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Feature article

Syntheses and characterizations of two curcumin-based cocrystals

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ABSTRACT

Two pharmaceutical cocrystals, named Jilin University China–Cocrystal-14 (JUC-C14) and Jilin University China–Cocrystal-15 (JUC-C15), which were composed of curcumin and 4, 4′-bipyridine-N, N′-dioxide, were successfully prepared by crystal engineering strategy. The crystal structures of the two cocrystals were solved and refined by single crystal X-ray diffraction. It is indicated that the crystal structures are assembled via intermolecular interactions including hydrogen bonds and π···π stacking. Additionally, in the structure of JUC-C15 curcumin existed in a di-keto form which is rare in other reported curcumin polymorphs. Power X-ray diffraction, Fourier-transform infrared spectra, thermogravimetric analyses and differential scanning calorimetry were executed as well to confirm the formation of the cocrystals.

Contents

During the past decade, cocrystallization has rapidly developed as an emerging approach to design and prepare pharmaceutical materials owing to the development of crystal engineering and supramolecular chemistry [1–4]. Most pharmaceutical cocrystals were constructed by active pharmaceutical ingredient (API) and cocrystal former (CCF) via intermolecular interactions such as hydrogen bonds, π···π stacking interactions, van der Waals interactions and halogen bonding [5–7]. Pharmaceutical cocrystals have attracted much attention as functional solid state materials mainly because of their ability of altering the physicochemical properties such as stability, solubility, melting point, bioavailability, and dissolution rate compared to the original APIs while retaining their pharmaceutical activities [8–12]. For most of the reported pharmaceutical cocrystals, API and CCF were connected via hydrogen bonds to form supramolecular synthons. According to the classification of Zaworotko, the synthons were subclassified to heterosynthon and homosynthon [13]. Among the heterosynthons, amide-pyridine-N-oxide has a high frequency of occurrence as CCF compared to other heterosynthons, such as carboxamide-pyridine-N-oxide heterosynthon and sulfonamide-pyridine-N-oxide [14,15]. In this paper, 4,4′-bipyridine-N,N′-dioxide (BPNO) which is a strong acceptor can form hydrogen bonds with hydroxyl groups to construct supramolecular synthon was selected as CCF.

Curcumin is a hydrophobic compound having the chemical name of (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione). It is derived from the rhizome of *Curcuma longa*, with a wide variety of medicinal benefits, such as anticancer, anti-inflammatory, anti-HIV, antimalarial, and antioxidant [16–18]. Commercially available curcumin crystals are monoclinic and the space group is P2/n. The molecule exists as tautomers of enolic form (enol) and β-diketonic form (di-keto) which are shown in Scheme 1. Besides, curcumin exists primarily in its enolic form in solution [19]. Nangia and co-workers have prepared two new crystalline polymorphs and an amorphous phase of the active ingredient curcumin [20]. After that, the same group reported two cocrystals of curcumin with resorcinol and pyrogallol via solid-state and liquid-assisted grinding strategy. These cocrystals exist primarily in

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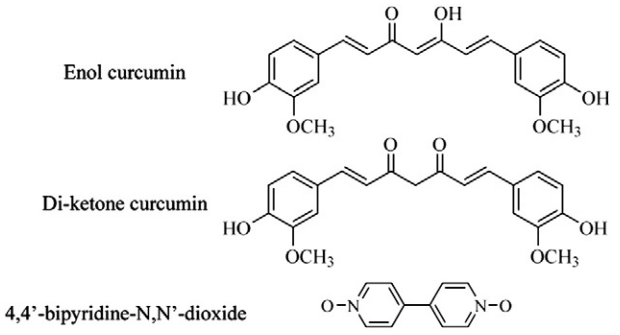

Scheme 1. Molecular structures of two forms of curcumin (enol and di-keto tautomers) and the co-crystal former of 4, 4′-bipyridine-N, N′-dioxide.

the enolic form with the O–H···O hydrogen bonds between the carbonyl group of curcumin and the phenolic OH groups of the cocrystal formers [21]. In this research, two new crystalline curcumin-based cocrystals were successfully synthesized using BPNO as CCF. One of them has a rarely observed di-keto form, which is probably achieved via the assistance of the solvent molecules.

Cocrystallization of curcumin and 4, 4′-bipyridine-N, N′-dioxide was carried out by slow evaporation from a different solution that contains stoichiometric amounts of the API and CCF. First, equal quality of curcumin and BPNO was suspended in a mixed solvent of absolute ethanol and acetone and stirred at room temperature. After the suspension was heated at 60 °C for 72 h, the mixture was completely dissolved and allowed to be evaporated at room temperature for 24 h. Yellow block crystals of JUC-C14 were obtained. The details of refinement and crystallographic data of JUC-C14 are listed in Table 1, and the hydrogen bonding distances and angles are detailed in Table 2.

The single-crystal X-ray diffraction confirmed that in JUC-C14 the curcumin and BPNO cocrystallized to form the cocrystals. JUC-C14 is resolved as a triclinic system and space group of P-1 with an asymmetric unit containing one curcumin molecule and one BPNO molecule. There were two types of hydrogen bonds in the structure: the intramolecular hydrogen bonds and the intermolecular hydrogen bonds. As shown in Fig. 1a, curcumin molecules form two intramolecular O–H···O hydrogen bonds: one is formed by connecting enolic OH with the nearby carbonyl group [O(3)–H(32)···O(4), 1.79 Å, 2.518(2) Å, 147°]. Single-crystal X-ray analysis revealed that curcumin existed in the enol form in JUC-C14,

Table 1
Crystal data and structure refinements.

Compound	JUC-C14	JUC-C15
Chemical formula	$C_{31}H_{28}N_2O_8$	$C_{33}H_{36}N_2O_{10}$
Formula weight	556.55	620.64
Crystal system	Triclinic	Orthorhombic
Space group	*P*-1	*Pccn*
a (Å)	9.8370 (9)	18.5630 (9)
b (Å)	10.5287 (9)	9.5014 (5)
c (Å)	14.3413 (13)	17.4834 (8)
α (°)	111.2870 (10)	90.00
β (°)	95.819 (2)	90.00
γ (°)	101.2270	90.00
V (Å^3)	1333.2 (2)	3083.6 (3)
Z	2	4
ρcalc (g/cm^3)	1.386	1.337
μ (mm^{-1})	0.101	0.099
N ref	6808	18188
T (K)	296 (2)	296 (2)
F (000)	584.0	1312.0
R int	0.0182	0.0216
Goodness-of-fit on F^2	1.083	1.081
R_1^a, wR_2^b [I > 2σ(I)]	0.0448, 0.1208	0.0732, 0.2266
R_1^a, wR_2^b (all data)	0.0587, 0.1299	0.09344, 0.2488

Table 2
Hydrogen Bond Length and the Angles of JUC-C14, JUC-C15.

	D–H···A	d (H···A)	D (D···A)	θ/°
JUC-C14	O(1)–H(1)···O(7)	1.86	2.614 (2)	153
	O(3)–H(32)···O(4)	1.79	2.518 (2)	147
	O(6)–H(33)···O(5)	2.23	2.6729 (19)	115
	O(6)–H(33)···O(8)	2.02	2.653 (2)	134
JUC-C15	O(2)–H(2)···O(1)	2.23	2.6652	114
	O(2)–H(2)···O(4)	1.95	2.6306	140
	C(17)–H(17B)···O(3)	2.21	2.9576	134

indicated by the intramolecular hydrogen bond which helps to stabilize the enol tautomer. The other hydrogen bond is formed between phenolic O–H group and the methoxy group via O(6)–H(33)···O(5) [2.23 Å, 2.6729(19) Å, 115°]. Besides the intramolecular hydrogen bonds, each curcumin molecule forms two intermolecular hydrogen bonds with two neighbouring BPNO molecules. The O atom of the BPNO pyridine ring interacts with the hydroxyl of the phenol ring of curcumin through O(1)–H(1)···O(7) and O(6)–H(33)···O(8) intermolecular hydrogen bonds, with O···O distances of 2.614(2) Å and 2.653(2) Å, respectively. Meanwhile, π···π interactions (3.485 Å) between the aromatic rings of two BPNO molecules in the adjacent chains result in the 1D double chain (Fig. 1b). Then, the 1D double chain repeats along the *a* axis and *b* axis to construct the long range ordered cocrystal structures as shown in Fig. 1c.

When ethanol for the synthesis of JUC-C14 was replaced by equal molar of methanol, the product was red crystals, named JUC-C15. The crystal structure of JUC-C15 was solved in the orthorhombic space group *Pccn* with half curcumin molecule, half BPNO molecule and one methanol molecule in the asymmetric unit. There are strong intermolecular O–H···O supermolecular heterosynthons between curcumin molecules and BPNO molecules which are the same as JUC-C14 (Fig. 2a). However the difference between JUC-C14 and JUC-C15 is that the methanol molecules interact with the carbonyl group of the curcumin molecules with a hydrogen bond distance of 2.953(8) Å. The interaction between methanol and curcumin results in the di-keto structure of curcumin molecule in JUC-C15, which is extensively used to construct curcumin metal complexes [22], but rarely reported in all the other curcumin polymorphs [20,21]. Being different from JUC-C14, in JUC-C15 a π···π interaction occurred between one pyridine ring of the BPNO and one phenyl ring of the curcumin. Similarly, the other pyridine ring of the same BPNO molecule interacts with a phenyl ring from another adjacent curcumin molecule (Fig. 2b), thus resulting in the formation of a 2D net structure as shown in Fig. 2c. The distance between two aromatic rings is 3.457 Å. The distances of the hydrogen bonds are summarized in Table 2. Methanol molecules interacting with the carbonyl on the other molecules were also reported by Michael J. Zaworotko and co-workers. They synthesized two cocrystals of quercetin:caffeine (QUECAF) and quercetin:caffeine:methanol (QUECAF·MeOH). The methanol molecule formed an O–H···O H-bonding with the carbonyl on the imide ring of a CAF molecule [5]. Then different cocrystals may be obtained through the methanol molecule adjusting the structure.

The PXRD was executed to detect the phase purity of JUC-C14 and JUC-C15 at room temperature. The experimental patterns of each cocrystal exhibited good agreement with those simulated from the single-crystal structures, verifying that the cocrystal has been successfully formed (Fig. 3). Especially, the PXRD patterns of JUC-C14 and JUC-C15 reveal the isostructural nature of two cocrystals. The DSC curves of cocrystals are shown in Fig. 4, which are similar to QUECAF and QUECAF·MeOH [5]. It can be found that their melting points are both 211 °C, which are different from the active pharmaceutical ingredient and the co-crystal former. The changes of the melting point indicate that the cocrystals have been successfully prepared.

In summary, two curcumin based cocrystals with BPNO as the co-crystal former were successfully synthesized through crystal engineering. Both cocrystals possess intermolecular O–H···O hydrogen