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Polymorphs of acyclovir-maleic acid salt and their reversible phase transition

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ABSTRACT

Acyclovir is a commonly used antiviral drug while its solubility is far from satisfied. It was reported that 1:1 acyclovir-maleic acid salt (ACV-MAL) possesses much higher maximum apparent solubility. In this contribution, a new crystal structure of ACV-MAL was solved at room temperature. This new crystal structure and previously reported structure at low temperature can transform to each other via a reversible solid phase transformation, which has been confirmed by single-crystal X-ray diffraction, solid state NMR and cycling differential scanning calorimetry tests. The phase change temperature is *ca.* 283 −293 K (10−20 °C), which is slightly lower than room temperature (298 ± 2 K/25 ± 2 °C), but is in the range of ambient temperature. This kind of near room temperature phase transformation is less concerned and tends to be neglected. This case report reminds that more attention should be paid to the polymorphism of pharmaceuticals at such temperature range due to its fundamental and practical significance.

1. Introduction

It's well known and recognized that an active pharmaceutical ingredient (API) may exist in various solid forms, such as polymorphs and amorphous forms of pure API compound, hydrates, solvates, salts, and cocrystals [1–4]. Different solid forms may exhibit different properties, such as solubility, chemical and physical stabilities, and bioavailability [1–4]. Thus, insight of the solid-form landscape of an API is very important for us to select optimal forms with desired properties.

Nowadays, solid-form screening has become a common practice for both new chemical entities and marketed products in pharmaceutical industry [1]. Many screening techniques, including experimental and computational approaches, have been developed [1,5,6]. However, we can hardly guarantee that all solid forms of an API can be discovered, since there are various of solid forms and effect factors in crystallization [7]. In order to identify the majority of solid forms of an API as much as possible, one thing we can do is increasing the number of carefully designed experimental trials, including those calculation (e.g., crystal structure prediction and hydrogen bond propensity) guided ones [1,6,8,9]. However, many reported cases continuously remind us that we should not get surprised to the emerging of new solid forms (or disappearance) of an API after careful screening, and the solid-state studies should be considered throughout the lifetime of a drug [7]. Additionally, it is crucial that the analytical results should always be treated carefully. For example, polymorph II of adenine [10] and luminal [11] were confirmed recently. Powder X-ray diffraction (powder XRD) provided subtle but important clues for these discoveries.

The crystal sample discussed in this study is acyclovir-maleic acid salt (ACV-MAL). ACV (Scheme 1a) is an antiviral medication used in the treatment of herpes simplex virus infections, chickenpox, and shingles. The reported solubility of ACV in water is about 1.1 mg/mL at room temperature [12]. Such low solubility is seen as an important factor resulting in its poor oral bioavailability

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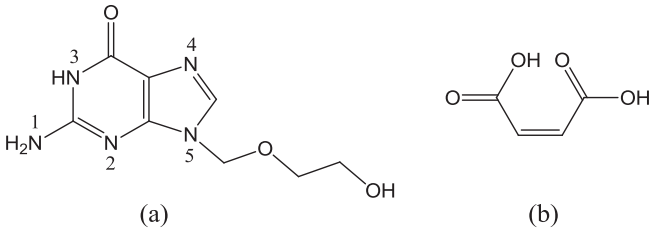

Scheme 1. Molecular structures of ACV (a) and MAL (b).

[12,13]. ACV-MAL was first prepared by Lu's group [14], which possesses much higher maximum apparent solubility. The enhanced solubility of ACV-MAL highlights its potential towards further pharmaceutical application. Crystal structure of one polymorph (here named form L) of ACV-MAL was solved in the same literature [14]. Here, another solid form (here named form R) of ACV-MAL was reported.

2. Material and methods

2.1. Materials and sample preparation

ACV (≥99%) and MAL (≥99%) were purchased from Titan Inc. (Shanghai, China) and Sinopharm Chemical Reagent Co., Ltd (Shanghai, China), respectively. Other chemicals used were of analytical grade and used as received without any further purification.

ACV (56.3 mg) and MAL (29.0 mg) were dissolved in methanol and then filtered through 0.22 μm PTFE syringe filter. The resulting solution was left to slowly evaporate at room temperature. Colorless crystals can be harvested after 2–3 weeks.

2.2. Characterization

Single-crystal X-ray diffraction (single-crystal XRD) data were obtained using a Agilent Gemini Atlas diffractometer (Agilent, Santa Clara,California) with graphite-monochromated Cu X-ray source (λ = 1.54184 Å) at 223 and 298 K. Powder XRD measurements were conducted on a PANalytical X'Pert Pro X-ray powder diffractometer (PANalytical B.V., Almelo, The Netherlands) equipped with an X'Celerator Real Time Multi-Strip detector. Salt sample (without mechanical grinding) was wrapped in two pieces of Mylar film and scanned in the transmission mode from 3.0 to 40.0°. Differential scanning calorimetry (DSC) experiments were carried out using a TA Q2000 differential scanning calorimeter (TA Instruments, New Castle, DE) with scan rate of 2.0 or 10.0 K min^{-1} under nitrogen atmosphere. ^{15}N Cross-Polarization/Magic Angle Spinning (CP/MAS) NMR experiments were performed with a 4-mm double-resonance MAS probe on a Bruker AVANCE III-500 spectrometer (Bruker BioSpin, Karlsruhe, Germany), or on Varian 600 MHz NMR system (Varian Inc. Palo Alto, CA). The ^{15}N NMR spectra were obtained at 8 kHz MAS spinning speed with a 5 ms contact time and 8 s recycle delay. ^{15}N chemical shift was externally referenced to L-glycine (−347.0 ppm).

2.3. Theoretical chemical shifts calculations

The crystal structure of ACV-MAL form L and form R were subjected to geometry optimization and NMR shielding calculation by using *MS CASTEP* program [15]. Calculations were carried out by using the generalized gradient approximation, Perdew-Burke-Ernzerhof functional with the Grimme dispersion correction. The optimization was carried out with an energy cutoff of 300 eV, ultrasoft pseudopotential and default K-point setting. While in the NMR shielding calculation, a fine K-point and energy cut-off of 550 eV were employed, combining with core-valance interactions described by ultrasoft pseudopotential generated on-the-fly.

3. Results and discussion

Single crystal sample of ACV-MAL can be obtained via slow evaporation of a methanol solution containing ACV and MAL in a molar ratio of 1:1 [14]. The crystal structure solved in our laboratory (CCDC No.: 1449676, $T = 223$ K) is in line with the reported one (CCDC No.: 915143, $T = 150$ K) [14]. The structural analysis reveals that ACV-MAL (ACV-MAL form L, Table 1 and Fig. 1a and b) crystallizes in the triclinic space group (*P*-1) with two asymmetric units in a unit cell and each asymmetric unit contains two ACV^+ cations and two MAL^- anions ($Z/Z' = 4/2$). In each ACV/MAL pair, one acidic proton transfers from MAL (Scheme 1b) to the N4 site of ACV. Differential scanning calorimetry (DSC, see Appendix A Fig. S1) test shows that the melting temperature (T_m) of this sample is 448.4 K (175.2 °C), and no additional endothermic/exothermic peak presents between room temperature and T_m.

The powder XRD pattern (Fig. 2a) was collected in the transmission mode at room temperature (298 K). Compared with the simulated powder XRD pattern of form L (Fig. 2b), some differences can be observed. Sometimes, such kind of difference may be ascribed to the different test temperatures for the single crystal and powder samples. Rietveld simulation was performed for ACV-MAL form L, but no acceptable XRD pattern was obtained, which should be in line with the experimental powder XRD pattern (Fig. 2a). This result reminds us that the bulk sample may not exist as form L.

Solid state NMR data provided further evidences for our doubt. The ^{15}N CP/MAS NMR spectra of ACV (Fig. 3a) and ACV-MAL (Fig. 3b) were recorded at room temperature (298.5 ± 0.2 K). The chemical shifts were empirically assigned with the help of Non-Quaternary Suppression data (not shown here). The significant ^{15}N chemical shift change (−73.7 ppm) of N4 site clearly reveals the formation of a salt [16]. Interestingly, each chemically distinct N site in the salt is represented by a single resonance peak (Fig. 3b), indicating the number of molecules per asymmetric unit, Z', should be equal to 1. Obviously, such result is inconsistent with the solved crystal structure of form L ($Z' = 2$, Table 1).

A probable speculation is that the two different molecules in the asymmetric unit of ACV-MAL form L are located in very similar chemical environments, and their difference cannot be distinguished by solid state NMR technique. Since the crystal structure of

Table 1
Crystallographic data of ACV-MAL salts.

Name	ACV-MAL form L	ACV-MAL form R
Formula	$C_{12}H_{15}N_5O_7$	$C_{12}H_{15}N_5O_7$
Molecular weight	341.29	341.29
Temperature/K	223 (2) K	297.6 (0.2) K
Crystal system	triclinic	triclinic
Space group	*P*-1	*P*-1
a (Å)	8.7710 (7)	7.2845 (6)
b (Å)	12.9117 (13)	8.7275 (7)
c (Å)	14.1186 (15)	11.9737 (10)
α (°)	67.308 (10)	104.655 (7)
β (°)	86.957 (8)	98.875 (7)
γ (°)	74.375 (8)	92.869 (7)
Volume ($Å^3$)	1418.3 (2)	724.48 (11)
Z/Z'	4/2	2/1
ρ_{calcd} (g cm^{-3})	1.598	1.564
GOOF	1.055	1.023
R_1/wR_2	0.0439/0.1042	0.0762/0.2316
CCDC	1449676	1449677