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Characterization of ofloxacin–oxalic acid complex by PXRD, NMR, and THz spectroscopy

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ABSTRACT

A novel ofloxacin–oxalic acid complex was prepared by the cogrinding method. The obtained complex was characterized by powder X-ray diffraction (PXRD), infrared (IR), solid-state nuclear magnetic resonance (NMR), and terahertz (THz) spectroscopy. The PXRD measurement revealed that the ofloxacin–oxalic acid complex induced by cogrinding was formed at a molar ratio of 1:2. Weak interaction between two components, not a hydrogen bonding, was found by IR and solid-state NMR spectroscopy. The distinctive THz spectrum showed that the vibrational modes of the complex were different from those of the starting materials, suggesting that THz spectroscopy is an alternative tool to evaluate complex formation through weak interactions.

1. Introduction

Nowadays, crystal engineering has been used to alter the physicochemical properties of active pharmaceutical ingredients (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 (Blagden et al., 2007).

Many techniques are used for investigating the solid-state properties of the solid sample, 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 solid state at the intramolecular and intermolecular levels. On the other hand, PXRD, terahertz (THz) spectroscopy, and various thermal techniques predominantly examine at the lattice level (i.e., at the intermolecular level) (Aaltonen et al., 2008, 2009). Recently, THz spectroscopy has gained more interest in the study of pharmaceutical materials (Tonouchi, 2007; Wu et al., 2007; McGoverin et al., 2008).

Terahertz spectroscopy covers the electromagnetic spectral range from 3 to 600 cm^{-1}, between the IR and microwave regions (Beard et al., 2002). One terahertz is equivalent to 33.33 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. Moreover, a THz wave has low energy and thus can be used to detect biological samples (Nakajima et al., 2007). Terahertz radiation can probe low-frequency crystal lattice vibration and weak intermolecular interactions such as hydrogen bonding and van der Waals force (Ueno and Ajito, 2008). For application, several studies have reported that THz spectroscopy can be used for differentiating and quantifying the different forms of APIs (Taday et al., 2003; Strachan et al., 2004, 2005; Zeitler et al., 2006; Nishikiori et al., 2008). THz spectroscopy has also been applied to monitor solid-state dynamic processes such as the dehydration process and cocrystal formation (Nguyen et al., 2007; Zeitler et al., 2007).

The purpose of the study was to prepare a new complex of ofloxacin having better physicochemical properties by forming a complex with oxalic acid. 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 (Koester et al., 2001; Macías et al., 2001). The effect of ofloxacin and β-cyclodextrin complexation on the solubility in water and photostability of the drug has been investigated (Koester et al., 2001). However, only a few studies have been reported about improving the solubility and dissolution rate of ofloxacin. This study also aimed to investigate the feasibil-

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ity of using THz spectroscopy as an evaluation method for complex formation.

2. Materials and methods

2.1. Materials

Ofloxacin and anhydrous oxalic acid were purchased from Wako Pure Chemical Industries, Ltd. (Japan). The chemical structures of ofloxacin and oxalic acid are shown in Fig. 1. Polyethylene (ultra-high molecular weight, surface-modified particles of size 53–75 μm) was obtained from Sigma–Aldrich, Inc. (U.S.A.). Ofloxacin, oxalic acid, maleic acid, malonic acid, glutaric acid, and polyethylene were of analytical grade and used without further purification.

2.2. 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.

2.3. 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 45 kV, a current of 35 mA, a scanning speed of 4°/min over a 2θ range of 5–40°.

2.4. 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 the result of averaging 32 scans and the resolution was 4.0 cm^{-1}.

2.5. Solid-state nuclear magnetic resonance (NMR) spectroscopy

All ^{13}C solid-state NMR spectra were recorded by using a JNM-ECA 600 NMR spectrometer, which had a magnetic field of 14.09 T (JEOL Ltd., Japan) and operated at 150 MHz for ^{13}C. Powder samples (*ca.* 100 mg) were filled into 4 mm silicon nitride (Si_3N_4) 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 ^{1}H decoupling. The total scan for each sample (2000–3600) depended on the signal-to-noise ratio required. Pertinent acquisition parameters included a CP contact time of 5 ms, a ^{1}H 90° pulse of 2.7 μs, and relaxation delays of 2–15 s. For each experiment, 2048 data points were acquired and zero-filled to 8192 points. All spectra were externally referenced to tetramethylsilane by setting the methine peak of hexamethylbenzene to 17.3 ppm.

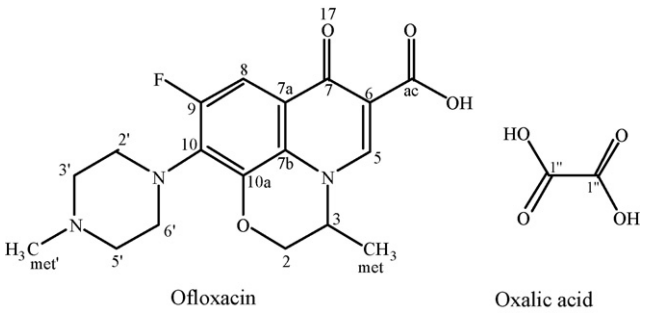

Fig. 1. Chemical structures of ofloxacin and oxalic acid.

2.6. 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. Polyethylene is a good diluent for measuring the spectra of APIs because it is featureless and relatively transparent in the range below 100 cm^{-1} (Spencer et al., 2007). The measurement covered the range of 0.1–2 THz with a resolution of 0.098 THz (3.255 cm^{-1}).

3. Results and discussion

In the present study, the cogrinding method was used to prepare the complex because mechanochemical technology was shown to be available to pharmaceutical fields and be friendlier to the environment than the solvent method. Fig. 2 shows the PXRD patterns of the ofloxacin–oxalic acid system. When ofloxacin was coground with oxalic acid at a molar ratio of 1:1 for 30 min, a halo pattern was mainly observed with the remaining peaks of crystalline ofloxacin (Fig. 2c). The PXRD pattern of the GM became halo after cogrinding for 60 min (Fig. 2d), 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 ofloxacin:oxalic acid ratio of 1:1 might not be a suitable stoichiometry for the complex. When the molar ratio of ofloxacin:oxalic acid was changed to 1:2, new PXRD peaks were found for the GM (Fig. 2f). The PXRD pattern of the PM at a molar ratio of 1:2 was the superimposition of the diffraction peaks of intact ofloxacin and oxalic acid (Fig. 2e). 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 oxalic acid (Fig. 2g). These results indicated that the ofloxacin–oxalic acid complex formed presumably at a molar ratio of 1:2 by cogrinding.

In addition to oxalic acid, the complex formation of ofloxacin with other dicarboxylic acids such as maleic acid, glutaric acid, and malonic acid was investigated. The PXRD patterns of ofloxacin–dicarboxylic acid system are shown in Fig. 3. Similar to the ofloxacin–oxalic acid system, GMs at a molar ratio of 1:2 (ofloxacin:dicarboxylic acid) showed new PXRD patterns, suggesting that a complex is formed between ofloxacin and dicarboxylic acid.

The physicochemical properties of ofloxacin, oxalic acid, PM, and GM at a molar ratio of 1:2 were investigated by other solid-state analytical methods. Molecular interaction between ofloxacin and oxalic acid was examined by FT-IR spectroscopy. All the spectra of the ofloxacin–oxalic acid system are depicted in Fig. 4. The spectrum of oxalic acid showed a peak corresponding to the carbonyl (C=O) stretching of carboxylic acid at 1683 cm^{-1}. In the spectrum of ofloxacin, 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 (Dorofeev, 2004; Sagdinc and Bayari,

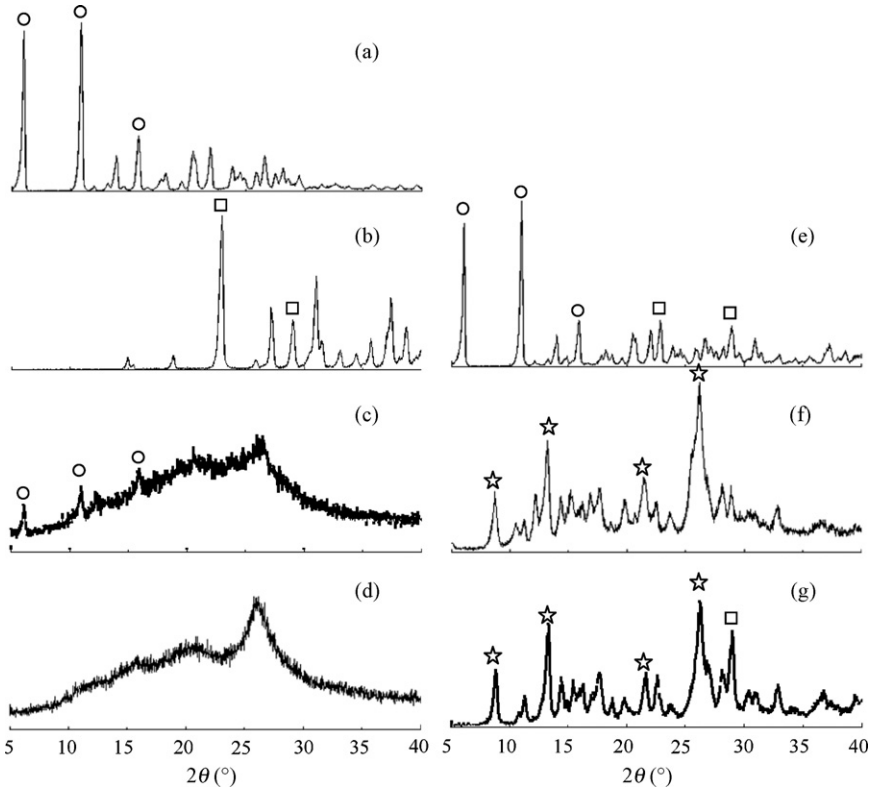

Fig. 2. Powder X-ray diffraction patterns of the ofloxacin–oxalic acid system: (a) ofloxacin, (b) oxalic acid, (c) ofloxacin:oxalic acid 1:1 GM 30 min, (d) ofloxacin:oxalic acid 1:1 GM 60 min, (e) ofloxacin:oxalic acid 1:2 PM, (f) ofloxacin:oxalic acid 1:2 GM 30 min, and (g) ofloxacin:oxalic acid 1:3 GM 30 min (◯, ofloxacin; □, oxalic acid; ☆, new peak).

2004a,b). 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 (Macías et al., 2002; Moribe et al., 2004).

However, some changes were found in the vibrational range of aromatic rings of ofloxacin. The bands at 1548 and 1521 cm^{-1} corresponding to the C=C stretching in aromatic rings (Dorofeev, 2004; Sagdinc and Bayari, 2004a,b) 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 ofloxacin attributed to the C–H stretching in the CH_3 group and CH_2 group (Wang et al., 2006) were observed for the PM but were not clearly observed for the GM. Furthermore, the O–H stretching frequency of oxalic acid shifted from 3087 to 3276 cm^{-1} in the GM, indicating that the intermolecular hydrogen bonds between oxalic acid molecules were broken. The results of the IR spectroscopy suggested that some interactions occurred between ofloxacin and oxalic acid at the aromatic ring and/or methyl group of ofloxacin with O–H group of oxalic acid.

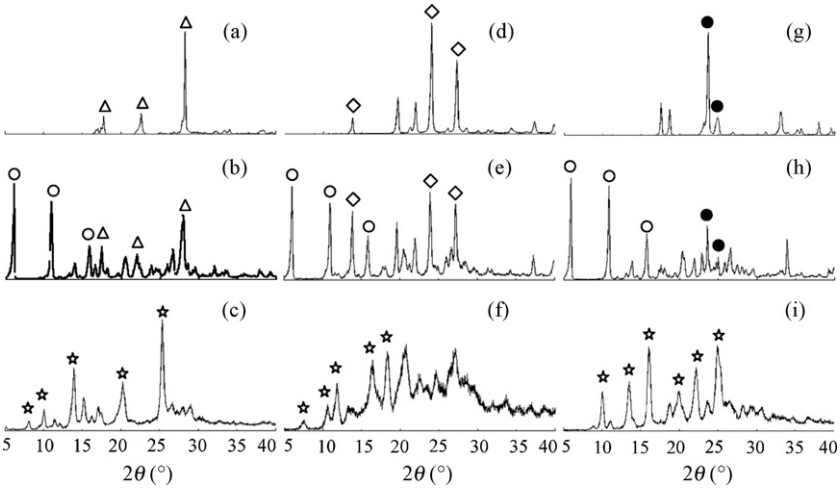

Fig. 3. Powder X-ray diffraction patterns of the ofloxacin–dicarboxylic acid system: (a) maleic acid, (b) ofloxacin:maleic acid 1:2 PM, (c) ofloxacin:maleic acid 1:2 GM, (d) glutaric acid, (e) ofloxacin:glutaric acid 1:2 PM, (f) ofloxacin:glutaric acid 1:2 GM, (g) malonic acid, (h) ofloxacin:malonic acid 1:2 PM, and (i) ofloxacin:malonic acid 1:2 GM (◯, ofloxacin; △, maleic acid; ◊, glutaric acid; ●, malonic acid; ☆, new peak).

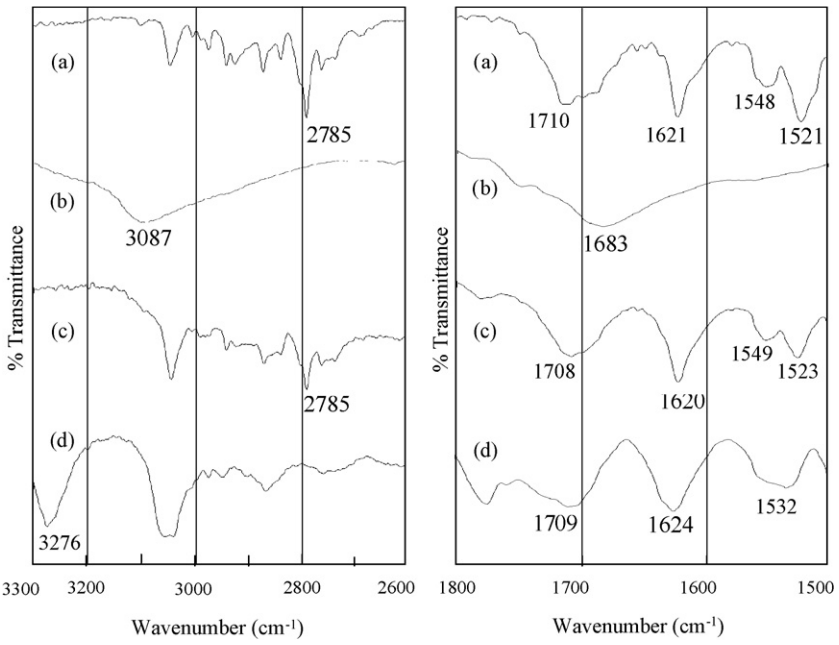

Fig. 4. Infrared spectra of the ofloxacin–oxalic acid system in the range of 3300–2600 cm^{-1} and 1800–1500 cm^{-1}: (a) ofloxacin, (b) oxalic acid, (c) PM, and (d) GM.

Solid-state NMR spectroscopy was used to confirm the interaction between ofloxacin and oxalic acid. The ^{13}C CP/MAS spectra for the ofloxacin–oxalic acid system are presented in Fig. 5. The chemical shifts of the carbon atoms in this system are summarized in Table 1. The chemical shift assignment of the carbon atoms of ofloxacin and oxalic acid was based on ChemDraw Ultra software (CambridgeSoft Corporation, Japan). The comparison between the spectrum of ofloxacin 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 ofloxacin, as shown in Table 1. On the other hand, the peaks of the carbon at position 5 and of the met of ofloxacin 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 oxalic acid exhibited a downfield shift in the complex. These results suggested that the tricyclic aromatic portion and/or methyl group of ofloxacin interacted with the hydroxyl group close to C1″ of oxalic acid.

Hydrogen bonding is an important intermolecular interaction mode, which is responsible for different crystal packing (Wenger and Bernstein, 2007). IR and NMR results did not confirm the presence of hydrogen bonding among the functional groups of ofloxacin and oxalic acid. This 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 (Oku et al., 2003, 2005).

Terahertz radiation has been used to investigate intermolecular interactions, and THz spectroscopy is one of the alternative meth-

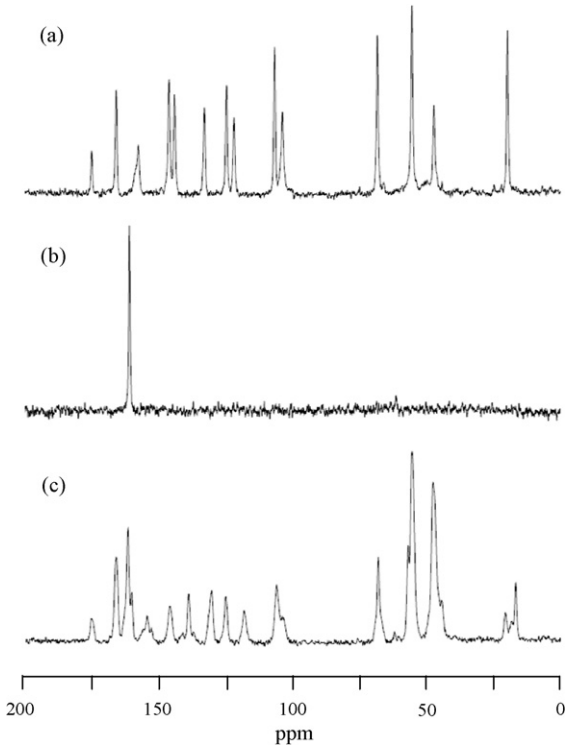

Fig. 5. ^{13}C solid-state NMR spectra of the ofloxacin–oxalic acid system: (a) ofloxacin, (b) oxalic acid, and (c) the ofloxacin–oxalic acid complex. Peak assignments are shown in Table 1.

Table 1
Chemical shifts (ppm) observed in ^{13}C CP/MAS NMR spectra of ofloxacin, oxalic acid, and the ofloxacin–oxalic acid complex.

Position of carbon[a]	Ofloxacin (ppm)	Oxalic acid (ppm)	The complex (ppm)
7	175.4		175. 7
ac	166.2		166.5
1″		160.8	162.0
5	157.9		154.9
9	144.5		146.3
10a	133.3		139.2
7b	125.0		130.7
10	122.2		125.4
7a	107.1		118.5
8, 6	104.2		106.4
2	68.7		68.2
2′, 3′, 5′, 6′,3	55.8		55.6
met′	47.5		47.7
met	20.1		16.7

[a] The position of carbon is according to the assignment shown in Fig. 1.

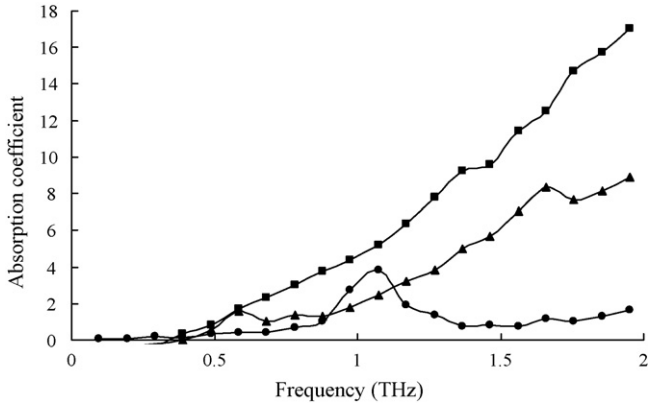

Fig. 6. Terahertz spectra of the ofloxacin–oxalic acid system: (●) ofloxacin, (■) oxalic acid, and (▲) the ofloxacin–oxalic acid complex.

ods for characterizing solid materials (Nguyen et al., 2007; Ueno and Ajito, 2008). Transmission THz-TDS was used as an evaluation method for complex formation. Fig. 6 depicts the THz spectra of the ofloxacin–oxalic acid system. Ofloxacin had a characteristic peak at 1.07 THz, while the THz spectrum of oxalic acid 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 the weak interaction in the ofloxacin–oxalic acid 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 ofloxacin interacted with oxalic acid. 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 our 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 (Aaltonen et al., 2008).

The THz spectra of other ofloxacin–dicarboxylic acid complexes were also investigated (Fig. 7). The ofloxacin–glutaric acid complex exhibited new peaks at 0.98 and 1.27 THz. The ofloxacin–malonic acid complex had a peak at 1.17 THz, while the THz spectrum of the ofloxacin–maleic acid complex was featureless. All these complexes showed distinct spectra (i.e., new peak and/or peak disappearance) from those of their starting materials, reflecting the difference in molecular packing.

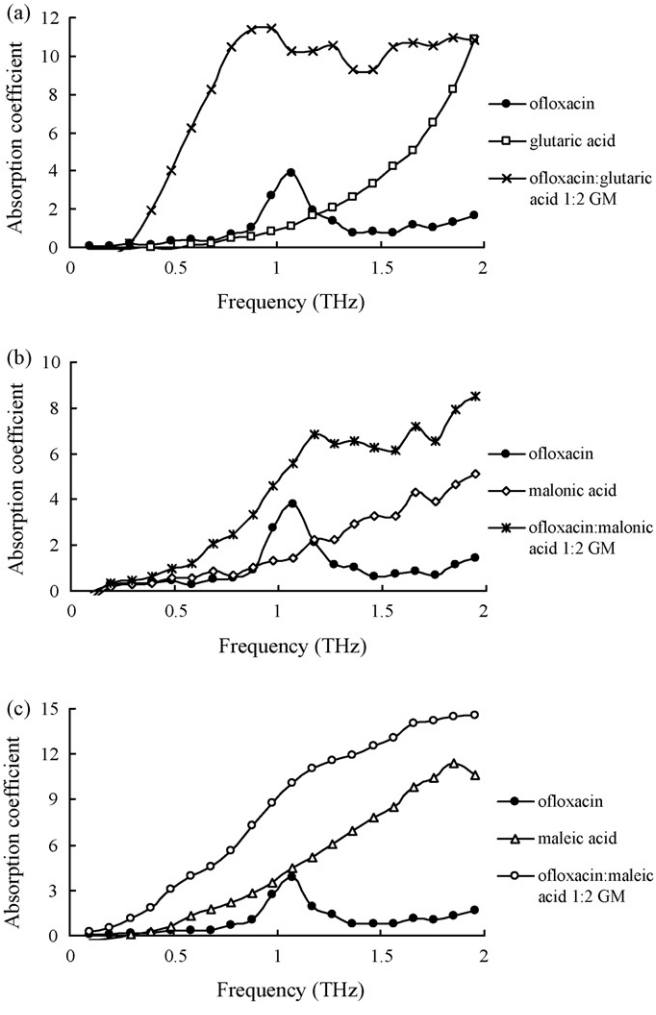

Fig. 7. Terahertz spectra of the ofloxacin–dicarboxylic acid system: (a) glutaric acid, (b) malonic acid, and (c) maleic acid systems.

4. Conclusions

A novel ofloxacin–oxalic acid complex was formed at a molar ratio of 1:2 by cogrinding. The complexation did not involve hydrogen bond formation between ofloxacin and oxalic acid. Weak interactions such as van der Waals force and/or OH-π interaction occurred, as indicated by the IR and NMR spectra. The weak intermolecular interactions could be detected in the THz range. The spectral patterns of ofloxacin, dicarboxylic acids, and the complex were different in the observed frequency range. THz-TDS can provide a convenient and rapid method for the evaluation of complex formation. The physicochemical properties such as solubility and dissolution rate of this complex will be further investigated.

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