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Solid-state cocrystal formation between acyclovir and fumaric acid: Terahertz and Raman vibrational spectroscopic studies

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ABSTRACT

The vibrational spectra of solid-state acyclovir, fumaric acid and their cocrystal have been investigated by using terahertz time-domain spectroscopy (THz-TDS) and Raman spectroscopy at room temperature. In experimental THz spectra, the cocrystal has absorption peaks in 0.65, 0.94 and 1.10 THz respectively, while the raw materials are absolutely different in this region. Raman spectra also show similar results about differences between the cocrystal and raw materials. Density functional theory (DFT) was performed to simulate vibrational modes of different theoretical forms between acyclovir and fumaric acid. The calculation of theoretical THz spectra shows that O8═C7—N1—H27 and the carboxyl group —COOH establish a dimer theoretical cocrystal form by the hydrogen bonding effect, which makes contributions to the formation of absorption peaks in 0.70, 1.01 and 1.34 THz, and agrees well with experimental observations. The theoretical Raman result also indicates that this dimer form matches with experimental results. The characteristic bands of the cocrystal between acyclovir and fumaric acid are also assigned based on the simulation results from the DFT calculation.

1. Introduction

Acyclovir (hereinafter simplified as ACV) is an antiviral drug for the treatment of infections such as herpes simplex virus type 1 (HSV-I), 2 (HSV-2) and varicellar-zoster virus (VZV) [1,2]. It is one of the most commonly used medicines, however, the drug has several problems due to its physicochemical properties. For example, low bioavailability of ACV in solid pharmaceutical drugs is related to its poor solubility in aqueous media [3] and its oral bioavailability is approximately 15–20%, with a short half-life of just 3 h [4–7]. More than half of all medicines are administered as salts, but this approach has some limitations compared with cocrystals. In fact, salt formation is confined to acid-base reaction, governed by an appropriate ΔpK_a value, while cocrystals offer a different pathway, where any pharmaceutical substance could potentially be cocrystallized without having ionizable groups [8]. Furthermore, there is a great number of potential nontoxic cocrystal formers (CCF) that can be used in cocrystallization [9,10]. One of the most important advantages of cocrystal is that the physicochemical properties of the drug can be improved without any change of active pharmaceutical ingredients (API), such as bioavailability, stability, mechanical behavior, solubility and dissolution rate [11–14].

Kristl [15] firstly found that ACV hydrated form has a better stability and quicker dissolution rate than the solid-state anhydrous forms. Katsuhide Terada [16] used powder x-ray diffraction, differential scanning calorimetry and made a very detailed analysis about the transformation between anhydrous forms and hydrated forms of ACV. Takaaki Masuda [14] reported the physicochemical properties of cocrystals between ACV and citric acid based on mid-infrared (mid-IR) spectroscopy, differential thermal analysis and also drug/excipient composition analysis. Giovanna Bruni [8] employed optical spectroscopy techniques, solid-state NMR and microscopic analysis to study solubility and dissolution rates between hydrate of ACV-fumaric acid (FA) cocrystal and ACV-glutaric acid cocrystal. Tong-Bu Lu group [17] enhanced the solubility and permeability of ACV by crystal engineering approach and achieved ACV—FA—H_2O cocrystal successfully. Anindita Sarkar [18] used the above relative techniques and also investigated the physicochemical properties, such as stability, solubility and dissolution rate between hydrated form of ACV and FA, malonic acid and tartaric acid. However, except for the physicochemical properties, the structural investigation also plays an important role in knowing more information about pharmaceuticals from molecular level comprehensively. Vibrational spectroscopic techniques, such as Raman and terahertz (THz) spectroscopy, could be capable of providing such structural information both from intramolecular and/or intermolecular interactions of specific pharmaceuticals, especially in their solid-state characterization. Raman spectroscopy is based on Raman scattering effect and an analytic technique which applied in analyzing vibration and rotation information of molecular and structures of materials [19,20]. Meanwhile, THz spectroscopy is an alternative and novel technique for study the structural

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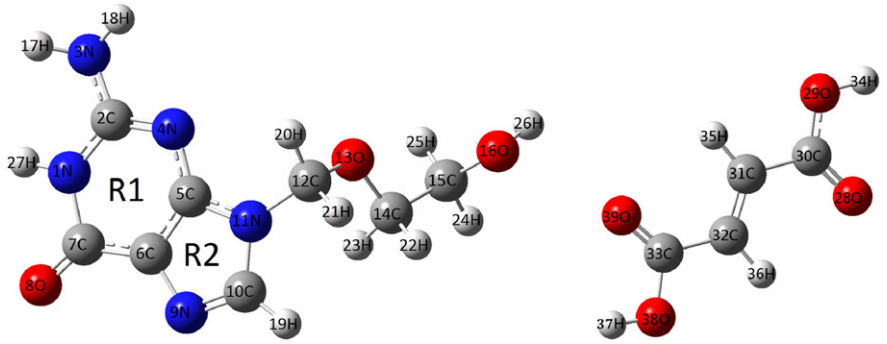
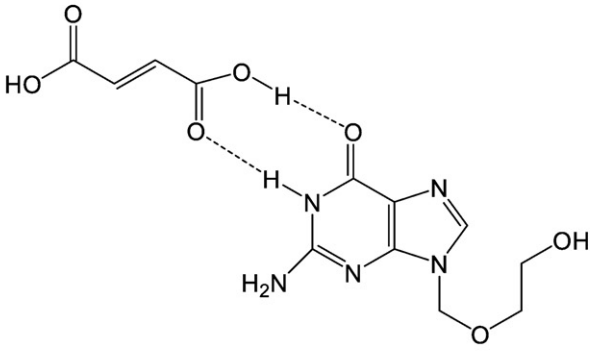
and interactions of chemical materials [21,22]. It is highly sensitive to the hydrogen bonding and has advantages of nondestructive detection and has been used in the cocrystal detection [23,24].

In the present work, THz and FT-Raman vibrational spectroscopy were used for the structural investigation of anhydrous ACV, FA and their cocrystal. FA, an ideal candidate for CCF, was used to form the



(a)



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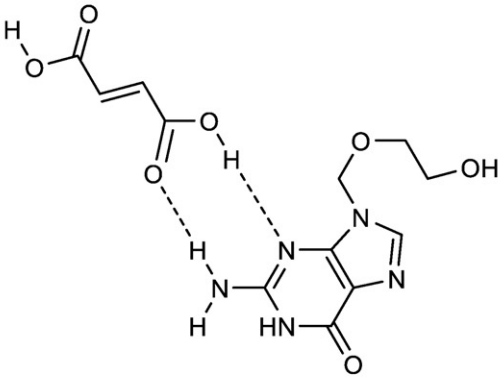

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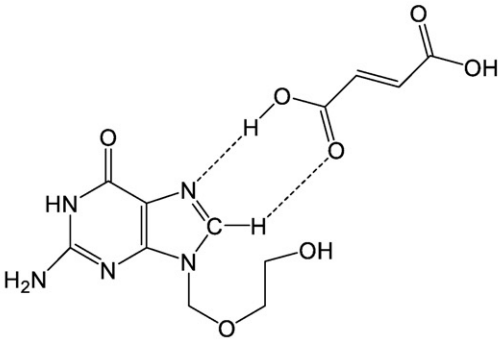

(d)

Fig. 1. Molecular structures of ACV, FA (a), and three kinds of possible theoretical cocrystal forms between them (form I (b), form II (c) and form III (d)).