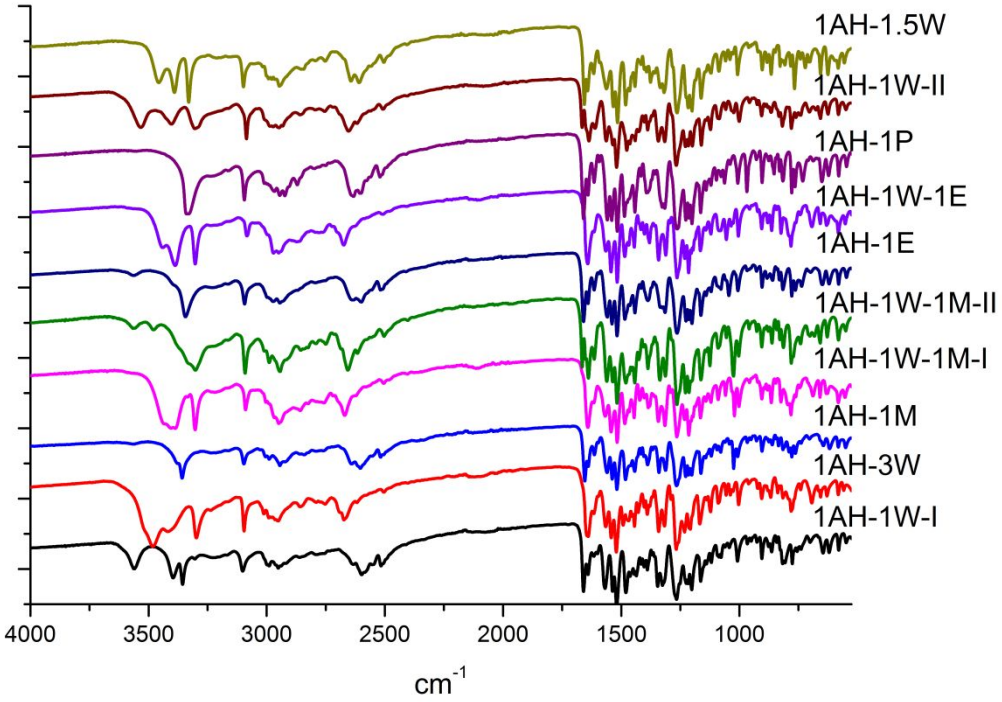

Figure 13. IR profiles of ten kinds of solid phase forms

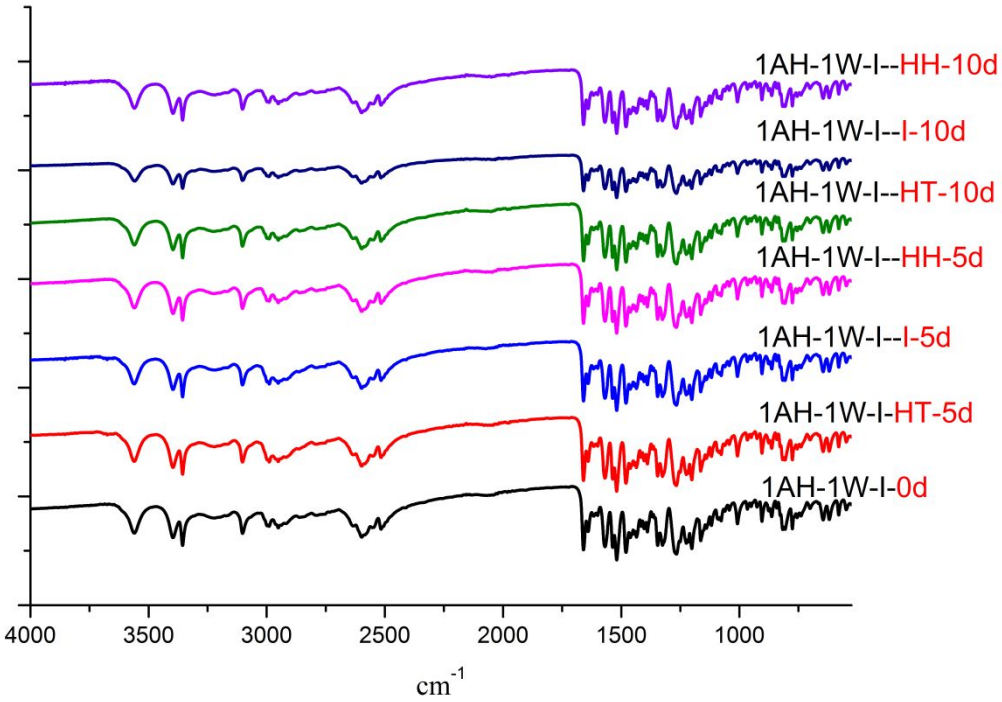

Figure 14. IR profiles of stability of 1AH-1W-I

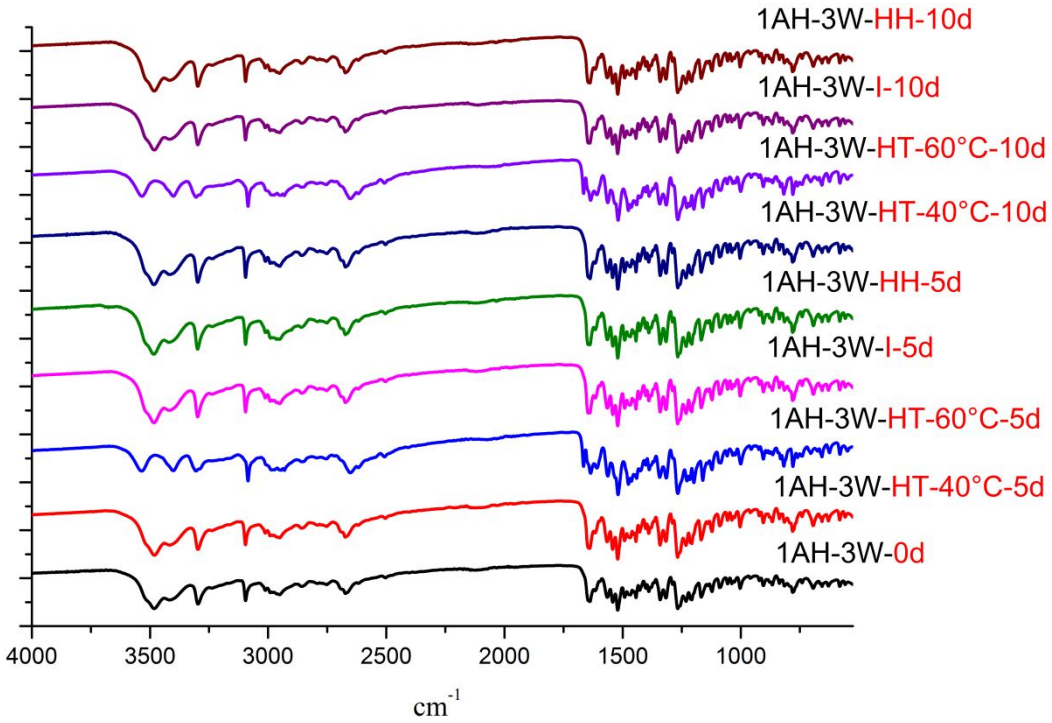

Figure 15. IR profiles of stability of 1AH-3W

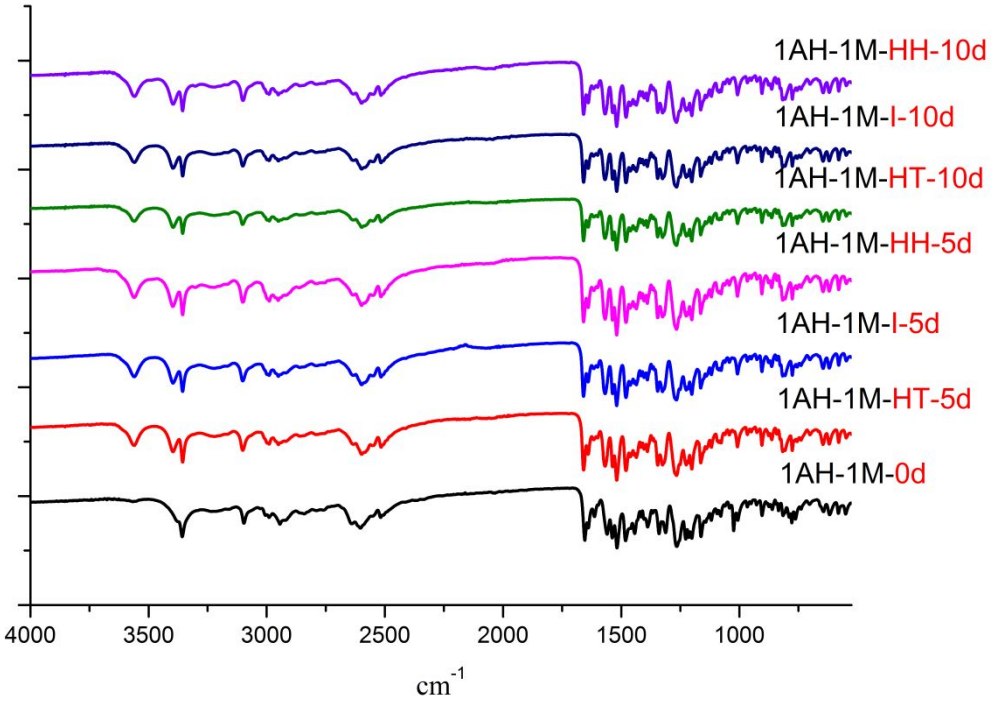

Figure 16. IR profiles of stability of 1AH-1M

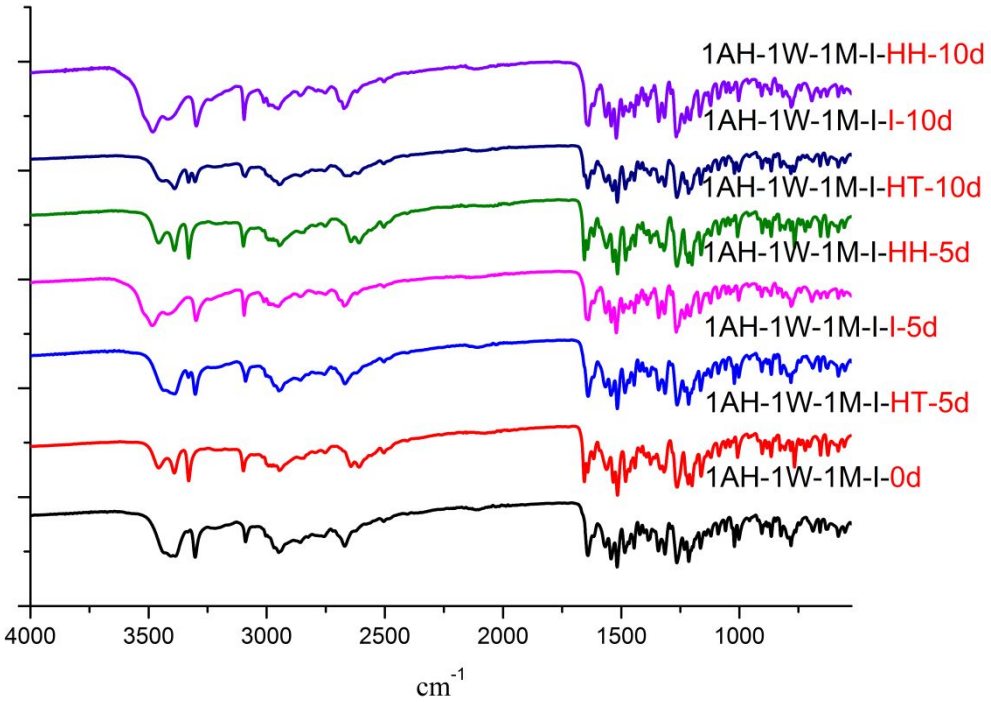

Figure 17. IR profiles of stability of AH-1W-1M-I

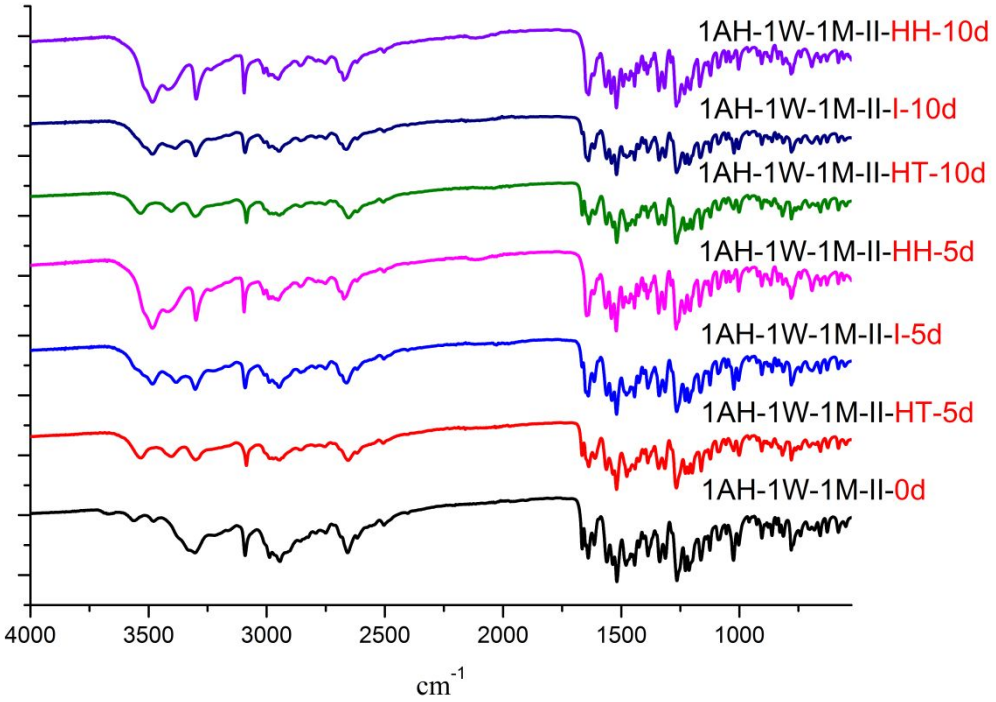

Figure 18. IR profiles of stability of 1AH-1W-1M-II

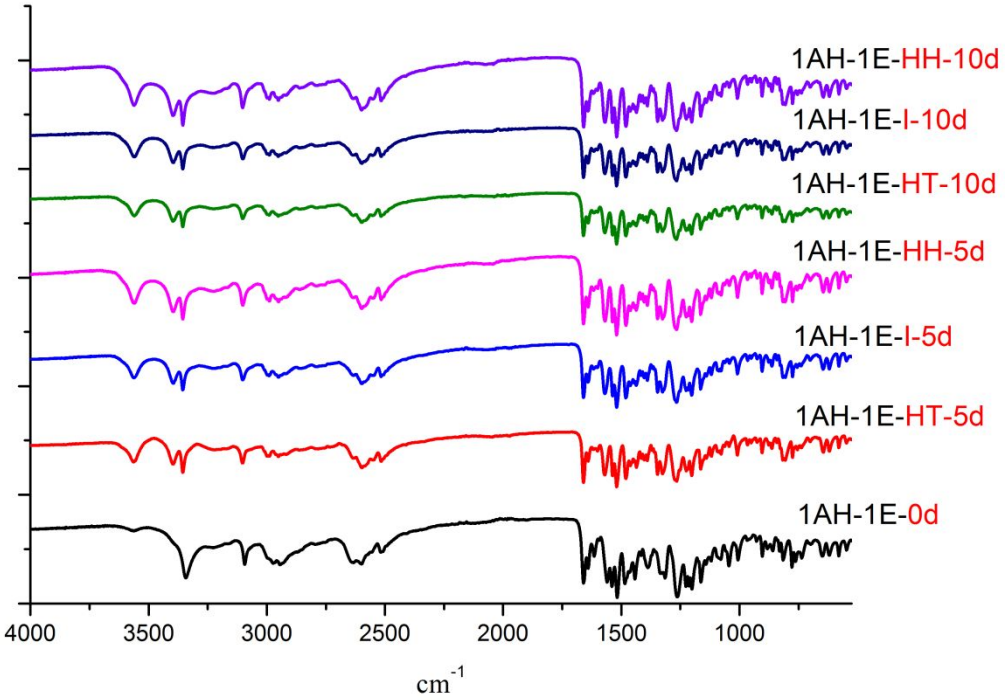

Figure 19. IR profiles of stability of 1AH-1E

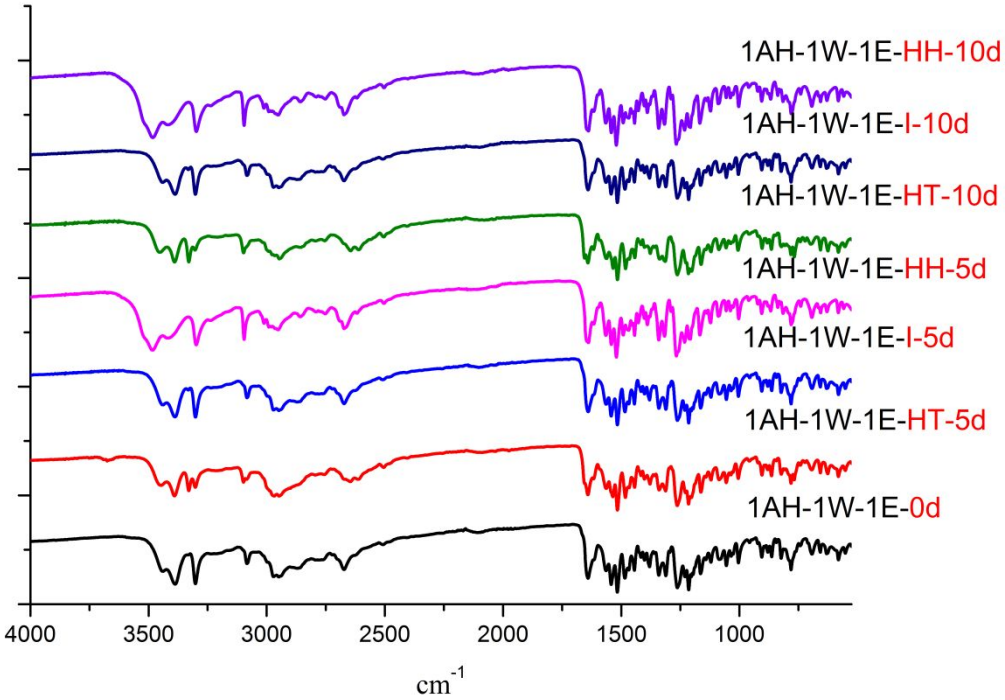

Figure 20. IR profiles of stability of 1AH-1W-1E

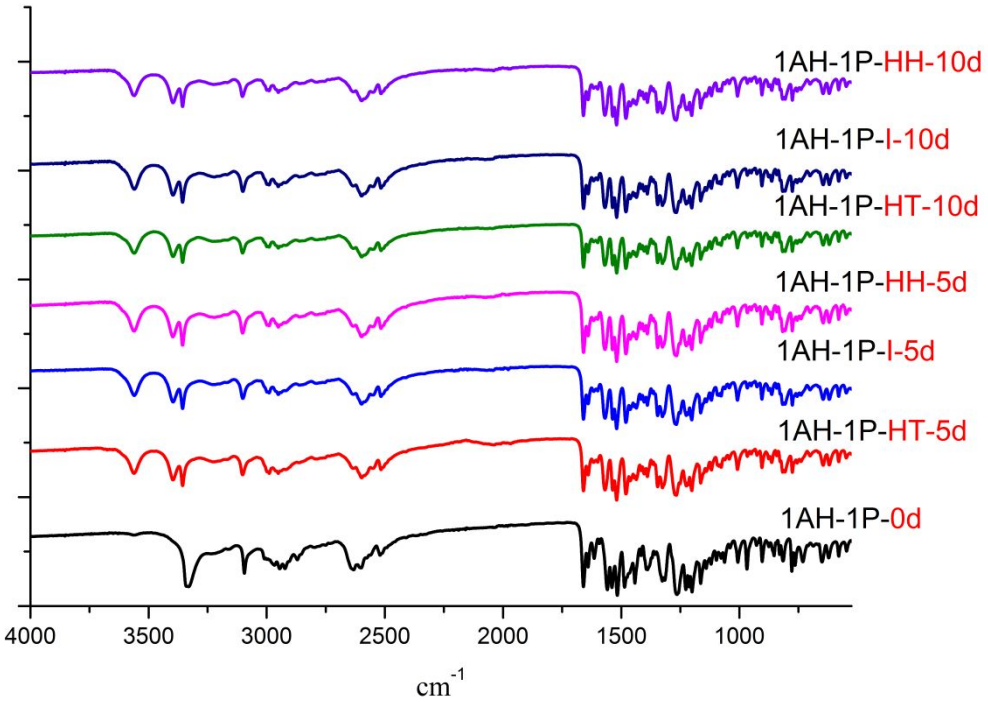

Figure 21. IR profiles of stability of 1AH-1P

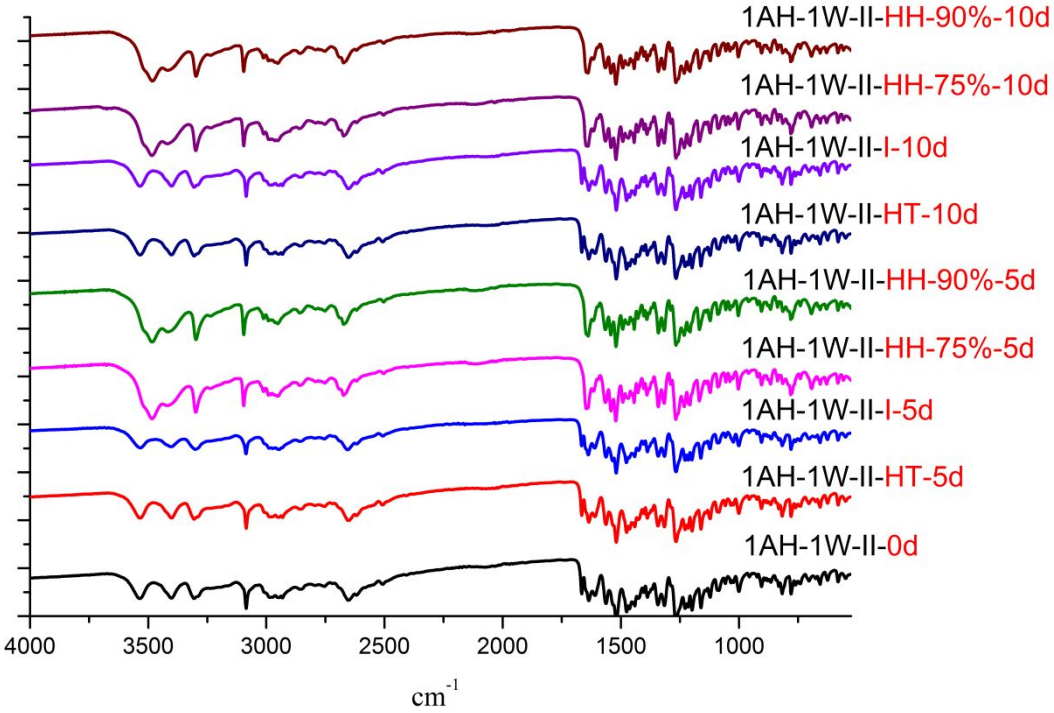

Figure 22. IR profiles of stability of 1AH-1W-II

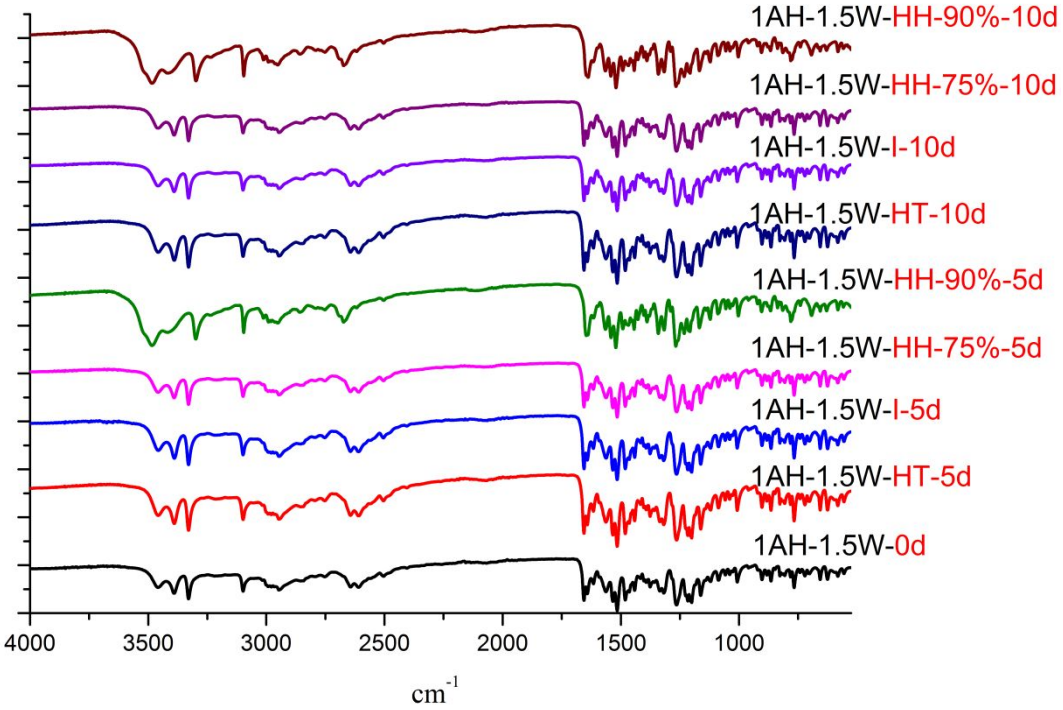

Figure 23. IR profiles of stability of 1AH-1.5W

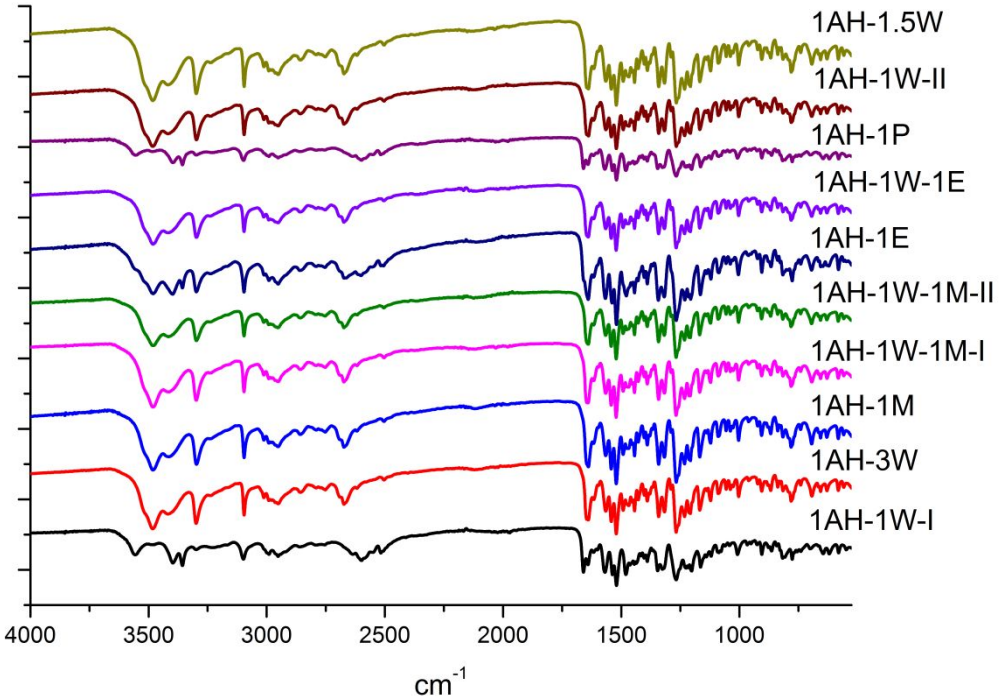

Figure 24. IR profiles of the undissolved solid phase forms in solubility experiment at 2 hours

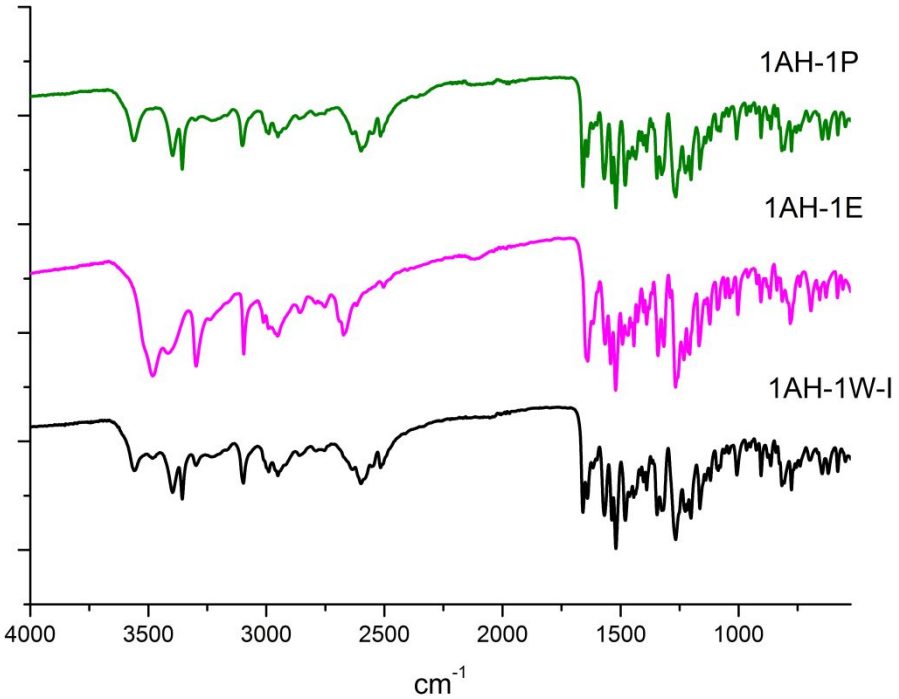

Figure 25. IR profiles of the undissolved solid phase forms in solubility experiment at 5 hours

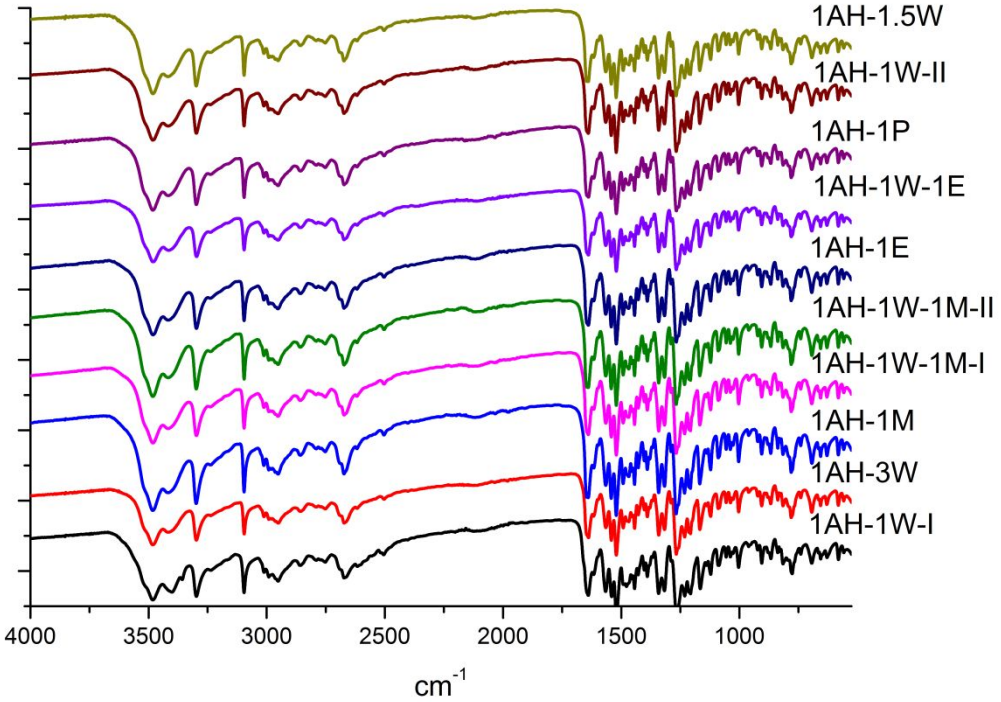

Figure 26. IR profiles of the undissolved solid phase forms in solubility experiment at 8 hours

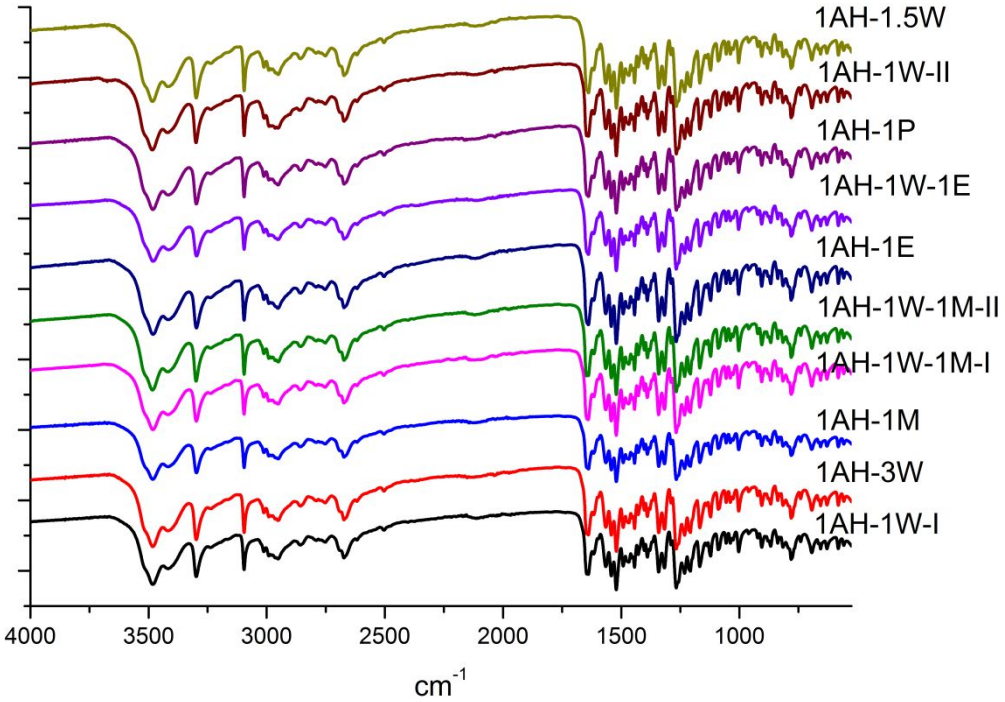

Figure 27. IR profiles of the undissolved solid phase forms in solubility experiment at 48 hours