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Simultaneous enhancements of solubility and dissolution rate of poorly water-soluble febuxostat *via* salts

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ABSTRACT

Novel crystalline forms of febuxostat (HFEB) salts were synthesized by liquid-assisted cogrinding with 2-methylimidazole (2MI) and di-2-pyridylamine (DPA) and characterized by Hirshfeld surface analysis, IR, ^{1}H NMR, single crystal and powder X-ray diffractions, TGA and DSC. Two new HFEB salts featured different stoichiometries: 2:1 molecular ratio in HFEB-2MI and 1:1 molecular ratio in HFEB-DPA. For HFEB-2MI salt, two HFEB molecules lost one proton forming a singly charged hydrogen carboxylate anion $H(FEB)_2^-$, which interacted with the disordered 2MI cation *via* the N3—H3A···O1^{i} (i: −x, −y, −z+1) and N4—H4B···O1^{ii} (ii: x, y+1, z−1) hydrogen bonds to form one-dimensional structure. For HFEB-DPA salt, one proton transferred from one HFEB to DPA, which were further connected by N4—H1···O1 and N3—H2···O2 hydrogen bonds to form an $R^2_2(8)$ ring motif. HFEB-2MI and HFEB-DPA salts exhibited increased equilibrium solubilities and intrinsic dissolution rates compared to those of HFEB in aqueous medium.

1. Introduction

In the past two decades, the researches on drug cocrystal and salt have been the focus issues due to their potential ability to improve solubility and dissolution rate of poorly water soluble active pharmaceutical ingredients (APIs) [1–3]. Moreover, the U.S. Food and Drug Administration (FDA) indicates that drug cocrystals would be considered as a new drug formulation and drug salts would be considered as a new drug entity [4].

Febuxostat (HFEB) is a nonpurine selective inhibitor of xanthine oxidase which is used for the treatment of gout [5,6]. Febuxostat has a low aqueous solubility of 12.9 mg L^{-1}, but shows a high permeability (*i. e.* Biopharmaceutics Classification System class II drug) [7]. The property is a common barrier in the drug development, which can be solved by transforming the drug into other forms such as solid dispersion, drug salts or drug cocrystals, etc [8]. In the search for the novel solid forms to meet the strict requirements in the formulation development, several crystal structures of solvates [9–11], polymorph, and cocrystals with urea, acetamide, nicotinamide and *p*-aminobenzoic acids have been reported [12]. However, there was no any report on the properties of HFEB salts. The objectives of this work were to improve the solubility of HFEB through salt formation.

2-Methylimidazole (2MI) and di-2-pyridylamine (DPA) are commonly basic molecules with multiple hydrogen-bonding sites, which make them a potential target for salt formation [13–20]. Herein, two novel HFEB salts with 2MI and DPA have been prepared by the liquid-assisted grinding method, which is a common method to screen cocrystal or salt formation [21]. The chemical structures of API and CCFs are shown in Scheme 1. The properties of HFEB salts have also been determined with different physical methods.

2. Experimental

2.1. Materials and equipments

The corresponding chemicals and reagents were obtained from commercial sources and used without further purification. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker 400 MHz instrument using DMSO-d_6 as solvent and TMS as an internal standard. Thermogravimetric analysis (TG) was carried out in a Perkin-Elmer TGA 4000 equipment with the heating rate of 10 °C/min under a nitrogen gas purge with a flow of 20 mL/min. Thermal analysis (DSC) was carried out using a Perkin-Elmer DSC 8000 differential scanning calorimeter at the rate of 10 °C/min in a

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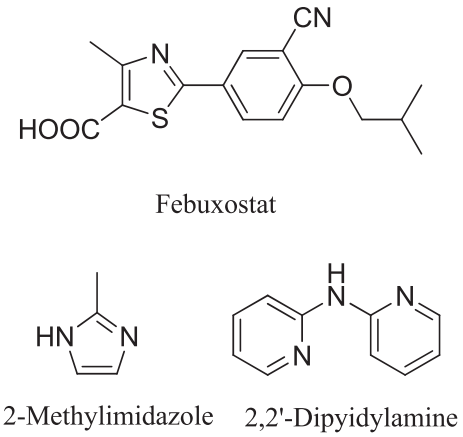

Scheme 1. Molecular structures of API and CCFs.

nitrogen atmosphere. Fourier infrared spectra (IR) were performed on a Bruker Vector 33 in the 4000–400 cm^{-1} range. Powder X-ray diffraction (PXRD) patterns were obtained with a German Bruker corporation D8 ADVANCE powder diffractometer coupled with a Cu Kα radiation tube (λ = 1.5418 Å, V = 40 kV and I = 40 mA) and 2θ scan in the 5–60° range.

2.2. Syntheses

2.2.1. Synthesis of HFEB

HFEB crystal was prepared by slow evaporation from acetonitrile at room temperature according to the literature [12]. ^{1}H NMR δ: 13.42 (s, 1H), 8.26 (s, 1H), 8.20 (d, J = 8.9 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 3.99 (d, J = 6.4 Hz, 2H), 2.66 (s, 3H), 2.14–2.04 (m, 1H), 1.02 (d, J = 6.6 Hz, 6H) (Fig. S1).

2.2.2. Synthesis of HFEB-2MI salt (2:1)

HFEB-2MI salt was obtained upon acetonitrile-assisted grinding about a total of 200 mg of a 2:1 stoichiometric ratio of HFEB and 2MI for 1 h, and then 30 mg of the resulting material was dissolved in 6 mL of hot ethyl acetate. After filtering, the filtrate was left for slow evaporation at the temperature of 5–10 °C. Colorless block crystals suitable for X-ray diffraction were obtained after 7–8 days. Yield: 18 mg (Yield: 60%). ^{1}H NMR δ: 8.22 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H),7.33 (d, J = 9.0 Hz, 1H), 7.18 (s, 1H), 3.98 (d, J = 6.4 Hz, 2H), 2.64 (s, 3H), 2.44 (s, 1.5H), 2.13–2.03 (m, 1H), 1.01 (d, J = 6.7 Hz, 6H) (Fig. S2).

2.2.3. Synthesis of HFEB-DPA salt (1:1)

HFEB-DPA salt was obtained upon acetonitrile-assisted grinding about a total of 200 mg of a 1:1 stoichiometric ratio of HFEB and DPA for 1 h, and then 30 mg of the resulting material was dissolved in 6 mL of acetonitrile. After filtering, the filtrate was left for slow evaporation at the room temperature. Fine needle crystals suitable for single crystal X-ray diffraction were obtained after 3–5 days. Yield: 22 mg (Yield: 73%). ^{1}H NMR δ: 9.66 (s, 1H), 8.27 (s, 1H), 8.20 (overlap, 3H), 7.72 (d, J = 8.4 Hz, 2H), 7.64 (t, J = 8.5 Hz, 2H), 7.35 (d, J = 8.7 Hz, 1H), 6.85 (t, J = 8.5 Hz, 2H), 3.99 (d, J = 6.0 Hz, 2H), 2.65 (s, 3H), 2.15–2.02 (m, 1H), 1.01 (d, J = 6.7 Hz, 6H) (Fig. S3).

2.3. X-ray crystallographic studies

All the crystal structures were determined by single-crystal X-ray diffraction and the diffraction data were collected on a Bruker Apex II CCD diffractometer operating at 50 kV and 30 mA using Mo Kα radiation (λ = 0.71073 Å). All the crystal structures were solved by direct method with SHELXS program and refined with SHELXL program [22]. The final refinements were performed by full-matrix least-squares methods with anisotropic thermal parameters for all non-hydrogen atoms on F^2. The hydrogen atoms on non-carbon atoms were located from difference Fourier maps and the hydrogen atoms riding on the carbon atoms were determined with theoretical calculation and refined isotropically. For HFEB-2MI salt, the disorder of protonated 2MI cation was refined freely with anisotropic thermal parameters and partial occupancy factors set at 0.5. Crystallographic parameters and hydrogen bonds were listed in Tables 1 and 2.

The Hirshfeld surfaces (mapped with d_{norm}) and fingerprint plot calculations were generated by CrystalExplorer 3.1 based on the single crystal structure of HFEB, HFEB-2MI salt and HFEB-DPA salt [23–26].

2.4. Equilibrium solubility and dissolution rate experiments

Equilibrium solubility experiments was measured on a round bottomed flask at 37 ± 0.5 °C in aqueous medium. In a typical experiment, 25 mL of aqueous medium was added to a round bottomed flask containing 200 mg of solid samples at 500 rpm. The resulting solution was filtered with 0.22 μm nylon filter and then diluted by aqueous medium. The HFEB concentrations in HFEB and HFEB-2MI salt were measured by the UV spectra in the range of calibration curves at 315 nm. Because DPA had a UV interference at 315 nm (Fig. S4), the equilibrium solubility of HFEB-DPA was measured by an Agilent 1100 HPLC system at 315 nm using a C_{18} column (ZORBAX SB-C18 column, 5 μm, 4.6 mm × 250 mm, USA). The mobile phase consisted of methanol/acetonitrile/0.05% phosphoric acid 24/46/30 (v/v/v) under isocratic elution with a flow rate of 1.0 mL/min (Fig. S5). After 24 h solubility experiments, the undissolved solids were filtered, dried and analyzed by PXRD.

Intrinsic dissolution rate (IDR) was measured on a RCZ-1A Dissolution Tester (Shanghai Huanghai Yaojian Instrument Distribution Co., Ltd.) according to the reported method [27]. 150 mg of the solid samples were compressed to 1.3 cm^2 disk using a rotary tablet press under 2.5 ton for 1 min. Paddle stirring method was

Table 1
Crystal data and structure refinement for HFEB-2MI and HFEB-DPA salts.

	HFEB [12]	HFEB-2MI	HFEB-DPA
Empirical formula	$C_{16}H_{16}N_2O_3S$	$C_{18}H_{19}N_3O_3S$	$C_{26}H_{25}N_5O_3S$
Formula weight	316.37	357.42	487.57
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	$P2_1/c$	P-1	P-1
a (Å)	4.6756(4)	8.8764(18)	8.1566(7)
b (Å)	17.6317(15)	10.137(2)	10.7944(9)
c (Å)	19.4992(15)	10.849(2)	15.0785(11)
α (°)	90	104.40(3)	95.472(7)
β (°)	94.523(8)	106.74(3)	93.227(7)
γ (°)	90	94.68(3)	111.630(8)
V (Å^3)	1602.5(2)	893.0(3)	1222.47(17)
Z	4	2	2
T (K)	298(2)	298(2)	298(2)
D_{calcd} (g cm^{-3})	1.311	1.329	1.325
Absorption coefficient (mm^{-1})	0.215	0.203	0.170
Parameters	207	256	327
F(000)	664	376	512
Goodness-of-fit on F^2	0.982	1.079	1.007
Reflns. collected	6299	8171	8362
Unique reflns	2099	3920	4299
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0549$ $\omega R_2 = 0.1043$	$R_1 = 0.0419$ $\omega R_2 = 0.1334$	$R_1 = 0.0455$ $\omega R_2 = 0.1012$
Δρmax/Δρmin (e·Å^{-3})	0.191/−0.215	0.359/−0.284	0.166/−0.293
CCDC	933586	1497075	1497077