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A terahertz spectroscopic imaging system was fabricated for the detection of two-dimensional molecular distributions in pharmaceutical tablets based on absorption peaks of intermolecular or intramolecular hydrogen bonds in crystals. The terahertz imaging system consists of a terahertz time-domain spectrometer and a three-dimension translational stage. Using the system, we obtained frequency-dependent terahertz images of famotidine polymorphic forms A and B. An offset subtraction process is useful for detecting the distribution in an inhomogeneous tablet containing a mixture of the two forms. The terahertz imaging technique is a valuable tool for the analysis of polymorphic forms of crystal in inhomogeneous pharmaceutical tablets.

Keywords Famotidine; hydrogen bonding; pharmaceutical tablets; polymorphism; terahertz imaging

Introduction

Terahertz (THz) waves occupy the region of the electromagnetic spectrum between microwaves and infrared light, which have frequencies in the range from 0.3 to 10 THz, corresponding to wavelengths from 33 to 1000 μm. THz waves are promising for safe, non-destructive inspection applications because they have linear propagation characteristics and, excluding metals and water, can penetrate a large variety of materials, such as plastic, paper, rubber, wood, and ceramics. THz spectroscopy is a kind of vibrational spectroscopy that is useful for studying the vibrational modes of weak chemical bonds, such as intermolecular or intramolecular hydrogen bonds in molecules. Amino acids and pharmaceuticals have hydrogen bonds, which show several peaks in THz spectra and make quantitative analyses possible [1,2]. Applications such as pathological examination of tissues or identification of drugs or explosives in postal packages have received attention [3–5]. THz waves have fundamental differences from X-rays in that they are safe and can use the vibration of molecules to identify specific materials. Terahertz imaging and spectroscopy have also shown attractive results on pharmaceutical applications. THz waves penetrate tablets and

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enable us to inspect the homogeneity of their coating [6] and identify polymorphic forms of crystals [7]. Polymorphic forms of molecular crystals have different crystal structures made by different types of hydrogen bonds between molecules in the crystals, which show different chemical properties, such as solubility, melting point, and bioavailability as drugs. Bioavailability is defined as the rate and extent of drug absorption, which is largely determined by the properties of the dosage form, rather than by the drug's physicochemical properties, which determine absorption potential.

In this paper, we present a two-dimensional THz imaging system fabricated by combining a THz time-domain spectrometer (THz-TDS) and a three-dimensional translational stage to obtain the distribution of two types of polymorphic forms of pharmaceutical molecules in tablets.

Experiments

THz Imaging System

Figure 1a shows a diagram of our THz-TDS imaging system. The system is composed of a THz-TDS with a vacuum chamber mounted on a three-dimensional translational stage. The THz-TDS is composed of a 10-fs near-infrared pulse laser (Integral Pro, Femtolasers), two gallium arsenide photoconductive antennas (AISPEC), a mechanical stage in a delay line, and mirrors. One photoconductive antenna is an emitter, and the other is a detector. The delay line is used to obtain a time-domain spectrum, which is converted to a frequency-domain spectrum by Fourier transformation. The spectrum covers frequencies from 0.1 to 7 THz. The three-dimensional translational stage with 0.1-mm-step resolution and the THz-TDS are controlled by a personal computer to obtain a THz-TD spectrum at each point in a tablet. Figure 1b shows the THz electric field image of a plastic IC card used for public transportation. The parallelogram-like antenna includes six loops of metal wire with 0.5-mm distance, and it was used to evaluate the focal spot and focal position of THz waves in the system before THz spectroscopic imaging measurements.

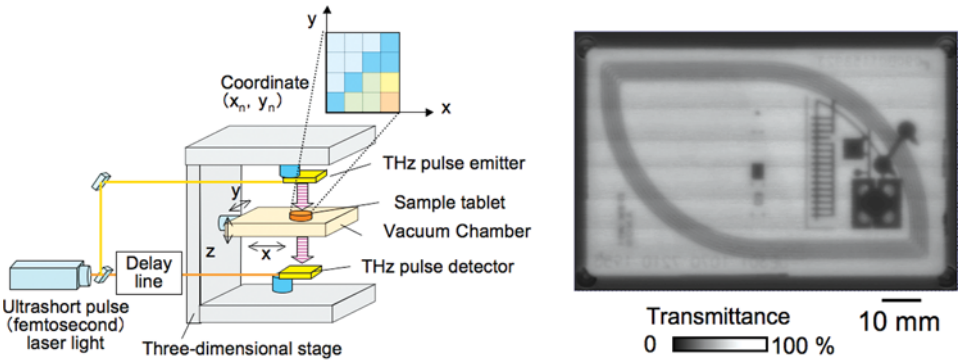

Figure 1. (a) Diagram of THz time-domain spectrometer (THz-TDS) imaging system. (b) THz electric filed image of a plastic IC card (86 mm × 54 mm) used for public transportation.

Sample Preparation

As sample tablets, we used famotidine, which is a histamine H2-receptor antagonist for the prevention and treatment of stomach and intestinal ulcers. Two polymorphic crystalline forms of famotidine, form A and form B, were obtained by recrystallization with hot water and hot methanol aqueous solution, respectively [8]. Original famotidine reagent was purchased commercially (ICN Pharmaceuticals, Inc). The polymorphic form was determined by differential scanning calorimetry (SSIC-5200, Seiko Instruments), which measured heat capacity at the melting point for each form. We crushed the crystals into fine powder and then diluted it to 30% with polyethylene powder (Aldrich). Then tablets were formed from the powder with a mechanical press machine. The tablet diameter and thickness for THz imaging were 10 and 1.5 ± 0.2 mm, respectively.

Results and Discussion

Figure 2a show THz absorbance spectra of the polymorphic forms of famotidine tablets measured in a vacuum chamber. Each spectrum ranging from 0.5 to 2 THz was accumulated 32 times to obtain a better signal to noise ratio. The spectrum of form A has a single main peak at around 1.6 THz and that of form B has main peaks between 1.1 and 1.3 THz. This indicates that the peak positions are different for the two forms, which is in good agreement with a previous report [8]. That means that the low-frequency vibrational modes of famotidine, such as the vibrational modes of hydrogen bonds between molecules, torsion or collective vibrational modes of molecules, or crystal phonon modes, are different in the two forms of crystal. Figure 2b show the differential scanning calorimetry (DSC) spectra of the two forms. The spectra of the two forms provide peaks at 163 and 169°C of heat capacity at melting points, respectively. The temperatures measured in DSC of the two forms agree with previous results [9]. From the DSC result, the purity of form A is about 100% and that of form B is about 85%. In the THz spectrum of form B, the very small peak at 1.6 THz indicates that the sample contains a small amount of form A, which agrees with the DSC data.

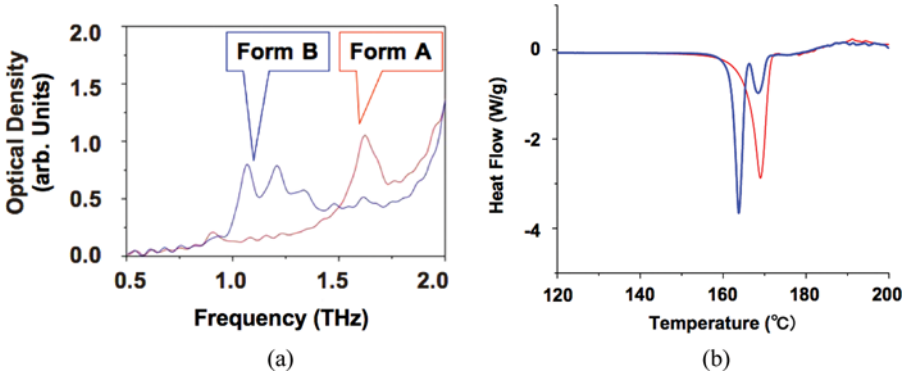

Figure 2. (a) THz absorbance spectra of the polymorphic forms A and B of famotidine tablets measured in the vacuum camber. (b) Differential scanning calorimetry spectra of the two forms.

Figure 3 shows a set of THz transmittance images of three kinds of tablets. Apertures in metal holders for the tablets in the vacuum chamber are 7 mm in diameter, which determines the diameter of each image. The image acquisition time for a tablet is about eight minutes with 1-mm spatial resolution. The images on the left are of polyethylene, which we used as a reference. The ones in the middle are of famotidine form A, and the ones on the right are of form B. From top to bottom, the measurement frequencies were 0.9, 1.2, 1.4, and 1.6 THz. There is no image for form A at 1.6 THz or for form B at 1.2 THz. This is because the vibrational mode of the crystal absorbed almost all the THz waves. This result is good agreement with the THz absorbance spectra of the two forms in Figure 2a.

Figure 4 shows the result of THz image measurement for an inhomogeneous tablet that contained both forms of famotidine. As shown in Figure 4a, the center part of the tablet is a small 1-mm-thick pellet of form B with a 5-mm diameter, which is covered with form A to make an inhomogeneous 1.5-mm-thick tablet with a 10-mm diameter. Figure 4b shows a set of THz absorbance images at 1.2 and 1.6 THz, which correspond to the typical peak positions of form B and form A, respectively. The part of each image outside of the circular sample in Figure 4b, which corresponds to the metal holder, is eliminated. A photograph of the sample is also shown for comparison with the THz images. The image acquisition time for a tablet is about three hours with 0.2-mm spatial resolution. The images in Figure 4 have 25 times higher spatial resolution than the images in Figure 3 and clearly show the molecular distribution of polymorphic forms in the tablet. The image at 1.2 THz is not satisfactory because it does not clearly show the distribution of form B. This phenomenon is caused by the sample structure in which the form B is completely covered by form A. To obtain more detail, we made an offset image at a frequency of 1.5 THz, which is far from the peaks for the two forms. Then, we subtracted the offset image from the raw images as shown in Figure 4c. The results

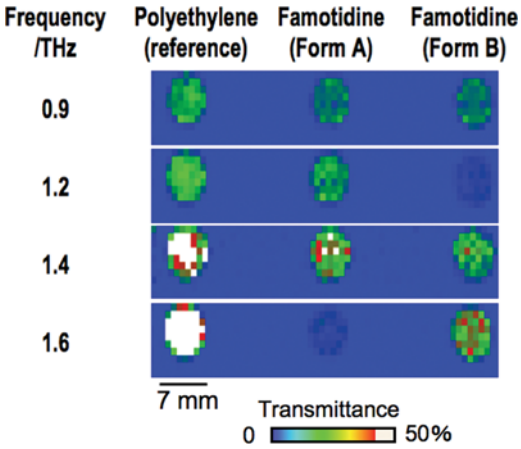

Figure 3. A set of THz transmittance images of three kinds of tablets contained in the metal holder with apertures of 7 mm in diameter. The tablets and metal holder are fixed inside the vacuum camber. The images on the left, middle, and right are of polyethylene as a reference, famotidine form A, and form B, respectively. From top to bottom, the measurement frequencies were 0.9, 1.2, 1.4, and 1.6 THz, respectively.

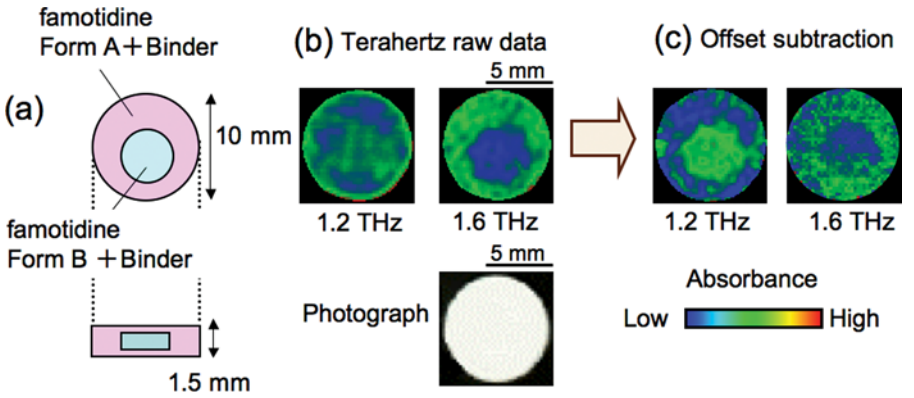

Figure 4. (a) Schematic of an inhomogeneous tablet structure containing both polymorphic forms of famotidine A and B. (b) A set of terahertz absorbance images of the tablet measured at 1.2 and 1.6 THz, which correspond to the typical peak positions of form B and form A, respectively. A photograph of the sample is also shown in the same magnification for comparison with the THz images. (c) A set of THz absorbance images after subtraction of offset images at 1.5 THz from the raw images in (b).

clearly show the distributions of the two forms at both frequencies. The offset subtraction process is useful for detecting the distribution of an inhomogeneous tablet.

Conclusion

A terahertz (THz) spectroscopic imaging system was fabricated for the detection of the two-dimensional molecular distribution in a pharmaceutical tablet. Frequency dependent THz images of famotidine polymorphic forms were obtained using the system. The offset subtraction process is useful for detecting the distribution of an inhomogeneous tablet containing a mixture of the two forms. Among the new types of pharmaceuticals will be multilayer tablets, which can control the release of medicine in different parts of the body. The results show the possibility of using the THz spectroscopic imaging technique for the analysis such multilayer tablets.

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