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Raman and terahertz spectroscopical investigation of cocrystal formation process of piracetam and 3-hydroxybenzoic acid

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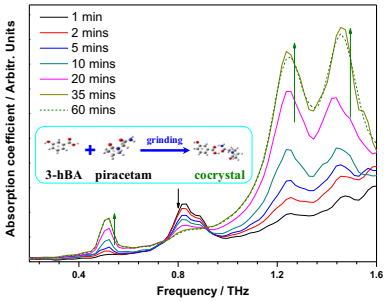
HIGHLIGHTS

- Raman and THz-TDS spectra of piracetam and its pharmaceutical cocrystal formed with 3-hydroxybenzoic acid are reported.
- The piracetam cocrystal formation process is monitored from both Raman and THz-TDS spectra.
- THz-TDS is potential to directly characterize the pharmaceutical cocrystal reactions in solid-state.

GRAPHICAL ABSTRACT



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ABSTRACT

Cocrystallization can improve physical and chemical properties of active pharmaceutical ingredient, and this feature has great potential in pharmaceutical development. In this study, the cocrystal of piracetam and 3-hydroxybenzoic acid under grinding condition has been characterized by Raman and terahertz spectroscopical techniques. The major vibrational modes of individual starting components and cocrystal are obtained and assigned. Spectral results show that the vibrational modes of the cocrystal are different from those of the corresponding parent materials. The dynamic process of such pharmaceutical cocrystal formation has also been monitored directly with Raman and THz spectra. The formation rate is pretty fast in first several 20 min grinding time, and then it becomes slow. After ~35 min, such process has been almost completed. These results offer us the unique means and benchmark for characterizing the cocrystal conformation from molecule-level and also provide us rich information about the reaction dynamic during cocrystal formation process in pharmaceutical fields.

Introduction

Pharmaceutical cocrystals formed from an active pharmaceutical ingredient (API) and a cocrystal former (CCF) show unique physicochemical properties compared to their parent APIs, such as dissolution rate, solubility, hydration stability and even bioavailability behavior [1–4]. Cocrystallization has special potential in improving characteristics and therapeutic utilities of drugs without altering the chemical nature and bioactivity of API. This feature makes cocrystal become an important branch in the field of pharmaceutical development. During the formation process of cocrystals, API and CCF interact due to non-covalent weak intermolecular interactions such as hydrogen bonding and van der Waals forces [5,6]. Candidates for crystallizing cocrystals with particular structural motifs for achieving desired physical properties are chosen according to the knowledge about intermolecular interactions between API and the appropriate CCF. Hydrogen bonds are among the strongest and most preferentially orientational intermolecular interactions, so that the presence of hydrogen bond donor and/or

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acceptor sites in API and CCF is usually a prerequisite factor in forming cocrystals [5]. Piracetam is a cyclic derivative of GABA (γ-aminobutyric acid), with chemical name 2-oxo-1-pyrrolidine acetamide. It is widely used for the treatment of post-stroke aphasia, epilepsy, cognitive decline following heart and brain surgery, and dementia [7]. Based on the tendency of hydrogen bonding motifs between amides and carboxylic acids, piracetam (as API) and 3-hydroxybenzoic acid (3-hBA, as CCF) are chosen as suitable model molecules in this study to investigate the formation of corresponding pharmaceutical cocrystal with chemical-green grinding method.

It is of great importance to use specific techniques to probe the cocrystal characteristics in order to directly obtain the conformational and dynamic information during reaction process involving two or more molecular crystals in-line to better know the cocrystal formation mechanism. Vibrational spectroscopy methods are well-built tools for the characterization of pharmaceutical compounds. Focusing on the investigation of the fundamental vibrational modes, the methods contain traditional Fourier transformation-infrared (FT-IR) absorption [8–10], Raman scattering [11–13], and also terahertz (THz) spectroscopy [14–18]. During the last 20 years the use of Raman and THz spectroscopical techniques in the study of solid-state pharmaceutical compounds has been growing rapidity. A detailed analysis of the literature in this filed reveals that the increased interest in vibrational spectroscopy including to monitor and investigate the solid-state polymorphism [19,20], crystallinity [21–23], mechanochemical solid-state reactions [24–26], and so on. The most frequent application of vibrational techniques in pharmaceuticals is based on the high sensitivity and selectivity in producing fingerprints of the crystalline structure related modifications in a molecular compound [13,18,19]. Vibrational spectroscopy methods have been demonstrated to be a high potential alternative to analytical tools such as X-ray power diffractometry (XRPD) and differential scanning calorimetry (DSC) in solid-state identification and quantification [14,15,18,19], especially in-line reaction process monitoring involving two or more molecular crystals [14,15] to obtain more useful information in pharmaceutics-related research fields.

In this study, Raman and THz vibrational spectroscopy of cocrystal obtained between API piracetam and cocrystal former 3-hBA compounds under solid-state grinding method has been obtained. The experimental results show large difference among spectra of the formed cocrystal and the involved parent starting molecules, and the major vibrational modes are assigned. With grinding method, the real reaction process of the cocrystal formation could be monitored directly from both Raman and THz spectroscopical techniques. The results indicate that Raman and THz vibrational technologies can offer us attractive experimental methods to identify and characterize pharmaceutical cocrystals, and also provide us potential tools for further monitoring the real-time reaction dynamic of cocrystals in-line to better know the corresponding reaction mechanism from molecule-level in pharmaceutical industry.

Experimental methods

Chemicals and sample preparation

The 3-hBA and piracetam samples were purchased from Sigma–Aldrich (structures shown in Fig. 1) and used without further purification. The API piracetam and cocrystal former 3-hBA were ground before mixing to achieve several micrometer particle size. Physical mixture was obtained by gently mixing two compounds above at a 1:1 M ratio in a glass vial by using a vortex mixer. Grinding cocrystal was performed by co-grinding

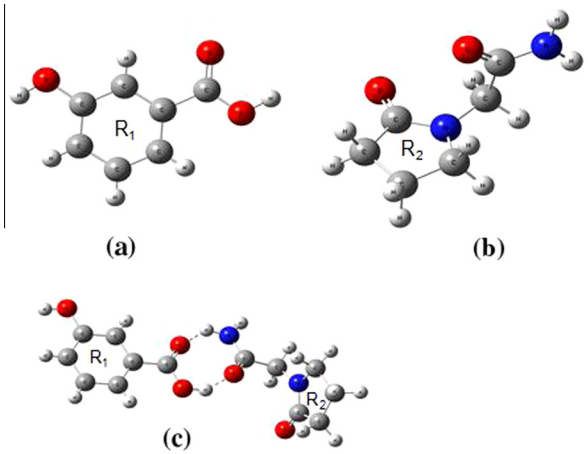

Fig. 1. Molecular structures of (a) 3-hBA, (b) piracetam, (c) cocrystal of piracetam and 3-hBA.

piracetam with 3-hBA at 1:1 M ratio in 25 mL stainless steel milling jars using a planetary ball mill (QM-3SP, gear type, Nanjing University Instrument Plant) with a frequency of 25 Hz at room temperature. A measured amount of product produced in the solid-state reaction at different grinding times was taken out for further spectra analysis. To confirm the formation of grinding cocrystal with dry-grinding method, the authentic solvent cocrystal with slow solvent evaporation method was also obtained by equimolar piracetam and 3-hBA dissolving in amount of acetonitrile at ambient temperature. The solution was slowly evaporated at room temperature during several days to produce needle-like crystal.

All the samples were weighted into ~150 mg aliquots and poured into a steel die and subjected to ~4 MPa pressure for several minutes. The sample discs ~13 mm in diameter, ~1.5 mm thick were obtained and sealed in plastic bags before spectroscopical analysis.

Apparatus and procedure

Raman spectra of all samples were obtained using Fourier Transform Raman (FT-Raman) spectrometer (Thermo Nicolet 960, USA) with diode pumped 1064 nm solid-state laser as the near-IR source. Spectra were acquired over 500 scans at 2 cm^{-1} resolution and a laser operating power ~150 mW. Total analysis time per sample was of the order of 6 min.

Terahertz time-domain spectroscopy (THz-TDS) measurement was performed using a commercial *Zomega-2* time-domain THz spectrometer (Zomega Terahertz Corp., Troy, USA) for which the experimental setup has been described previously in detail [27]. The THz beam is produced by a Ti:Sapphire oscillator ultrafast laser with a 75 MHz repetition rate, 780 nm center wavelength and ~100 fs pulse duration. The terahertz spectrometer was purged with high-purity nitrogen gas to reduce absorption from water vapor. A total of three THz spectra representing three complete sets of sample and reference measurements were averaged for each final spectrum. The spectral resolution of the terahertz spectrometer is around 0.02 THz (~0.6 cm^{-1}) and total analysis time per sample was of the order of 4 min. The time-domain of the THz electric field was recording for the reference (without sample) and each sample. After the fast Fourier transform (FFT) operation, the THz absorption spectra were obtained by dividing the sample response by that of the reference.