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Synthesis, characterization and dissolution of three pharmaceutical cocrystals based on deferiprone

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ABSTRACT

In this paper we present three new cocrystals based on deferiprone which is the first oral medicine as iron chelator. Solitary deferiprone possesses some known problems due to its good solubility and frequent dosing side effects. For these three novel co crystals, deferiprone is the active pharmaceutical ingredient (API), *p*-hydroxybenzoic acid (1, $C_7H_9NO_2 \cdot C_7H_6O_3$), 2, 5-dihydroxybenzoic acid (2, $C_7H_9NO_2 \cdot C_7H_6O_4$) and maleic acid (3, $C_7H_9NO_2 \cdot C_4H_4O_4$) are used as cocrystal formers (CCFs), respectively. Their structures were characterized by single crystal X-ray diffraction, powder X-ray diffraction (PXRD) analysis, thermogravimetric analyses (TGA), differential thermal analysis (DTA), elemental analysis (EA) and infrared spectral analysis (IR). Single crystal X-ray diffraction demonstrates that all three cocrystals **(1–3)** possess strong hydrogen-bondings assembled through hydroxyl of API and carboxylic acids of CCFs. The PXRD results indicate their high purity of as-synthesized samples. TGA, DTA, EA, IR and dissolution study of API and cocrystals were also measured and discussed, respectively. The results suggest that the cocrystals exhibit low dissolution rates comparing with solitary deferiprone, which is very advantageous for the oral medicine with frequent dosing side effects.

1. Introduction

Most recently, pharmaceutical cocrystals have received attention in pharmaceutical industry due to their potential for their readily tuned physicochemical and biological properties of free active pharmaceutical ingredient (API) [1,2]. Cocrystals are usually designed and synthesized in the form of stable solid-state structures based on $\pi\cdots\pi$ stacking interaction or hydrogen bond interactions. The construction of a variety of organized frameworks, often with potentially demanded chemical and physical properties, is one of the aims of crystal engineering [3,4]. This could be achieved by a flexible approach of introducing another molecular component into the crystal lattice, making it possible to establish the linkage between the compounds that mainly refers to API and cocrystal former (CCF) [5–7]. Under ambient conditions, most APIs are crystalline solids at room temperature and commonly delivered as a solid oral dosage form [8], and it is well established that different solid forms of the same compound have different chemical and physical properties [9]. The CCFs were included in the pharmaceutically acceptable formers list, a classification known as Generally Recognized As Safe (GRAS) [10]and Everything Added to Food in the United States (EAFUS) list [11]. The pharmaceutical cocrystal would be safe to use in pharmaceutical formulations [12–15] and regulate and modify the solubility and bioavailability of different drugs [16–19].

Deferiprone (1,2-dimethyl-3-hydroxy-4-pyridinone) [20–22] is approved by the U. S. Food and Drug Administration (FDA) in 2011 for treatment of thalassemia patients which is a genetic blood disease caused by transfusion of iron overload in patients with anemia and poorly response to previous chelation therapy patients. Deferiprone is the first orally iron chelator, which is inexpensive and has good compliance. It is sparingly soluble in water at neutral pH and highly soluble in acidic solutions [23]. In the dissolution test experiment, it was confirmed that some co-crystals based on deferiprone has a lower dissolution rate. They could be used as a drug extended releasing agents, in order to overcome the shortcoming of the frequent dosing of single deferiprone.

In this research, considering the structure of deferprone as a

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hydroxyl-pyridinone derivative, introducing carboxyl derivatives such as *p*-hydroxybenzoic acid, 2, 5-dihydroxybenzoic acid and maleic acid would form cocrystals due to the interactions such as hydrogen bonds and π···π stacking structure. The chemical structures of API and CCFs are shown in Scheme 1. Herein, we synthesized three novel cocrystals **(1–3)** of deferiprone with *p*-hydroxybenzoic acid, 2, 5-dihydroxybenzoic acid and maleic acid respectively. The cocrystals were synthesized by refluxing method which was similar to a commonly used reaction crystallization method (RCM). In addition, the refluxing method was especially suitable for those insoluble reactants. Single crystal X-ray diffraction analysis demonstrates all the synthesized cocrystals are formed by strong hydrogen bonds and π-π interactions. In addition, powder X-ray diffraction (PXRD), thermogravimetric analysis (TGA), differential thermal analysis (DTA), elemental analysis (EA), IR analysis and dissolution study are also used to characterize these cocrystals.

2. Experimental

2.1. Materials

Deferiprone (white amorphous powder) was provided by Huameihua Technology Group Wuhan Co., Ltd. *p*-hydroxybenzoic acid, 2, 5-dihydroxybenzoic acid and maleic acid with purity of 99% were purchased from Aladdin Reagent Co., Ltd. All other chemicals in analytical grade were used as received without further purification. Distilled water prepared from demineralized water was used throughout the study.

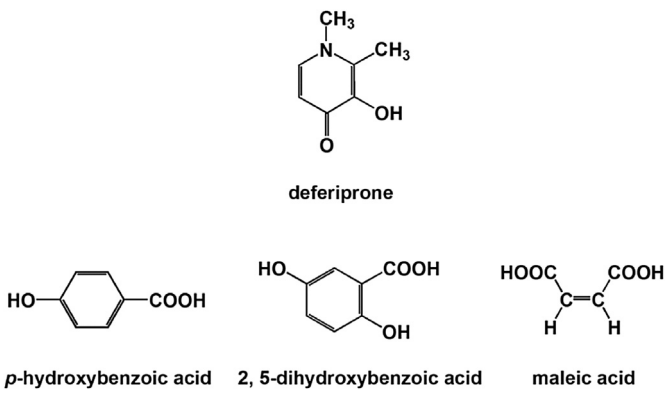
2.2. Equipments

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). 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.



Scheme 1. Molecular structures of API and CCFs.

Table 1
Crystallographic data and structure Refinement Parameters for 1–3.

Compounds	1	2	3
chemical formula	$C_{14}H_{15}NO_5$	$C_{14}H_{15}NO_6$	$C_{11}H_{13}NO_6$
original API	deferiprone	deferiprone	deferiprone
cocrystal former	PHA	2,5-DHBA	Maleic acid
formula weight	277.27	293.27	255.22
crystal system	Triclinic	Monoclinic	Triclinic
space group	*P*-1	*P2(1)/c*	*P*-1
a (Å)	7.4128(5)	13.1801(5)	7.6433(17)
b (Å)	8.5138(6)	9.9196(4)	8.2780(18)
c (Å)	11.1298(7)	10.7365(4)	9.687(2)
α (°)	94.550(2)	90	81.723(4)
β (°)	92.3710(10)	105.7970(10)	87.976(4)
γ (°)	111.0850(10)	90	83.789(4)
vol ($Å^3$)	651.47(8)	1350.69(9)	602.8(2)
dcal ($g \cdot cm^{-3}$)	1.413	1.442	1.406
Z	2	4	2
N_{ref}	5493	8025	3622
T (K)	296(2)	273(2)	273(2)
R1	0.0447	0.0390	0.0447
wR2	0.1195	0.0916	0.1375
Gof	1.057	0.888	1.136

2.2.3. Thermal gravity analysis (TGA) and differential thermal analysis (DTA)

Thermogravimetric analysis (TGA) and differential thermal analysis (DTA) were performed under N_2 atmosphere at 1 atm with a heating rate of 10 °C/min in the temperature range of 30–500 °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 a SHIMADZU IRPrestige-21 Fourier-transform infrared spectrometer.

2.2.6. Liquid chromatography–tandem mass spectrometry (LC-MS/MS)

Analysis was performed on a LC-MS/MS system comprising Agilent 1100 Series HPLC sys-tem (Agilent Technologies, Palo Alto, CA, USA) and Q-Trap 2000 mass spectrometer (Applied Biosystems MDS Sciex, Ontario, Canada). Chromatographic separation was achieved using an MP-C18 column (100 mm × 4.6 mm I.D., 5 μm particle size, Agilent Technologies) at 35 °C with a mobile phase of acetonitrile: ammonium acetate (5 mM) (80:20, v/v), at 1 mL/min. Analysis was carried out with an electrospray ionization (ESI) source using positive ion (ESI+) mode. The instrument parameter settings were as follows: ions pray voltage (IS) 5500 V, declustering potential (DP) 55 V, collision energy (CE) 35 eV, collision cell exit potential (CXP) 15 V, channel electron multiplier (CEM) 2000 V, nitrogen curtain gas 20 psi, gas 1 (GS1) and gas 2 (GS2) at 40 and 55 psi, source temperature 450 °C, and dwell time 200 ms. Data were acquired using Analyst Software 1.3.2 (Applied Biosystems MDS Sciex, Ontario, Canada).

2.3. Synthesis

2.3.1. Synthesis of cocrystal 1 ($C_7H_9NO_2.C_7H_6O_3$)

Deferiprone (28.20 mg, 0.2 mmol) and p-hydroxybenzoic acid (28.9 mg, 0.1 mmol) were added in a 25 mL round bottom flask, and the mixture was refluxed with 8 mL of water at 60 °C using oil bath for about 2 h. After refluxing, the resulting mixture was filtered and