Supporting Information for

The role of water in the formation of crystal structure: a case study of valnemulin hydrochloride

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Preparation of VHWE and VHWMS

VHWES and VHWMS were prepared by the method of Ouyang et al[1]. First, about 5 g of the raw material, amorphous VH, was dissolved in 10 mL of an ethanol + water mixture (molar ratio of 1 : 1) and an methanol + water mixture (molar ratio of 1 : 1) at 323.15 K, respectively. After a transparent solution was obtained, the solution was then cooled to 278.15 K at a cooling rate of 0.2 K min−1 and a lot of crystals emerged during the cooling process by immersing an ultrasound probe. Finally, after the system reached equilibrium for enough time, the products were then filtered and dried in a vacuum oven at 298.15 K

Preparation of VHW

VHW is obtained by the transformation of VHWES. At a temperature of 5 ^{o}C, VHW can be obtained by suspending 1g VHWES in the aqueous solution of 2ml for 8 hours. The products were then filtered and dried in a vacuum oven at 303.15 K

The preparation of single crystals of VHW.

Certain amounts of VH solids were dissolved into water . Then, the suspension was filtered after reaching equilibrium. The beaker with solution was placed into an oven and kept at 298.15 K. The solvent evaporated slowly then VHW with appropriate size for single crystal X-ray diffraction were obtained after several weeks.

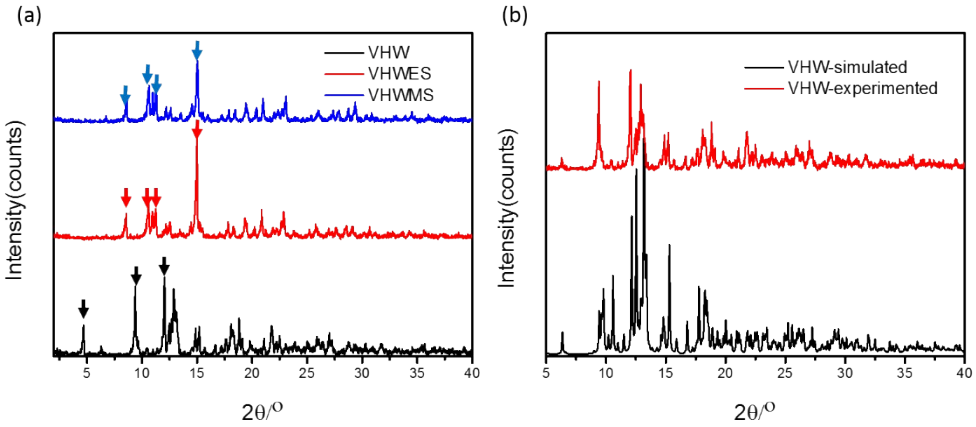

Fig.S1 (a) PXRD patterns of three crystal forms of valnemulin hydrochloride. (b) The XRD pattern of VHW experimental sample and simulated XRD pattern of VHW single Crystal.

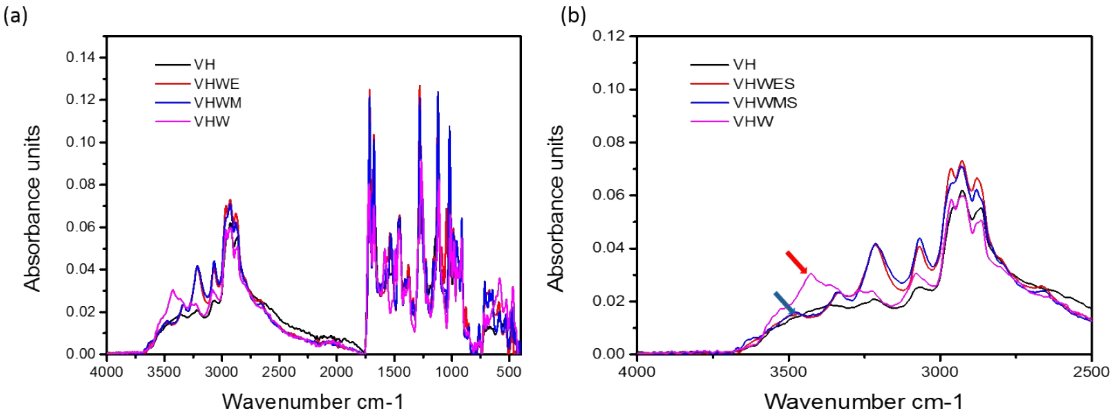

Fig. S2 (a) FTIR spectra of VH, VHWES, VHWMS and VHW. (b) An enlarged view of Fig. S2a（the wavenumber range is 4000-2500）. The peak indicated by the blue arrow corresponds to the water molecule -OH stretching vibration of the two solvates, while the peak indicated by the red arrow corresponds to the water molecule -OH stretching vibration of VHW.

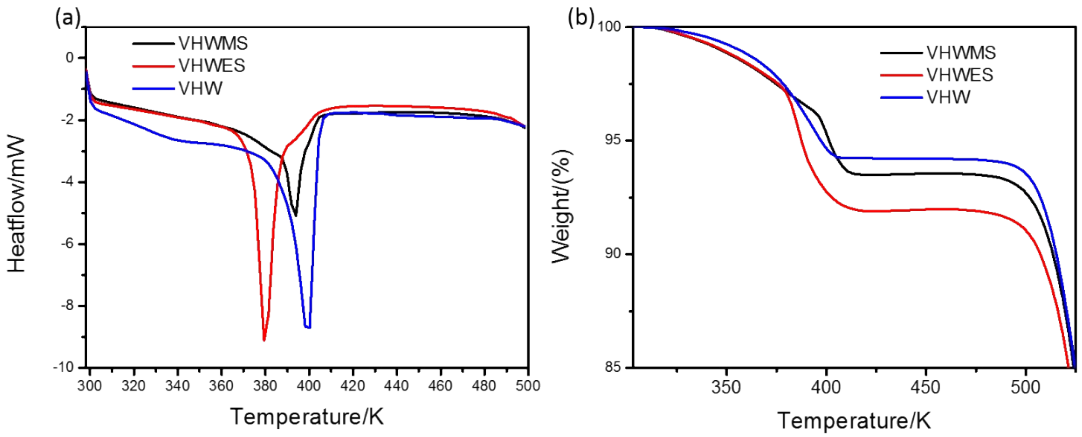

Fig. S3 (a) DSC and (b) TG thermograms of VHW, VHWES and VHWMS.

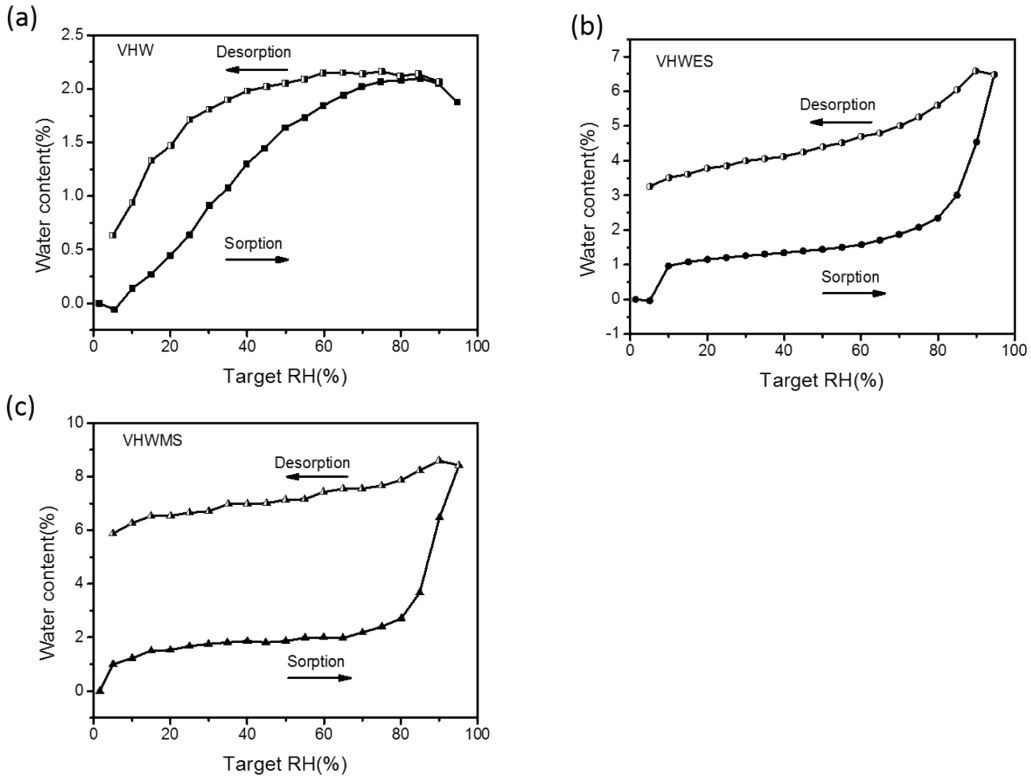

Fig. S4 DVS diagrams of three solid forms of valnemulin hydrochloride: (a) VHW, (b)VHWES, (c) VHWMS.

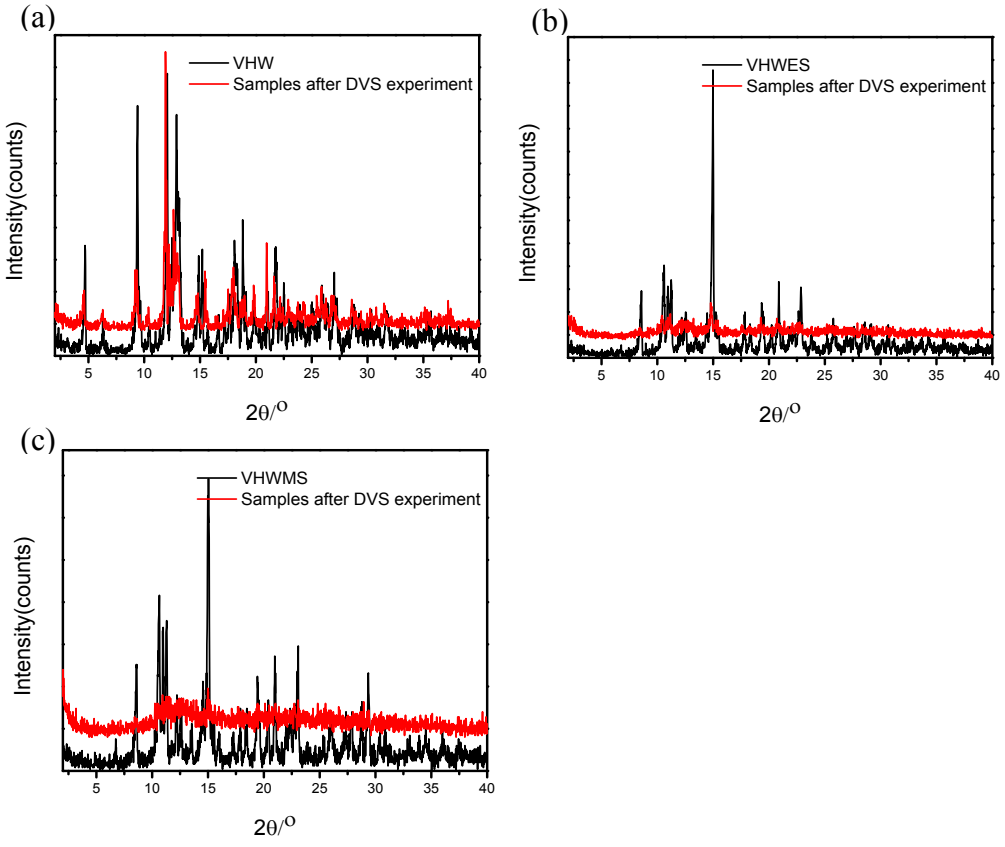

Fig. S5 Comparison between the sample after DVS experiment and its initial sample

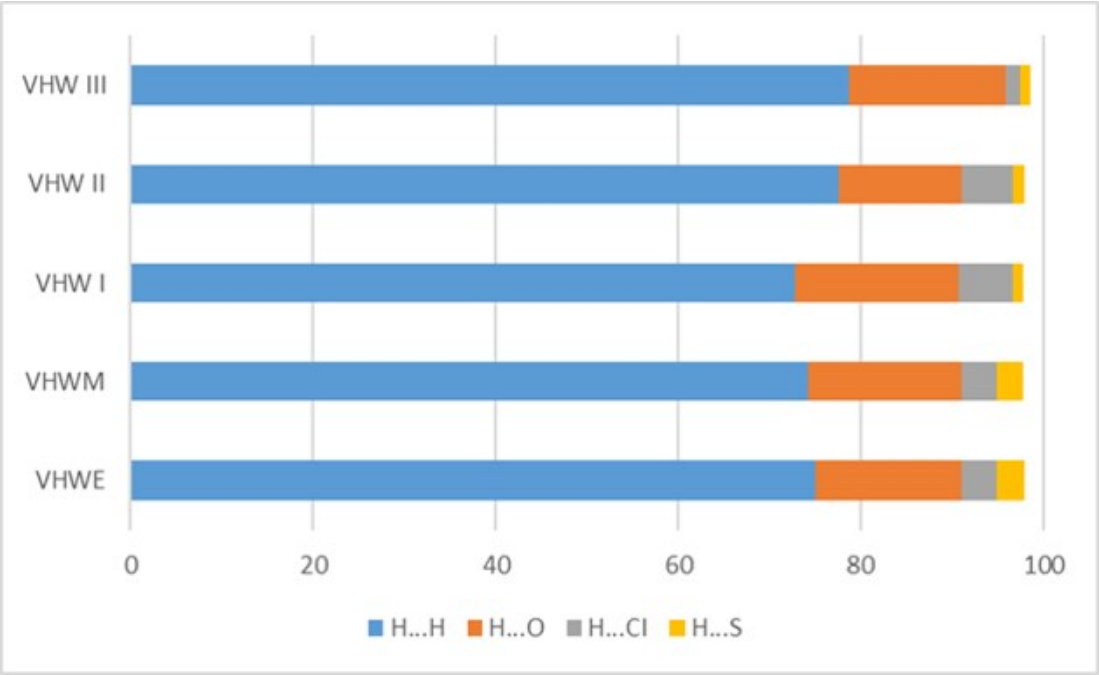

Fig. S6 The relative contribution of different interactions to the Hirshfeld surface.

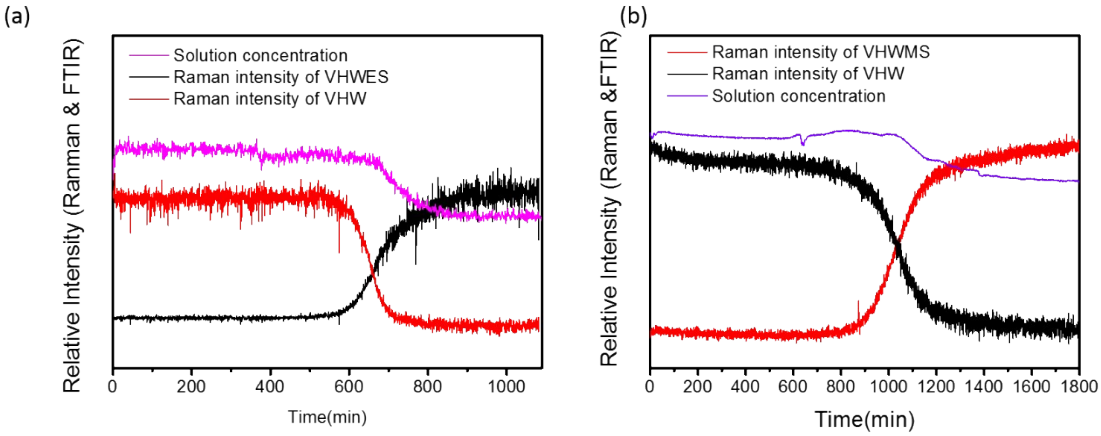

Fig. S7 The solvent-mediated crystallization process of (a) VHW to VHWES in ethanol+water mixed solution and (b) VHW to VHWES in methanol+water mixed solution.

Table S1. Hydrogen Bond Data for three Solid Forms of valnemulin hydrochloride

Form	D-H···A	D-H (Å)	H···A (Å)	D···A (Å)	θ(DHA) (°)
VHWES	O(2)–H(2)···O(5)	0.84	2.019	2.748	144.65
	O(7)–H(7B)···O(1)	0.867	2.001	2.770	147.22
	N(2)–H(2A)···O(7)	0.909	1.881	2.770	165.61
	N(2)–H(2B)···O(2)	0.918	1.952	2.828	158.82

	N(2)–H(2C)···O(6)	0.923	1.881	2.747	155.45
	O(6)–H(6)···Cl(1)	0.840	2.231	3.054	166.65
	O(7)–H(7A)···Cl(1)	0.862	2.315	3.147	162.28
	N(1)–H(1)···Cl(1)	0.898	2.354	3.208	158.84
VHWMS	O(5)–H(5)···O(1)	0.840	2.043	2.783	146.61
	N(1)–H(1A)···O(5)	0.898	1.985	2.856	162.76
	N(1)–H(1B)···O(7)	0.900	1.917	2.787	162.05
	N(2)–H(2)···Cl(1)	0.912	2.316	3.207	165.57
	N(1)–H(1C)···O(6)	0.917	1.871	2.774	167.59
	O(6)–H(6)···Cl(1)	0.840	2.243	3.062	164.82
	O(7)–H(7A)···Cl(1)	0.894	2.322	3.149	153.85
	O(7)–H(7B)···O(4)	0.892	2.382	2.910	118.01
VHW	N6-H(6C) ···Cl(3)	0.911	2.341	3.220	162.06
	N6-H(6B) ···O(19)	0.910	1.962	2.854	166.38
	N1-H(1C) ···O(5)	0.910	2.057	2.743	131.16
	N5-H(5) ···O(20)	0.880	1.917	2.786	169.20
	O(20)-H···O(4)	0.851	2.614	2.735	89.05
	O(16)-H(16B) ···O(2)	0.849	2.408	2.911	118.47
	O(2)-H(2A) ···Cl(2)	0.840	3.029	3.130	89.03
	N(4A)-H(4AB) ···Cl(2)	0.911	2.216	3.102	156.38
	N(4A)-H(4AC)···Cl(1)	0.910	2.299	3.126	150.91
	O(17)-H(17B)···O(7)	0.850	2.154	2.931	151.76
	O(7)-H(7)···O(18)	0.84	1.847	2.701	167.84
	N(1)-H(1A)···O(16)	0.910	1.979	2.861	162.63
	N(1)-H(1B)···Cl(1)	0.909	2.715	3.060	164.25
	N(2)-H(2)···O(17)	0.880	2.153	3.021	168.66
	O19-H(19B)···O(16)	0.850	2.818	2.962	91.32
	O19-H(19A)···O(17)	0.850	2.215	2.853	131.80
	O(17)-H(17A)···Cl(2)	0.850	2.341	3.155	160.38

	O(16)-H(16A)···Cl(3)	0.850	2.218	3.043	163.78
	O(18)-H(18A)···Cl(2)	0.850	2.647	3.133	117.64
	O(20)-H(20B)···Cl(1)	0.851	2.422	3.239	161.27
	N(4A)-H(4AA)···O(21A)	0.907	2.353	3.200	155.41

Table S2 The influence of experimental conditions on the crystal formation of VH

Experiment	Temperature °C	Amount of VH g/ml	Stirring rate rpm	Solvent	results
1	5	0.2	100	Ethanol	sticky solution
2	5	0.3	100	Ethanol	sticky solution
3	5	0.4	100	Ethanol	sticky solution
4	5	0.4	50	Ethanol	sticky solution
5	5	0.4	150	Ethanol	sticky solution
6	25	0.6	100	Ethanol	sticky solution
7	5	0.2	100	Methanol	sticky solution
8	5	0.3	100	Methanol	sticky solution
9	5	0.4	100	Methanol	sticky solution
10	5	0.4	50	Methanol	sticky solution
11	5	0.4	150	Methanol	sticky solution
12	25	0.6	100	Methanol	sticky solution

Table S3 The influence of experimental conditions on solution-mediated polymorphic transformations

Experiment	Temperature °C	Supersaturation	Stirring rate rpm	Solvent	results
1	5	1.7	100	Ethanol+Water(1:1)	VHWES
2	5	1.5	100	Ethanol+Water(1:1)	VHWES
3	5	1.9	100	Ethanol+Water(1:1)	VHWES
4	5	1.5	50	Ethanol+Water(1:1)	VHWES

5	5	1.5	150	Ethanol+Water(1:1)	VHWES
6	25	1.1	100	Ethanol+Water(1:1)	VHWES
7	5	1.7	100	Methanol+Water(1:1)	VHWMS
8	5	1.5	100	Methanol+Water(1:1)	VHWMS
9	5	1.9	100	Methanol+Water(1:1)	VHWMS
10	5	1.5	50	Methanol+Water(1:1)	VHWMS
11	5	1.5	150	Methanol+Water(1:1)	VHWMS
12	25	1.1	100	Methanol+Water(1:1)	VHWMS

1. J. Ouyang, B. Na, L. Zhou, S. Xiao, G. Xiong and T. Jin, *CrystEngComm*, 2018, **20**, 563-569.