BL-4B2/2011G544

Polymorphic transformation behavior of acyclovir evaluated by crystal structure analysis

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1 Introduction

Acyclovir (ACV) is a synthetic purine nucleoside analogue with inhibitory activity against herpes simplex virus, which has several kinds of polymorphs and hydrates. Birnbaum et al. [1-3] reported the crystal structure of commercial ACV, a 3:2 ACV/water hydrate and discussed its conformational feature. Lutker et al. [4] have studied the crystal structure of anhydrate and dehydrate using not only single X-ray diffraction but also various spectroscopic techniques, such as Raman, IR, and NMR. They have demonstrated the crystal structure of anhydrate. (Form I) and dehydrate (Form VI). They have also demonstrated that ACV displays, at minimum, two anhydrous forms stable under ambient conditions, two forms that do not exist under ambient conditions, and two hydrates. However, the transformation behavior of each form is not fully understood. We have analyzed the crystal structure of each polymorphs and pseudomorphs based on single crystal X-ray structural analysis and powder X-ray structural analysis.

In this research, the mutual transformation behavior of each form of ACV was evaluated by thermal and crystal structure analysis.

2 Experiment

2/3 hydrate was purchased from Kouki Co. Ltd. and the sample was used without further purification. Anhydrate form 1 was crystallized by adding acetonitril to the N,N-dimethyl formamide solution. Anhydrate form 2 was prepared by heating 2/3 hydrate at 180 °C.

When a single crystal of suitable size and quality for single-crystal X-ray diffraction analysis could not be obtained, even for the stable dehydrate phase, crystal structures of anhydrous phase of ACV were determined from powder XRD data. Synchrotoron X-ray powder diffraction data of the anhydrous phase of ACV were recorded under ambient conditions on beamline 4B2 at the Photon Factory (Tsukuba, Japan). Dehydrated sample was sealed in a borosilicate glass capillary in order to prevent rehydration during measurement. Indexing of the powder diffraction pattern was carried out using the program DICVOL04, giving the unit cell with monoclinic metric symmetry. The Pawley refinement was used by DASH to fit the peak profiles. The refined unit cell and profile parameters were used in the subsequent structure solution calculation. The simulated annealing method was used by DASH for structure determination. The best structure obtained in the structure solution calculation was used as the initial structure model for Rietvelt refinement, which was carried out using the program RIETAN-FP.

3 Results and Discussion

Dehydration properties of ACV hydrate by simultaneous measurement of XRD-DSC

The phase transformation of ACV hydrates on temperature was evaluated by simultaneous measurement of XRDDSC. Figure 1 shows the simultaneous measurements of XRD-DSC of 2/3 hydrate. 2/3 hydrates dehydrated to anhydrate form 3 at about 80 °C, and transformed to anhydrate 4 at about 170 °C. Figure 2 shows the simultaneous measurements of XRD-DSC of dihydrate. Dihydrate dehydrated to anhydrate form 2 at about 43 °C, and transformed to anhydrate 4 at about 170 °C.

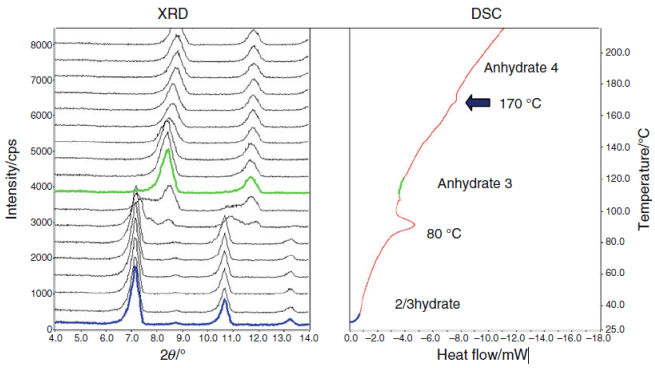

Fig. 1: Simultaneous XRD-DSC measurement plot of acyclovir 2/3 hydrate.

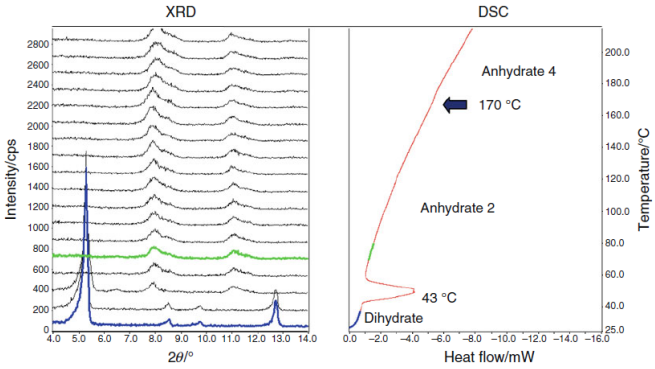

Fig. 2: Simultaneous XRD-DSC measurement plot of acyclovir dihydrate.

On the basis of DSC and dynamic vapor sorption analysis, anhydrate 1 was transform to 2/3 hydrate at above RH 95 % at 25 °C. Continued storage of 2/3 hydrate, it transformed to dehydrate above RH95 %. 2/3 hydrate was transformed to anhydrate 2 at RH 0 % and dihydrate was transformed to 2/3 hydrate below RH 20 %. Dihydrate and 2/3 hydrate were reversibly transformed dependent on the relative humidity. However, 2/3 hydrate did not transformed to anhydrate 1, and also anhydrate 2 did not directly transform to 2/3 hydrate at arbitrary temperature and RH. 2/3 hydrate was transformed to anhydrate 3 by heating above 120 °C, moreover, the anhydrate 3 was change to the anhydrate 4. Anhydrate 2 also transformed to the anhydrate 4 by heating above 170 °C, as a result, anhydrate 4 would be most stable form above 170 °C. The schematic drawing of the relation of each polymorph and pseudomorph was shown in Fig. 3.

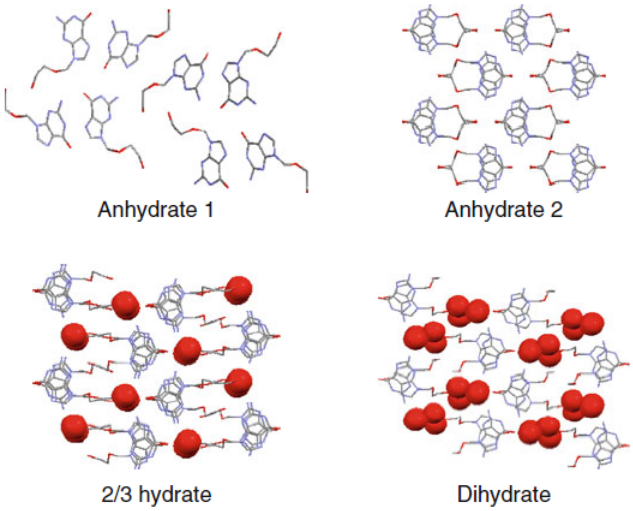

Fig. 3: Molecular packing of acyclovir polymorphs and pseudo-morphs red ball shows the oxygen atom of water.

Polymorphic and pseudomorphic transformation on the basis of molecular packing in the crystal structure

The crystal structure of 2/3 hydrate has already been analyzed by Birnbaum et al. [3]. According to the paper, three ACV molecules were stacked to parallel manner in a unit cell and two water molecules were present in a hollow space to the stacking unit of three ACV molecules. We have analyzed another three crystal structures by single crystal analysis for ACV dihydrate and ACV anhydrate 1, also powder X-ray diffraction structure analysis for ACV anhydrate 2. Structural data of anhydrate 1, 2, 2/3 hydrate, and dihydrate are shown in Table 1.[5] Figure 4 shows the molecular packing of ACV in the crystal. According to the molecular packing for four crystals, there are two packing manners for purine moiety. Anhydrate 1, anhydrate 2, 2/3 hydrate and ACV dihydrate were packed in parallel, antiparallel, mixture of parallel - anti-parallel and parallel manners, respectively. Based on the packing manner of ACV, it can be seen why the phase transformation occurs with readily or with difficulty as shown in Fig. 4. Due to similar packing manner, anhydrate 2 were readily transform to dihydrate according to RH and temperature. On the other side, Anhydrates I and II were not directly transform each other due to significantly different molecular packing manner of purine moiety.

Thermodynamic relation of each ACV anhydrate polymorphs

The thermodynamic relation of ACV anhydrate 1, 2, 3, and 4 was evaluated by DSC. Anhydrate 1 was melted at 253.7 °C (526.7 K) and the heat of fusion was confirmed to be 86.9 J g^{-1}. Anhydrate 2 was transformed to a new form, form 3 at 170.2 °C (519.5 K) with the transition energy of 13.2 J g^{-1}, then it melted at 246.5 °C (526.7 K) with the heat of fusion of 72.9 J/g. The heat of solution of anhydrate 1 and 2 was measured by microcalorimeter at 25 °C (298 K) and confirmed to be 37.4 and 55.9 J g^{-1}, resulting that the free energy difference in these hydrates

Table 1 Structural data of anhydrate 1, 2, 2/3 hydrate, and dehydrate [3,5]

	Anhydrate 1	Anhydrate 2	2/3 Hydrate	Dihydrate
Method	Single crystal	Powder		Single crystal
Crystal system	Orthoronbic	Monoclinic	Monoclinic	Triclinic
Space group	$P2_12_12_1$	$P2_1/c$	$P2_1/n$	P-1
Unit cell				
a/Å	4.53870 (10)	10.9399 (6)	25.459 (1)	6.838 (6)
b/Å	15.0308 (3)	11.1837 (6)	11.282 (1)	11.3679 (14)
c/Å	28.3320 (6)	8.1164 (4)	10.768 (1)	14.942 (2)
α/°	90	90	90	82.845 (4)
β/°	90	108.6277 (34)	95.16	82.419 (3)
γ/°	90	90	90	89.326 (3)
Volume/Å^3	1932.82	941.009	3080.342	1142.5 (2)
Z	8	4	12	4
R factor/%	9.88	9.71	5.3	7.71

was 18.48 J g^{-1}.

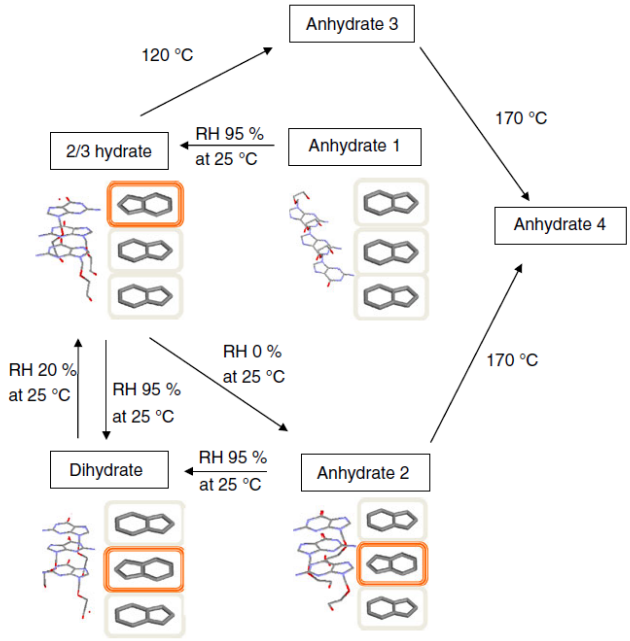

Fig. 4: Relation between packing manner of furan moiety of acyclovir and phase transition induced by humidification and temperature

The relative thermodynamic relation of anhydrate 1, 2, 3, and 4 was as shown in Fig. 5. [5] Obtained data clarified the anhydrate 1 and the others were in the monotoropic relationship, on the other hand, the enantiotropic relationship was observed among anhydrates 2, 3, and 4. Crystallographic data was helpful to understand the thermodynamic relationship between polymorphs and pseudopolymorphs.

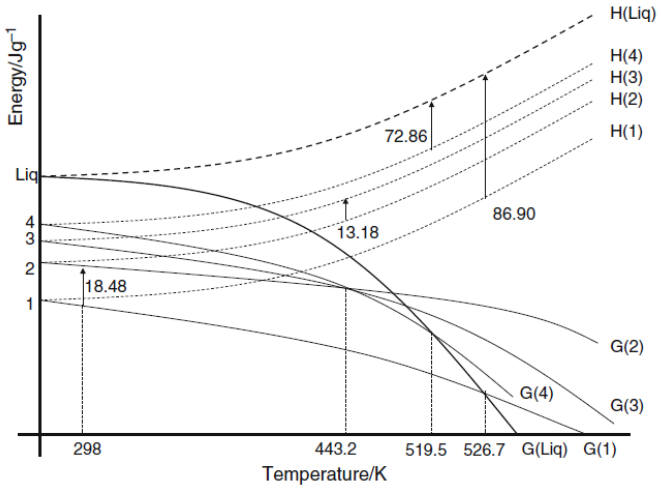

Fig. 5: Thermodynamic energy - temperature diagram of acyclovir anhydrates
H; enthalpy, G; gibbs free energy, Liq; liquid state,
1; anhydrate 1, 2; anhydrate 2, 3; anhydrate 3,
4; anhydrate 4

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