PREPARATION OF NOVEL OFLOXACIN-DICARBOXYLIC ACID COMPLEX
AND CHARACTERIZATION BY TERAHERTZ SPECTROSCOPY

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ABSTRACT

Many techniques are used for investigating the properties of the solid compounds, for example, powder X-ray diffraction (PXRD), thermal analysis, vibrational spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy. Among these techniques, terahertz (THz) spectroscopy has recently gained more interest in the study of pharmaceutical materials. The femtosecond laser innovation enables to measure a new THz frequency range. Terahertz radiation lies in the frequency gap between the IR and microwave regions. One of the attractive properties of THz radiation is its ability to pass through a wide variety of materials, thus allowing the non-destructive inspection. Terahertz radiation can probe low-frequency crystal lattice vibration and weak intermolecular interactions such as hydrogen bonding and van der Waals force. Several studies have reported that THz spectroscopy can be used for monitoring solid-state dynamic processes (e.g. the dehydration process), differentiating and quantifying the different forms of active pharmaceutical ingredients. In my study, I emphasized on investigating the feasibility of THz spectroscopy as a characterizing tool for solid compounds.

In Part I, the purpose of the study is to examine the potential use of THz spectroscopy for evaluating the formation of cocrystal. Seven known cocrystals were
prepared by cogrinding method and characterized by PXRD and THz spectroscopy. PXRD patterns of the prepared cocrystals were consisted with those of the reported cocrystals; this confirmed the formation of cocrystals. Terahertz spectra of cocrystals were different from those of the components, reflecting the changes in vibrational mode of molecule induced by cocrystal formation. The spectral changes observed are classified into 2 groups: new peak appeared and peak disappeared groups.

In Part II, the purposes of the study are to prepare a novel complex and to investigate the feasibility of THz spectroscopy as a new evaluation method for complex formation. Ofloxacin (OFC) was used because of its poor solubility in water and photoinstability. I prepared a new complex of OFC with oxalic acid (OXA) by means of cogrinding. The obtained complex was characterized by PXRD, FT-IR spectroscopy, solid-state $^{13}$C NMR spectroscopy and THz spectroscopy. The results of PXRD indicated that OFC-OXA complex induced by cogrinding formed presumably at a molar ratio of 1:2. Molecular interaction between OFC and OXA was examined by FT-IR spectroscopy. No spectral changes in functional groups of OFC and OXA were observed by the complex formation, suggesting that the interaction modes of carboxylic and ketonic group with the surrounding functional groups might be similar before and after grinding. The spectral changes were different from those of other cocrystals.
wherein hydrogen bond formation was clearly observed by FT-IR spectroscopy. Solid-state NMR spectroscopy was used to confirm the interaction between OFC and OXA. Chemical shifts found by NMR measurement suggested that the tricyclic aromatic portion and/or methyl group of OFC interacted with the hydroxyl group closed to carbon of OXA. IR and NMR results did not confirm the presence of hydrogen bonding among the functional groups of OFC and OXA. This complex appeared to be formed by weak interaction such as van der Waals and OH-π interaction. From THz spectroscopy measurement, the THz spectrum of complex exhibited a distinctive absorption peak as compared to those of the starting materials. The change observed in the THz spectrum of the complex reflected the weak interaction in the OFC-OXA complex. It is worth noting that THz spectroscopy can probe the weak interactions comparing to FT-IR spectroscopy. In addition to OXA, the complex formation of OFC with other dicarboxylic acids such as maleic acid, glutaric acid and malonic acid was investigated as well. PXRD results suggested that a complex was formed between OFC and dicarboxylic acid at molar ratio of 1:2. Terahertz spectra of all these complexes showed distinct spectra from those of their components, indicating the difference in molecular packing. It can be assumed that THz spectroscopy is an alternative tool to evaluate complex formation.
INTRODUCTION

It has been reported that more than 40% of active pharmaceutical ingredients (APIs) are poorly water soluble\(^1\). These APIs may potentially show slow dissolution, improper bioavailability, and insufficient therapeutic efficacy, especially when APIs were delivered via oral administration\(^2\). Therefore, modification of APIs to improve the solubility, dissolution rate and subsequent bioavailability is needed.

Crystal engineering has recently been investigated as a means of tailoring the physicochemical properties of APIs. It offers many methods to improve the physicochemical properties of APIs, such as complexation and cocrystal formation. The formation of crystalline molecular complexes involves the incorporation of an API with another pharmaceutically acceptable molecule in the crystal lattice. Consequently, this multicomponent crystal will gain a distinct physicochemical profile, which has the potential to improve the properties of API, such as solubility, dissolution rate, and even physical stability\(^2-3\). There are many methods to make the complex e.g. evaporation and coprecipitation. Cogrinding, in which two substances or more are mixed and ground together, is an alternative method to prepare the complex easily without using organic solvents\(^4-6\).
In addition to the modification of APIs, analyzing different solid forms of APIs has become an essential part of drug development. Many techniques are used for investigating the solid-state properties of the solid samples, for example, powder X-ray diffraction (PXRD), thermal analysis, vibrational spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy. Among the vibrational spectroscopies, Raman and IR spectroscopy mainly probe the intramolecular vibration of molecules. On the other hand, PXRD, terahertz (THz) spectroscopy, and various thermal techniques predominantly examine the intermolecular vibration (i.e., at the lattice level). Recently, THz spectroscopy has gained more interest in the study of pharmaceutical materials.

![Terahertz spectral region](image)

**Fig.1.** Terahertz spectral region.

Terahertz spectroscopy covers the electromagnetic spectral range from 3 cm\(^{-1}\) to 600 cm\(^{-1}\), between the IR and microwave regions (Fig. 1.). One THz is equivalent to 33.3 cm\(^{-1}\). One of the interesting properties of THz radiation is its ability to penetrate
various materials such as clothing, paper, cardboard, wood, leather, plastic, and ceramic. This property allows the non-destructive inspection of such items as mail envelopes at post offices and luggages at airports\textsuperscript{15}. Moreover, a THz wave has low energy and thus can be used to detect biological samples\textsuperscript{16}. Terahertz radiation can probe low-frequency crystal lattice vibration and weak intermolecular interactions such as hydrogen bonding and van der Waals force\textsuperscript{15}.

For application, several studies have reported that THz spectroscopy can be used for differentiating and quantifying the different forms of APIs\textsuperscript{10,12,17-20}. Terahertz spectroscopy has also been applied to monitor solid-state dynamic processes such as phase transformation and dehydration process\textsuperscript{21,22}. Although many applications of THz spectroscopy for single component system have been reported, its use for multicomponent system stills a few. For example, there is a report that examining the cocrystal formation of phenazine and mesaconic acid\textsuperscript{23}. Further investigation for general utility of THz spectroscopy as an evaluation method for cocrystal formation is needed. Hence, one part of this study was undertaken to determine the feasibility of using THz spectroscopy as a characterization method for formation of cocrystals.

The purpose of another part is to prepare a novel complex of ofloxacin (OFC) having better physicochemical properties by complex formation. Ofloxacin is a
fluoroquinolone antibiotic drug, which has a broad spectrum of antibacterial activity and good pharmacokinetic properties. It is practically insoluble in water and is photochemically unstable\textsuperscript{24, 25}. The effect of OFC and β-cyclodextrin complexation on the solubility in water and photostability of the drug has been investigated\textsuperscript{24}. However, only a few studies have been reported about improving the solubility and dissolution rate of OFC. This study also aimed to investigate the feasibility of using THz spectroscopy as an evaluation method for complex formation.
EXPERIMENTAL

Part I Characterization of cocrystals by terahertz spectroscopy

Materials

Piracetam (PRC) and polyethylene (ultra-high molecular weight, surface-modified particles, size: 53–75 µm) were obtained from Sigma-Aldrich, Inc. (U.S.A.). Carbamazepine (CBZ), saccharin (SAC), p-hydroxybenzoic acid (HBA), gentisic acid (GTS), anhydrous oxalic acid (OXA), malonic acid (MLO), and maleic acid (MLE) were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Theophylline (TP) and glutaric acid (GLU) were supplied by Nacalai Tesque, Inc. (Japan). All chemicals were of analytical grade and used as received.

Preparation of cocrystals

Cocrystals studied in this work are as follows:

1. PRC/GTS cocrystal at a molar ratio of 1:1
2. PRC/HBA cocrystal at a molar ratio of 1:1
3. CBZ/SAC cocrystal at a molar ratio of 1:1
4. TP/OXA cocrystal at a molar ratio of 2:1
5. TP/MLO cocrystal at a molar ratio of 1:1
6. TP/MLE cocrystal at a molar ratio of 1:1
7. **TP/GLU** cocrystal at a molar ratio of 1:1

All cocrystals were prepared by cogrinding. Firstly, the physical mixtures (PMs) were prepared at a specified molar ratio in a glass vial by using a vortex mixer. The PMs were ground by a vibrational rod mill (CMT T1-200, CMT Co., Ltd., Japan) for 30 min (except for PRC/GTS system 60 min) to obtain the ground mixtures (GMs).

**Powder X-ray diffraction (PXRD) measurement**

Powder X-ray diffraction (PXRD) measurement was conducted by using a Rigaku Miniflex II diffractometer with CuKα radiation (Rigaku Corporation, Japan) at an ambient temperature. Measurements were performed at a voltage of 30 kV, a current of 15 mA, a scanning speed of 4 °/min over a 2θ range of 5–40°.

**Terahertz time-domain spectroscopy (THz-TDS)**

Terahertz time-domain spectroscopy (THz-TDS) measurement was performed by a Rayfact SpecTera (Tochigi Nikon Corporation, Japan) with the transmission method. Tablets, with a diameter of 13 mm and a thickness of 1 mm, were prepared by mixing 10 mg of sample with 90 mg of polyethylene and manual pressing in a mould. Polyethylene is featureless and relatively transparent in the range below 100 cm\(^{-1}\) and is a good diluent for measuring the spectra of APIs\(^{26} \). The measurement covered the range of 0.1–2 THz with a resolution of 0.098 THz (3.255 cm\(^{-1}\)).
Part II Preparation of novel ofloxacin-dicarboxylic acid complex and characterization by terahertz spectroscopy

**Materials**

Ofloxacin (OFC), anhydrous oxalic acid (OXA), maleic acid (MLE), and malonic acid (MLO) were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Glutaric acid was obtained from Nacalai Tesque, Inc. (Japan). Polyethylene (ultra-high molecular weight, surface-modified particles, size: 53–75 µm) was obtained from Sigma-Aldrich, Inc. (U.S.A.). All chemicals were of analytical grade and used without further purification.

*Preparation of ofloxacin-oxalic acid physical mixtures (PMs) and ground mixtures (GMs)*

Ofloxacin-oxalic acid PMs were prepared at various molar ratios in a glass vial by using a vortex mixer. The PMs were ground by a vibrational rod mill (CMT T1-200, CMT Co., Ltd., Japan) for 30 min to obtain the GMs.

*Powder X-ray diffraction (PXRD) measurement*

X-ray diffractograms were obtained by using a Rigaku Miniflex II diffractometer with CuKα radiation (Rigaku Corporation, Japan) at an ambient
temperature. The following conditions were used: a voltage of 30 kV, a current of 15 mA, a scanning speed of 4 °/min over a 2° range of 5–40°.

**Fourier transform infrared (FT-IR) spectroscopy**

Fourier transform infrared spectroscopy measurements were performed by the attenuated total reflectance (ATR) method. The IR spectra of the pure components, PMs, and GMs were recorded using a FT-IR 230 spectrophotometer (JASCO Corporation, Japan) in the range of 650–4000 cm⁻¹. All spectra were recorded under the conditions: number of scan, 32; resolution, 4.0 cm⁻¹.

**Solid-state nuclear magnetic resonance (NMR) spectroscopy**

All ¹³C solid-state NMR spectra were recorded by using a JNM-ECA 600 NMR spectrometer, which had a magnetic field of 14.09 T (JEOL, Japan) and operated at 150 MHz for ¹³C. Powder samples (*ca.* 100 mg) were filled into 4 mm silicon nitride (Si₃N₄) rotors. All spectra were acquired using variable amplitude cross-polarization (CP) together with magic angle spinning (MAS) at 15 kHz and a high power two-pulse phase-modulation ¹H decoupling. The total scan for each sample (2,000–3,600) depended on the signal-to-noise ratio required. Pertinent acquisition parameters included a CP contact time of 5 ms, a ¹H 90° pulse of 2.7 μs, and relaxation delays of 2–15 s. For each experiment, 2,048 data points were acquired and zero-filled to 8,192
points. All spectra were externally referenced to tetramethylsilane by setting the methine peak of hexamethylbenzene to 17.3 ppm.

**Terahertz time-domain spectroscopy (THz-TDS)**

The THz spectra of the samples were acquired by using a Rayfact SpecTera (Tochigi Nikon Corporation, Japan) with the transmission method. Ten milligram of sample and 90 mg of polyethylene were thoroughly mixed and then manually pressed in a mould to form a measuring tablet with a diameter of 13 mm and a thickness of approximately 1 mm. Measurement were performed over the range of 0.1–2 THz with a resolution of 0.098 THz (3.255 cm\(^{-1}\)).
Principle of terahertz time-domain spectroscopy (THz-TDS)

Terahertz measurements have been challenging due to the difficulty associated with generating and detecting the THz radiation. In addition, ambient conditions create considerable noise in the THz region. However, recent femtosecond laser innovation enables to measure a new THz frequency range. The development of commercial instruments that utilize THz pulses has opened up the area of study to the wider scientific area, particularly the pharmaceutical field. Techniques using pulsed THz radiation are THz time-domain spectroscopy (THz-TDS) and THz imaging\(^8,11,12\).

Figure 2 presents the THz-TDS equipment used throughout this study. It can be operated without purging dry nitrogen; this makes it easy and convenient to measure. Terahertz spectra were measured by transmission method. The typical setup of transmission THz-TDS is shown in Fig. 3. The femtosecond laser light is emitted and separated by a beam splitter into two beams: pump light and probe light. Pump light passes through the THz emitter to generate the THz light whereas probe light is focused onto the detector. When the THz light goes through the sample, the light is distorted by selective absorption of the sample, causing the delay in its arrival time at the detector. This transmitted beam is then focused onto a detector and detected as a time-domain
waveform. The data are processed by fast Fourier transform analysis in order to convert the delay time into the frequency of the THz signal that arrives at the detector \cite{8,12}.
Fig. 2. Rayfact Spectera (Tochigi Nikon Corporation, Japan) – THz-TDS equipment.

(Image from www.tochigi-nikon.co.jp)
Fig. 3. Schematic setup of transmission THz-TDS.
RESULTS AND DISCUSSION

Part I Characterization of cocrystals by terahertz spectroscopy

Cocrystal is defined as a crystalline material that two or more components that are solid at ambient condition held together by hydrogen bonding\textsuperscript{27, 28}. The main difference between cocrystal and salt is that in salt a proton is transferred from the acidic to the basic functionality of the constituent free base molecule, or vice versa if applicable\textsuperscript{28, 29}. Cocrystal has been increasingly recognized as an attractive alternative for solid forms of drug products\textsuperscript{29, 30}. Generally, methods used for characterization of cocrystal are X-ray diffraction (single crystal and powder), FT-IR spectroscopy and thermal analysis. In order to investigate the potential use of THz spectroscopy to monitor the cocrystal formation, seven kinds of cocrystals, the structure of which has been reported\textsuperscript{3, 31, 32}, were prepared by cogrinding method. PXRD patterns of prepared cocrystals (Figs. 4-10) agreed with those of the reported cocrystals, confirmed that cocrystals were formed.

Figure 11 shows THz spectra of PRC/GTS system. Terahertz spectrum of PRC has no characteristic peak in the observed range, whereas that of GTS had absorption peaks at 0.88 and 1.85 THz. The cocrystal exhibited a distinctive absorption peak at 0.68, 1.27, and 1.76 THz. Terahertz spectra of PRC/HBA system are shown in Fig. 12.
Absorption peak of HBA was found at 1.17 THz, while broad peak was observed at 1.47 THz in the cocrystal. For the CBZ/SAC system (Fig. 13), no peak was observed in THz spectrum of SAC, while CBZ had absorption peaks at 1.27 and 1.85 THz. After forming cocrystal, new peaks were found in 1.07 and 1.66 THz. The changes found in PRC/GTS, PRC/HBA and CBZ/SAC cocrystals indicated that vibration modes changed due to the cocrystal formation. Figures 14-17 show the THz spectra of TP/OXA, TP/MLO, TP/MLE and TP/GLU systems, respectively. Theophylline showed characteristic peaks at 0.98 and 1.66 THz, while all of dicarboxylic acids used had no absorption peaks in the observed frequency range. Absorption peaks of TP disappeared in the cocrystals (defined in the figures as GMs). These results suggested that vibrational mode of TP was changed by forming cocrystal.

The spectral changes found in this study can be classified in two groups. One is PRC/GTS, PRC/HBA, and CBZ/SAC cocrystals where new peak appeared. Another is TP/OXA, TP/MLO, TP/MLE, and TP/GLU cocrystals where peak disappeared. Terahertz spectra of drugs were changed by cocrystal formation, reflecting the differences in molecular packing and vibrational modes from those of the components. As THz radiation probes weak interaction such as hydrogen bonding and van der Waals
force, it is intrinsically sensitive to changes in crystalline structure\textsuperscript{9, 15}. Hence, THz spectroscopy could be a convenient analytical method to detect the cocrystal formation.
Fig. 4. Powder X-ray diffraction patterns of PRC-GTS system: (a) PRC, (b) GTS, (c) 1:1 PM, and (d) 1:1 GM 60 min (□ PRC, △ GTS, ☆ new peak).
Fig. 5. Powder X-ray diffraction patterns of PRC-HBA system: (a) PRC, (b) HBA, (c) 1:1 PM, and (d) 1:1 GM 30 min (□ PRC, △ HBA, ☆ new peak).
Fig. 6. Powder X-ray diffraction patterns of CBZ-SAC system: (a) CBZ, (b) SAC, (c) 1:1 PM, and (d) 1:1 GM 30 min (○ CBZ, □ SAC, ☆ new peak).
Fig. 7. Powder X-ray diffraction patterns of TP-OXA system: (a) TP, (b) OXA, (c) 2:1 PM, and (d) 2:1 GM 30 min ( □ TP, △ OXA, ☆ new peak).
Fig. 8. Powder X-ray diffraction patterns of TP-MLO system: (a) TP, (b) MLO, (c) 1:1 PM, and (d) 1:1 GM 30 min ( □ TP, ◊ MLO, ☆ new peak).
Fig. 9. Powder X-ray diffraction patterns of TP-MLE system: (a) TP, (b) MLE,
(c) 1:1 PM, and (d) 1:1 GM 30 min (□ TP, ○ MLE, ☆ new peak).
Fig. 10. Powder X-ray diffraction patterns of TP-GLU system: (a) TP, (b) GLU, (c) 1:1 PM, and (d) 1:1 GM 30 min (□ TP, △ GLU, ★ new peak).
Fig. 11. Terahertz spectra of PRC-GTS system: (●) PRC, (▲) GTS, and (○) PRC-GTS cocrystal.
Fig. 12. Terahertz spectra of PRC-HBA system: (●) PRC, (△) HBA, and (□) PRC-HBA cocrystal.
Fig. 13. Terahertz spectra of CBZ-SAC system: (▲) CBZ, (■) SAC, and (○) CBZ-SAC cocrystal.
Fig. 14. Terahertz spectra of TP-OXA system.
Fig. 15. Terahertz spectra of TP-MLO system.
Fig. 16. Terahertz spectra of TP-MLE system.
**Fig. 17.** Terahertz spectra of TP-GLU system.
Part II Preparation of novel ofloxacin-dicarboxylic acid complex and characterization by terahertz spectroscopy

Figure 18 shows PXRD patterns of the OFC-OXA system. When OFC was coground with OXA at a molar ratio of 1:1 for 30 min, a halo pattern was mainly observed with the remaining peaks of crystalline OFC (Fig. 18c). The PXRD pattern of the GM became halo after cogrinding for 60 min (Fig. 18d), indicating that a prolonged grinding time could induce the disorder of solid into the amorphous phase but could not facilitate complex formation. On grinding each component individually for 60 min, the PXRD peaks were still observed (data not shown). These results suggested that the OFC:OXA ratio of 1:1 might not be a suitable stoichiometry for the complex. When the molar ratio of OFC:OXA was changed to 1:2, new PXRD peaks were found for the GM (Fig. 18f). The PXRD pattern of the PM at a molar ratio of 1:2 (Fig. 18e) was the superimposition of the diffraction peaks of intact OFC and OXA (Fig. 18a and 18b). The PXRD pattern of the GM differed from those of the constituents; this confirmed the formation of a new complex phase. For the GM with a molar ratio of 1:3, new diffraction peaks were observed in addition to those corresponding to the excess amount of OXA (Fig. 18g). These results indicated that the OFC-OXA complex formed presumably at a molar ratio of 1:2 by cogrinding.
Fig. 18. Powder X-ray diffraction patterns of the OFC–OXA system: (a) OFC, (b) OXA, (c) 1:1 GM 30 min, (d) 1:1 GM 60 min, (e) 1:2 PM, (f) 1:2 GM 30 min, and (g) 1:3 GM 30 min (○ OFC, □ OXA, ☆ new peak).
The physicochemical properties of OFC, OXA, PM, and GM at a molar ratio of 1:2 were investigated by other solid-state analytical methods. Molecular interaction between OFC and OXA was examined by FT-IR spectroscopy. All the spectra of the OFC-OXA system are depicted in Fig. 19. The spectrum of OXA showed a peak corresponding to the carbonyl (C=O) stretching of carboxylic acid at 1683 cm\(^{-1}\). In the spectrum of OFC, the bands observed at 1710 and 1621 cm\(^{-1}\) were assigned to the C=O stretching of carboxylic group and the stretching of the ketonic group, respectively\(^{33-35}\). These bands were also observed in the IR spectra of the PM and GM (1708 and 1620 cm\(^{-1}\) for PM; 1709 and 1624 cm\(^{-1}\) for GM), suggesting that the interaction modes of carboxylic and ketonic groups with the surrounding functional groups might be similar before and after grinding. This system is different from other typical complex formation systems wherein hydrogen bond formation is clearly observed by FT-IR spectroscopy\(^{5,36}\).

However, some changes were found in the vibrational range of aromatic rings of OFC. The bands at 1548 and 1521 cm\(^{-1}\) corresponding to the C=C stretching in aromatic rings\(^{1-3}\) changed to a broad peak at 1532 cm\(^{-1}\) in the spectrum of the GM. In the region of 2750–3000 cm\(^{-1}\), bands of OFC attributed to the C-H stretching in the CH\(_3\) group and CH\(_2\) group\(^{37}\) were observed for the PM but were not clearly observed for the
Fig. 19. Infrared spectra of the OFC-OXA system in the range of 3300–2600 cm$^{-1}$ and 1800–1500 cm$^{-1}$: (a) OFC, (b) OXA, (c) PM, and (d) GM.
GM. Furthermore, the O-H stretching frequency of OXA shifted from 3087 cm$^{-1}$ to 3276 cm$^{-1}$ in the GM, indicating that the intermolecular hydrogen bonds between OXA molecules were broken. The results of the IR spectroscopy suggested that some interactions occurred between OFC and OXA at the aromatic ring and/or methyl group of OFC with O-H group of OXA.

Solid-state NMR spectroscopy was used to confirm the interaction between OFC and OXA. The $^{13}$C CP/MAS spectra for the OFC-OXA system are presented in Fig. 20. The chemical shifts of the carbon atoms in this system are summarized in Table 1. The chemical shift assignment of the carbon atoms of OFC and OXA was based on ChemDraw Ultra® software (CambridgeSoft Corporation, Japan). The comparison between the spectrum of OFC and that of the complex revealed that there was no significant change in the chemical shift of the carbons at positions ac and 7 of OFC, as shown in Table 1. On the other hand, the peaks of the carbon at position 5 and of the met of OFC shifted upfield, while those of the carbons at positions 6, 7a, 7b, 8, 9, 10, and 10a of the aromatic rings shifted downfield. The chemical shift of the C1” of OXA exhibited a downfield shift in the complex. These results suggested that the tricyclic aromatic portion and/or methyl group of OFC interacted with the hydroxyl group close to C1” of OXA.
Fig. 20. $^{13}$C solid-state NMR spectra of the OFC-OXA system: (a) OFC, (b) OXA, and (c) OFC-OXA complex. Peak assignments are shown in Table 1.
**Table 1** Chemical shifts (ppm) observed in $^{13}$C CP/MAS NMR spectra of OFC, OXA, and OFC-OXA complex.

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Hydrogen bonding is an important intermolecular interaction mode, which is responsible for different crystal packing. IR and NMR results did not confirm the presence of hydrogen bonding among the functional groups of OFC and OXA. Hence, according to the definition of cocrystal mentioned in Part 1, I classified OFC-OXA compound as a complex. Complex is defined as a compound that two or more components are held together through weak interactions such as van der Waals force and π-stacking, regardless of hydrogen bonding. The OFC-OXA complex appeared to be formed by weak interactions such as van der Waals force and OH-π interaction, instead of hydrogen bonding. It has been reported that the OH-π interaction is involved in the formation of the trehalose-benzene complex and trehalose-unsaturated fatty acid complex.

Terahertz radiation has been used to investigate intermolecular interactions, and THz spectroscopy is one of the alternative methods for characterizing solid materials. Transmission THz-TDS was used as an evaluation method for complex formation. Figure 21 depicts the THz spectra of the OFC-OXA system. OFC had a characteristic peak at 1.07 THz, while the THz spectrum of OXA was featureless. The complex exhibited a distinctive absorption peak at 0.59 THz as compared to those of the starting materials. The change observed in the THz spectrum of the complex reflected
Fig. 21. Terahertz spectra of OFC-OXA system – (●) OFC, (■) OXA, (▲) OFC-OXA complex.
the weak interaction in the OFC-OXA complex. From this result, it is worth noting that THz spectroscopy can probe weak interactions, comparing to FT-IR spectroscopy. The difference in the THz spectra between the complex and the starting components indicated that OFC interacted with OXA. As reported by Nguyen et al. (2007), THz-TDS has been used to monitor the cocrystal formation induced by cogrinding phenazine and mesaconic acid. Even though the assignment of THz peak is still difficult in this experiment owing to the lack of crystallographic data and the subsequent vibrational mode calculation, a distinguished spectral difference suggested complex formation induced by cogrinding. In recent years, computational simulation of vibrational spectra to obtain molecular level information has become increasingly common.

In addition to OFC-OXA complex, the complex formation of OFC with other dicarboxylic acids such as MLE, GLU, and MLO was investigated. The PXRD patterns of OFC-dicarboxylic acid system are shown in Fig. 22. Similar to the OFC-OXA system, GMs at a molar ratio of 1:2 (OFC: dicarboxylic acid) showed new PXRD patterns, suggesting that a complex was formed between OFC and dicarboxylic acid. The THz spectra of other OFC-dicarboxylic acid complexes were also investigated (Fig. 23). The THz spectrum of the OFC-MLE complex was featureless, while the OFC-GLU complex
Fig. 22. Powder X-ray diffraction patterns of OFC-dicarboxylic acids systems: a) MLE, b) OFC:MLE 1:2 PM, c) OFC:MLE 1:2 GM, d) GLU, e) OFC:GLU 1:2 PM, f) OFC:GLU 1:2 GM, g) MLO, h) OFC:MLO 1:2 PM, i) OFC:MLO 1:2 GM (○ OFC, △ MLE, ◇ GLU, ● MLO, ★ new peak).
Fig. 23. Terahertz spectra of the OFC-dicarboxylic acid system: (a) MLE, (b) GLU, and (c) MLO systems.
exhibited new peaks at 0.98 and 1.27 THz. The OFC-MLO complex had a new peak at 1.17 THz. All these complexes showed distinct spectra (i.e., new peak appearance or peak disappearance) from those of their starting materials, reflecting the difference in molecular packing.
CONCLUSIONS

Seven cocrystals were prepared and characterized by THz spectroscopy. It was found that THz spectra of cocrystals were different from those of their starting materials. The spectral patterns were changed by the cocrystal formation. Therefore, THz spectroscopy was appeared to be a convenient analytical method to detect the cocrystal formation.

When OFC and OXA were coground at molar ratio of 1:2, the complex was formed. This complexation did not involved hydrogen bond formation between OFC and OXA. Weak interaction such as van der Waals force and/or OH-π interaction occurred, as indicated by the IR and NMR spectra. The THz spectral patterns of OFC, OXA, and complex were different in the observed frequency range. The distinctive THz spectrum of complex showed that the vibration modes were different from those of starting materials, reflecting the weak interaction in the complex. Though the assignment of THz peaks is still difficult now, further progress of computational calculation will make it possible to do vibrational mode calculation for the peak assignment. Terahertz spectroscopy can provide a convenient and rapid method for the evaluation of the complex formation especially for the complexes which hydrogen bonding is not clearly observed by FT-IR spectroscopy.
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