Terahertz Investigation of Drug-Drug Cocrystal Involving 4-aminosalicylic Acid and Pyrazinamide

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***Abstract*—The drug-drug cocrystal between pyrazinamide (PZA) and 4-aminosalicylic acid (PASA) was prepared with the water-assisted grinding approach. The THz absorption spectra presented that there were significantly different peaks between the parent materials and the cocrystal. In addition, density functional theory (DFT) calculations were used to simulate cocrystal structures and provided vibrational modes of the PASA-PZA cocrystal.**

I. INTRODUCTION

Pharmaceutical cocrystals are crystalline single-phase materials synthesized by two or more solid-state compounds via non-covalent or nonionic intermolecular interactions in a predesigned molar ratio[1]. The 4-aminosalicylic acid (PASA) is an oral second-line anti-TB drug that is extensively used as to inhibit the growth and reproduction of mycobacterium tuberculosis. Its molecular structure is presented in Figure 1(left). However, as an unstable compound, PASA may tend to undergo an irreversible decarboxylation reaction in acid medium to yield a toxic product called “m-aminophenol”[2]. It is vital to find a method to prevent decarboxylation of the active pharmaceutical ingredient (API) [3]. Cocrystallization is such an approach that stops PASA from decarboxylation by improving its stability. Likewise, as the typical anti-tubercular drug, pyrazinamide (PZA) is a typical and essential first-line drug. Figure 1 (right) illustrated its molecular structure. PZA can be used independently or in fixed-dose combination (FDC) with rifampicin and ethambutol, but the combined chemotherapy has a better anti-TB effect[4-6]. In this work, the structures and spectra of PASA, PZA, their physical mixture and the corresponding drug-drug cocrystal were analyzed using THz vibrational spectroscopic techniques.

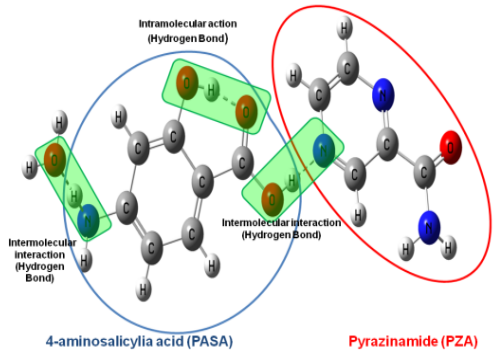

Figure 1. Molecular structures of 4-aminosalicylia acid (PASA, left) and pyrazinamide (PZA, right).

II. RESULTS

Figure 2 showed the THz absorption spectra of PASA, PZA, the physical mixture and the grinding PASA-PZA drug-drug cocrystal in the range of 0.20-1.60 THz. It was clearly observed that, three characteristic peaks of physical mixture were observed at 0.65, 1.26, 1.02, and 1.44 THz (Figure 2 (c)), respectively. Meanwhile, the corresponding drug-drug cocrystal exhibited three characteristic peaks at 0.65, 1.01, and 1.38 THz (Figure 2 (d)), respectively. The absorption peaks at 0.65 and 1.26 THz were mainly indexed to PASA at 0.65 and 1.27 THz (Figure 2 (a)), while the 1.44 THz peak was related to PZA at the same intensity band. PZA showed weak peaks at 0.51 and 0.73 THz (Figure 2 (b)), all the peaks are consistent with the previous results from Wang Q. et al[7]. To sum up, the spectrum of physical mixture was just on the basis of the linear addition of two parent materials (PASA and PZA). Besides the peak at 0.65 THz, the spectral results of the physical mixture were distinctly different from the PASA-PZA drug-drug cocrystal, especially the 1.01 THz position, which indicated that potent hydrogen bond through intra-molecular and/or intermolecular interactions was involved in such cocrystallization during the solvent-drop grinding process. Thus, the THz spectroscopy can offer obvious fingerprint information for various molecular structures of solid-state pharmaceutical cocrystalline forms.

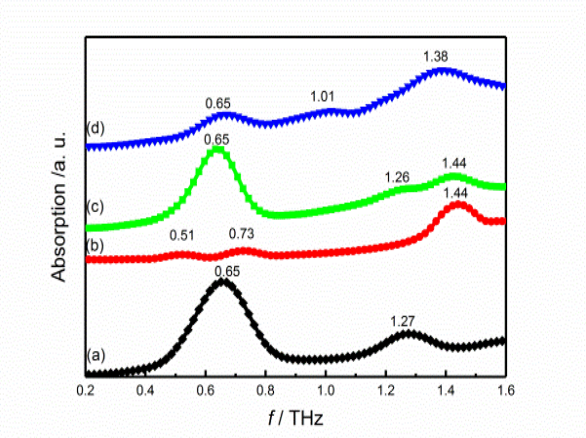

Figure 2. The THz spectra of PASA (a), PZA (b), physical mixture (c), and PASA-PZA cocrystal (d).

Figure 3 compared the THz absorption spectra between the experimental results and simulated calculations of PASA-PZA drug-drug cocrystal. As exhibited in the figure, the theoretical form at 0.45, 0.65, 1.07, and 1.43 THz

(Figure 3 (a)) showed four characteristic peaks, which were highly consistent with the experimental results at 0.65, 1.01, and 1.43 THz (Figure 3 (b)), respectively. Compared with the simulated calculations, the peak at 0.45 THz in the experimental results did not appear, and the reason for this inconsistency phenomenon may because our calculation was on basis of a single molecule structure while disregarded the intermolecular force in the crystalline unit cell. Meanwhile, two characteristic peaks of the experimental results showed red shifts relative to the theoretical form, in addition to the basis set choice, this spectral shift can be explained as the theoretical simulation was carried out at absolute zero temperature, but the experimental THz absorption spectra was obtained at room temperature[8].

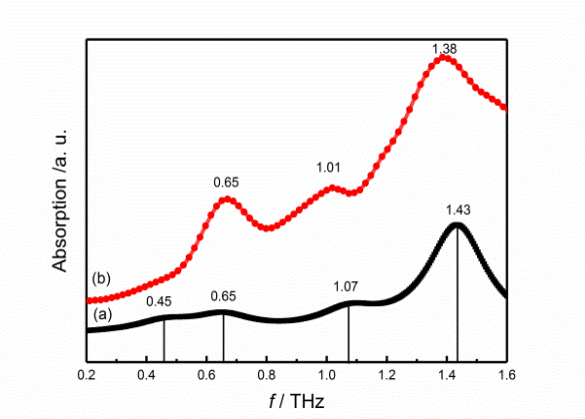

Figure 3. The comparison of THz spectra between simulated (a) and experimental (b) results of PASA-PZA cocrystal in the spectral region of 0.20–1.60 THz.

Table 1 presented the distribution of all these vibrational modes provided by the dynamic observation help of Gaussian-View software. The peak at 0.45 THz position in theoretical results was associated with the PASA, PZA torsional vibration and H_2O out-plane bending vibration. The experimental peak at 0.65 THz position, which was totally agreement well with the theoretical spectrum, may result from the PASA, PZA torsional vibration and H_2O torsional vibration. The characteristic peak at 1.01 THz showed little difference with the theoretical calculation mode at 1.07 THz, which was caused by the in plane bending vibration of PASA and PZA as well as the in-plane bending vibration of H_2O. The PASA torsional vibration, PZA out of plane bending vibration, H_2O out-plane bending vibration, and O27=C26-N28-H29H30 torsional vibration together made contribution to the 1.38 THz distribution. At a result, the connecting experimental THz absorption spectra and DFT simulation helped us to better understand the intermolecular hydrogen bonding effect between PASA and PZA molecules, and also showed different peaks of the PASA-PZA cocrystal compared with the two starting parent compounds.

Table 1. Vibrational modes assignment of the PASA-PZA drug-drug cocrystal shown in the THz spectrum.

Experimental result f/THz	Theoretical calculation f/THz	Mode assignment
—	0.45	PASA and PZA torsional vibration; H_2O out-plane bending vibration
0.65	0.65	PASA and PZA torsional vibration; H_2O torsional vibration
1.01	1.07	PASA and PZA in plane bending vibration; H_2O in-plane bending vibration
1.38	1.43	PASA torsional vibration; PZA out of plane bending vibration; O27=C26-N28-H29H30 torsional vibration; H_2O out-plane bending vibration

III. SUMMARY

The structure and vibrational mode of PASA-PZA drug-drug cocrystal was characterized by THz-TDS combining with DFT calculations. The results indicated that the cocrystalline structure was formed by the inter-molecular hydrogen bonding of carboxyl pyridine heterozygote (carboxylic···pyridine). The cocrystal formulation confirmed by our work may provide an immediate solution as adjunctive therapy, largely improving the efficacy of anti-TB treatment and mitigating the issue of multi-drug-resistant tuberculosis. Notably, it is easily to discern the structural information of drug-drug cocrystal by comparing the experimental results with theoretical ones. The present study demonstrates the superiority of vibrational spectroscopy, which contributes to directly analyzing the material structures, distinguishing the diverse molecular configurations, as well as the inter-molecular and/or intra-molecular hydrogen bond interactions in the emerging pharmaceutical cocrystallization field.

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