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Three pharmaceuticals cocrystals of adefovir: Syntheses, structures and dissolution study

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ABSTRACT

We report here three novel cocrystals, which are composed of adefovir as the API (Active Pharmaceutical Ingredient) with *p*-aminobenzoic acid (**1,** $2C_8H_{12}N_5O_4P{\cdot}C_7H_6NO_2{\cdot}3H_2O$), 3,5-dihydroxybenzoic acid (**2,** $C_8H_{12}N_5O_4P{\cdot}C_7H_6O_4{\cdot}H_2O$) and 2,6-pyridinedicarboxlic acid (**3,** $C_8H_{12}N_5O_4P{\cdot}C_7H_5NO_4$) as CCFs (cocrystal formers) respectively by crystal engineering strategy. Their structures were characterized by single crystal X-ray diffraction, powder X-ray diffraction (PXRD) analysis, thermogravimetric analyses (TGA), elemental analysis (EA) and infrared spectral analysis (IR). The analysis of single crystal X-ray diffraction demonstrate that cocrystal **1** and **2** form a strong hydrogen-bonded assembly through the phosphoric acids of API with water in the lattice and carboxylic acids of CCF respectively. Cocrystal **3** is formed in which the phosphoric acid groups of API are also held by the carboxylic acid groups of CCF. The PXRD results indicate their high purity of as-synthesized samples. The TGA, EA, IR and dissolution study of API and the cocrystals were also measured and discussed.

1. Introduction

The synthon approach is of great importance to realize a synthetic approach in crystal engineering, and it is a dependable technique for the new structure in the crystalline state [1–3]. Cocrytstal are formed between a molecular or ionic Active Pharmaceutical Ingredient (API) and a cocrystal former (CCF) that is a solid under ambient conditions [4–8]. Cocrystalline materials containing APIs are continuing to gain interest within the pharmaceutical industry, due to their ability to alter the physicochemical properties of solid dosage forms, and the other component is conformer that must be safe and applicable [9–13]. Systematic introduction of acid groups in an aromatic periphery with a heteroatom was carried out to observe the changes in original structure. Accordingly, identification of new heterosynthons changes in properties upon interacting with the ratio of the API and coformers [14–17].

The hydrogen bond is relatively strong among the non-covalent interactions, and many hydrogen bond motifs have already been reported as building blocks for crystal engineering and crystal design [18,19]. Based on the basic building blocks, adefovir is expected to produce the new crystal forms because of the affluent groups and extensive application prospect in pharmaceutical industry. Adefovir dipivoxil, a precursor of adefovir which is a nucleoside analogue antiviral drugs, is a prescription drug for the treatment of hepatitis B even under a low dose of 10 mg. It was approved by American Food and Drug Administration (FDA) in 2002 for the treatment of hepatitis B with the commercial name Hepsera®, and was also approved in Europe in the next year. In our report on the bonding interaction of carboxyl derivatives such as aminobenzoic acid, hydroxybenzoic and pyridine carboxylic acid, the introduction of a benzyl or carboxyl group effectively induced bonding interaction due to the hydrogen bonds and stacking structure. The chemical structures of API and CCFs are shown in Scheme 1.

Slow evaporation and grinding are the most commonly used techniques for producing cocrystals [20]. In most cases, evaporation probes the formation of new form and is potentially able to selectively measure by a single crystal X-ray analysis [21]. In addition, a number of cocrystals were reported in the literature using the

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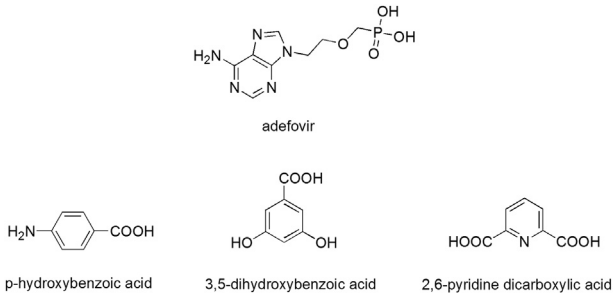

Scheme 1. Molecular structures of API and CCFs.

grinding method, making it possible in high throughput screening of conformer [22]. However, evaporation is not suitable to give bulk samples with large scale, and grinding method wouldn't give a suitable crystal for single crystal diffraction analysis. Herein, we synthesized three novel cocrystals (1–3) of adefovir with p-aminobenzoic acid, 3, 5-dihydroxybenzoic acid and 2, 6-pyridinedicarboxlic acid respectively using the refluxing method which was similar to reaction crystallization method (RCM), which is a common method to synthesize the crystal products. In addition, the refluxing method was generally used on the occasion of the reactants which were insoluble.

Their structures were characterized by single crystal X-ray diffraction, which shows that they are all formed by strong hydrogen bonds and π-π interactions. In addition, they were all characterized by powder X-ray diffraction (PXRD), thermogravimetric analyse (TGA) and the dissolution study.

2. Experimental

2.1. Materials

Adefovir (white amorphous powder) was provided by East west China Co., Ltd. *P*-aminobenzoic acid, 3, 5-dihydroxybenzoic acid and 2, 6-pyridinedicarboxlic acid with a purity of 99% were purchased from Aladdin Reagent Co., Ltd. All other chemicals of analytical grade were used as received without further purification. Distilled water prepared from demineralized water was used throughout the study.

2.2. Equipments

2.2.1. Single-crystal X-ray diffraction

Single crystal was picked and mounted for X-ray structural analysis on a Bruker SMART CCD diffractometer with Mo-Kα radiation (λ = 0.71073 Å) at 296 K. The structures were solved by direct methods and refined by full matrix least-squares on F^2 values (SHELXL-97). Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at calculated positions and refined using a riding mode. The parameters of the cocrystals were summarized in Table 1. The hydrogen bond distances were listed in Table 2.

2.2.2. Powder X-ray diffraction (PXRD)

Crystals were characterized by a Scintag X1 diffractometer with Cu-Kα (λ = 1.5418 Å) at 40 kV, 35 mA. Data were collected over an angular range of 4–40° 2θ value in continuous scan mode using a step size of 0.05° 2θ value and a scan speed of 1.0°/min.

2.2.3. Thermal gravity analysis (TGA)

Thermogravimetric analysis (TGA) were performed under N_2 atmosphere at 1 atm with a heating rate of 10 °C/min in the temperature range of 35–800 °C on a Perkin–Elmer Diamond TGA.

2.2.4. Elemental analysis (EA)

Elemental analysis (C, H and N) were carried out on a Perkin–Elmer 240 analyzer.

2.2.5. Infrared spectral analysis (IR)

Infrared spectral analysis was collected in a range of 3600–1600 cm^{-1} using KBr pellets and an SHIMADZU IRPrestige-

Table 1
Crystallographic data and structure refinement parameters for 1–3.

Compounds	1	2	3
Chemical formula	$C_{23}H_{36}N_{11}O_{13}P_2$	$C_{15}H_{20}N_5O_9P$	$C_{15}H_{17}N_6O_8P$
Original API	adefovir	adefovir	adefovir
Cocrystal former	PABA	3,5-DHBA	2,6-PDA
Formula weight	736.57	445.33	440.32
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	*P*2(1)	*P*2(1)	*P*-1
a (Å)	13.2675(5)	7.1660(5)	7.0202(10)
b (Å)	7.9044(3)	12.0808(9)	11.8680(18)
c (Å)	16.4202(6)	21.9062(16)	11.9713(18)
α (°)	90	90	76.35(2)
β (°)	112.554(10)	90.497(2)	76.52(2)
γ (°)	90	90	77.04(2)
vol ($Å^3$)	1590.31(10)	1896.4(2)	927.3(2)
dcal (g cm^{-3})	1.538	1.560	1.566
Z	2	4	15
N_{ref}	6744	4501	4270
T (K)	273(2)	273(2)	298
R1	0.0492	0.0579	0.074
wR2	0.1283	0.1454	0.189
Gof	1.005	1.066	1.113

Table 2
Hydrogen bond lengths (Å) and the angles (°) of 1–3.

Compound	D–H···A	d(D–H)	d(H···A)	d(D···A)	∠ D–H···A
1	N(1)–H(1A)···O(12)	0.86	2.58	3.411(5)	162
	N(1)–H(1B)···O(4)	0.86	2.49	3.263(5)	150
	O(5)–H(5C)···O(10)	0.81	1.95	2.715(4)	156
	O(5)–H(5D)···O(9)	0.81	1.95	2.702(4)	154
	O(6)–H(6C)···O(8)	0.81	1.99	2.717(4)	149
	O(6)–H(6D)···O(11)	0.80	1.86	2.628(4)	161
	O(9)–H(9)···O(2)	0.82	2.14	2.941(4)	154
	N(10)–H(10A)···O(6)	0.86	2.14	2.941(4)	154
	N(10)–H(10B)···N(7)	0.86	2.04	2.844(4)	154
	N(11)–H(11A)···O(5)	0.86	2.01	2.871(4)	176
	N(11)–H(11B)···N(5)	0.86	2.21	3.034(4)	161
	O(12)–H(12A)···O(6)	0.82	1.84	2.647(4)	168
	C(11)–H(11D)···O(2)	0.93	2.43	2.740(5)	100
	O(16)–H(16B)···O(11)	0.97	2.58	3.498(5)	158
2	N(1)–H(1A)···O(5)	0.86	2.11	2.950(3)	164
	N(1)–H(1B)···O(8)	0.86	1.98	2.821(3)	166
	O(2)–H(2B)···O(8)	0.76	1.97	2.760(3)	177
	O(3)–H(3D)···O(9)	0.80	1.84	2.635(3)	177
	O(5)–H(5D)···O(6)	0.81(5)	1.87(5)	2.614(3)	151(4)
	P(1)–H(6A)···N(2)	1.63	2.36	3.596(2)	128
	O(7)–H(7A)···O(9)	0.82	2.40	3.167(3)	157
	O(9)–H(9C)···O(6)	0.86	1.97	2.827(3)	176
	O(9)–H(9D)···O(1)	0.92	2.56	3.089(3)	117
	O(9)–H(9D)···O(8)	0.92	1.98	2.866(3)	160
	C(4)–H(4A)···O(5)	0.93	2.42	2.733(3)	100
	C(12)–H(12A)···O(3)	0.93	2.43	3.250(3)	147
	O(14)–H(14B)···O(4)	0.97	2.60	3.313(3)	131
3	O(5)–H(20)···O(3)	0.82(4)	1.78(4)	2.589(3)	170(5)
	N(1)–H(21)···O(2)	0.84(4)	1.99(4)	2.815(3)	170(4)
	N(1)–H(22)···N(5)	0.86(3)	2.16(3)	2.963(3)	154(4)
	C(1)–H(1)···O(6)	0.93	2.13	3.023(3)	161
	C(6)–H(6A)···O(1)	0.97	2.43	3.308(4)	150
	C(8)–H(8A)···O(6)	0.97	2.49	3.296(4)	140