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Preparation of Indomethacin Co-Crystals; Comparison of XRD, THz, and FT-IR Spectral Analyses; and Enhancement of Solubility

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Abstract: Background: The aqueous solubility of indomethacin, a poorly water-soluble anti-inflammatory drug, was enhanced by co-crystallization with co-formers. The co-crystals were characterized and compared by an X-ray diffraction (XRD) analysis, terahertz (THz) spectroscopy, and Fourier transform infrared (FT-IR) spectroscopy. Methods: Indomethacin co-crystals with either amides (saccharin, nicotine amide, and urea) or amino acids (lysine and histidine) as co-formers were prepared through the solvent evaporation method. The co-crystals were characterized by XRD, THz, and FT-IR analyses, followed by solubility tests to examine the solubility enhancement. Results: Both the XRD and THz analyses were capable of distinguishing co-crystals from physical mixtures; however, the THz spectra were relatively simpler and clearer than the XRD analysis. Furthermore, the solubility of indomethacin was successfully increased by two to three times that of pure indomethacin after co-crystallization with the above five co-formers. Conclusion: Five kinds of indomethacin co-crystals (with enhanced solubility) were successfully prepared and confirmed by the three spectroscopy techniques, XRD, THz, and FT-IR. The identification of co-crystals was achieved by a THz analysis, giving relatively simpler and clearer spectra with less noise. Hence, in addition to an XRD analysis, a THz analysis (a non-destructive, non-ionizing radiative, and relatively rapid measurement technique which is convenient and safe to use) is a good alternative method to characterize co-crystals.

Keywords: indomethacin; co-crystallization; solvent evaporation method; X-ray diffraction (XRD); terahertz (THz) spectroscopy; Fourier transform infrared (FT-IR) spectroscopy; solubility

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1. Introduction

According to the Biopharmaceutics Classification System (BCS), around 90% of new active pharmaceutical ingredients (APIs) have poor aqueous solubility, which is a characteristic of BCS II or BCS IV drugs [1]. A drug with low solubility may have limited oral absorption and bioavailability [2]. Therefore, solubility enhancement is one of the most important tasks in the research and development of drugs. For instance, salification is one of the commonly used methods to improve the solubility of poorly soluble APIs [3,4], but it is not suitable for APIs lacking ionizable groups, and the number of non-toxic salt formers is also limited. Hence, people also try other methods such as changing the API to other solid forms to improve its solubility. For example, the preparation of drugs as amorphous solid forms can effectively improve the solubility, dissolution rate, and potential bioavailability of the API. However, the low stability associated with amorphous solid forms becomes a major disadvantage in biological applications [5].

In the present study, the manufacturing of API in the form of co-crystals was utilized to enhance the pharmaceutical properties of API, such as solubility, bioavailability, and stability [6]. Co-crystals consist of API and a co-former with a fixed stoichiometric ratio, forming a crystalline phase in which two different molecular components are connected by hydrogen bonds and other nonionic interactions. The formation of co-crystals is a commonly used technique to improve the solubility, dissolution rate, and bioavailability of a drug without altering the chemical nature of pure API [4,6]. Owing to this advantage, an increasing amount of research has been conducted since the 2000s [7]. For instance, Srivastava et al. doubled the solubility of glibenclamide via a co-crystallization technique with malonic acid [8]. Furthermore, the use of the co-crystal formation technique possesses the advantage of having a variety of co-former selections. Good et al. studied seven carbamazepine co-crystals and found that the aqueous solubility of these co-crystals was 2−152 times greater than that of carbamazepine [9]. Also, Vemuri et al. used a co-crystallization technique to enhance both the solubility and dissolution rate of rosuvastatin simultaneously [10]. Furthermore, Eesam et al. successfully prepared several co-crystals of gliclazide to improve its physicochemical properties [11]. Therefore, the use of suitable co-formers can enhance the pharmaceutical effect. If both components are APIs, then the co-crystal can be called a drug–drug co-crystal (DDC) [12]. In brief, the co-crystallization technique plays an important role in augmenting the physical, chemical, and pharmaceutical properties of APIs [6,7,12]. Among the various methods used for preparing co-crystals, solvent evaporation is one of the most commonly used methods. Compared with another common method, the grinding method, the solvent evaporation method provides several advantages; it is suitable for generating single crystals [13,14] and it is more efficient than the grinding method. In addition, it can produce co-crystal products with high purity.

In 1995, Desiraju proposed a concept called "supramolecular synthon" [15], which can be further utilized to produce co-crystals of APIs based on noncovalent intermolecular interactions such as hydrogen bonding [16]. Common supramolecular synthons can be classified into homosynthons and heterosynthons. In homosynthons, the interaction between two identical functional groups (such as carboxylic acid–carboxylic acid or amide–amide dimer) exists. In heterosynthons, the interaction between two different functional groups (such as carboxylic acid–amide dimer) exists [16].

Indomethacin (IND), a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic, and analgesic properties, was selected in this study as a model API that exhibits poor water solubility. It is frequently used to treat patients with moderate to severe rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute gouty arthritis [13,15]. Indomethacin generally exists in at least two polymorphic forms, the α-form and γ-form, and the latter is thermodynamically stable at room temperature [17]. Thus, the γ-form was used in this study, which has low solubility in water (0.937 mg/L) at 25 °C, belonging to BCS class II [18].

In indomethacin, carboxylic acid is the major functional group. In a study by Basavoju et al. [13], they found that the carboxylic acid homodimer synthon exists in pure indomethacin (γ-form). On the other hand, in pure saccharin, which contains a hydrogen bond acceptor (C=O) and donors (N–H), an imide homodimer synthon exists. They also prepared indomethacin/saccharin co-crystals for structural analysis, revealing that indomethacin still forms an acid dimer synthon and saccharin still forms an imide dimer synthon [13]. Moreover, an additional interaction between the acid dimer and imide dimer synthons is present (due to weak O$\cdots$N–H hydrogen bonds) in indomethacin/saccharin co-crystals by using a molecular modeling technique [13]. Notably, compared with pure indomethacin, the co-crystals demonstrated a higher dissolution rate [13].

Based on the above evidence, in this research, indomethacin was selected as a model API, with three kinds of amides (saccharin, nicotinamide, and urea) and two kinds of amino acids (L-lysine and L-histidine) as co-formers to prepare co-crystals by the solvent evaporation method. The following describes the characteristics of these five co-formers. Saccharin has imino and carbonyl functional groups that can easily form hydrogen bonds.

Thus, it is often used as a co-former to form co-crystals with other APIs. Pagire et al. prepared co-crystals of carbamazepine and saccharin by solvent evaporation to increase the solubility of carbamazepine in water up to 1 mg/mL [19]. Nicotinamide has an amide group and an aromatic ring with a nitrogen atom, which makes it easy to form hydrogen bonds with other compounds, so it is often used as a co-former to form co-crystals with other APIs. Qiao et al. used solvent evaporation to form co-crystals of carbamazepine and nicotinamide, which exhibits improved solubility and the dissolution profile of carbamazepine [20]. The third co-former, urea, has an acyl group and two amine groups that help it to establish hydrogen bonds with other species, also making it possible to form co-crystals with other APIs. Thayer et al. reported the successful co-crystal preparation of diketopiperazine and urea by solvent evaporation [21]. L-lysine, belonging to a basic amino acid, has a carboxyl group and two amine groups that easily form hydrogen bonds with other substances. The synthesis of a curcumin and L-lysine co-crystal has already been reported [22]. L-histidine, also belonging to a basic amino acid, has a carboxyl group, an amine group, and an aromatic ring with two nitrogen atoms, which can easily form hydrogen bonds as well. For example, it was confirmed that L-histidine can form co-crystals with 4, 5-imidazole dicarboxylic acid in the work of Gorbitz et al. [23].

In total, five kinds of indomethacin co-crystals including indomethacin/saccharin, indomethacin/nicotinamide, indomethacin/urea, indomethacin/L-lysine, and indomethacin/L-histidine co-crystals were prepared in this study. Afterwards, three common characterization techniques [24,25], namely powder X-ray diffraction (XRD) analysis, terahertz time-domain spectroscopy (THz-TDS), and Fourier transform infrared absorption spectroscopy (FT-IR), were employed to investigate whether these analyses were capable of distinguishing co-crystals from physical mixtures. Also, a comparison of XRD, THz-TDS, and FTIR analyses in the identification of co-crystals, raw materials, and physical mixtures of indomethacin and co-formers was made. Finally, the solubility of indomethacin and its co-crystals was determined to see if the formation of co-crystals could significantly enhance the solubility of indomethacin.

The principles and applications of powder XRD, THz-TDS, and FT-IR analyses are briefly described here. In an XRD analysis, if indomethacin and a co-former form a co-crystal with intermolecular hydrogen bonds, the difference in the crystal lattice arrangement will lead to a shift in the characteristic peaks of the XRD pattern. In contrast, if indomethacin and a co-former form only a physical mixture, which retains the features of the original individual components, the XRD pattern will be a superposition of the inherent characteristic peaks of indomethacin and the specific co-former. In the characterization of a THz analysis, the spectrum between 0.6 and 2.6 THz (THz: 10^{12} Hz) is mainly the vibrational spectrum between molecules. It can detect weak intermolecular forces, such as hydrogen bonds. When a co-crystal with intermolecular hydrogen bonds forms, the characteristic peaks will shift. As for physical mixtures, since indomethacin and the specific co-former do not establish any hydrogen bonds between them, the characteristic peaks will only be the superpositions of the THz spectra of indomethacin and the co-former. It is noteworthy that THz analysis is a relatively new, non-destructive, and non-ionizing radiative technique that is more convenient and safer to use than XRD analysis. Moreover, in FT-IR spectroscopy, far-infrared light is applied to detect intramolecular vibrational modes to identify various functional groups. When an indomethacin co-crystal forms, the specific functional groups of indomethacin and the co-former are connected by hydrogen bonds. In that case, the characteristic absorption peak of a specific functional group can still be seen, but the position of the peak may shift, or the peak may be broader. But for physical mixtures, because there is no hydrogen bond formation between indomethacin and the specific co-former, the position of the characteristic peak should not shift significantly.

2. Materials and Methods

2.1. Materials

The API, indomethacin, in this study, was ordered from Wako Co., Ltd, (Osaka, Japan). Two of the co-formers, saccharin and nicotinamide, were procured from Acros Organics

(Geel, Belgium). In addition, urea was bought from Showa Co., Ltd., (Osaka, Japan). The other two co-formers, L-lysine and L-histidine, were obtained from Wako, Japan as well. The solvents used in this research, ethyl acetate and ethanol, were purchased from Fisher Chemical (Schwerte, Germany) and Eco Chemical (Tainan, Taiwan), respectively.

2.2. Preparation of Various Indomethacin/Co-Former Co-Crystals by Solvent Evaporation

Briefly, the solvent evaporation method is described below. Indomethacin and one of the co-formers were mixed in equimolar ratios, and an appropriate amount of corresponding solvents was added to the mixture. For amide co-formers, such as saccharin, nicotinamide, and urea, ethyl acetate was used as the solvent; for amino acid co-formers such as L-lysine and L-histidine, 66.6% (*v*/*v*) and 50.0% (*v*/*v*) ethanol aqueous solutions were used as the solvents, respectively. Then, the solutions were heated to 55 °C and were stirred evenly until the powder was completely dissolved, and afterwards, the solution was placed in a chemical hood (temperature: 25 °C; suction wind speed: 0.8 m/s) for 24–72 h so that the solvent would evaporate slowly to form a co-crystal in the container, and then the co-crystal was moved into a vacuum oven at 25 °C for 24 h to completely remove the moisture of the co-crystal powder before collecting.

2.3. Identification of Co-Crystal by Powder X-ray Diffraction (XRD)

An appropriate amount of sample was put onto the holder on top of a glass slide, and another glass slide was used to compact and smooth the powder, and subsequently, a Rigaku SmartLab SE X-ray diffractometer (Tokyo, Japan) was utilized to measure the powder XRD spectrum of the sample. The scan rate was set to 2°/min. Additionally, the scan range (2θ) was 5° to 50°. Later, Origin (ver. 8.5) software was utilized to plot the XRD spectrum and to analyze the signal peak position.

2.4. Identification of Co-Crystals by Terahertz Time-Domain Spectroscopy (THz-TDS)

First, 20–40 mg of the sample was put into a cylindrical mold with a diameter of 1 cm, and then the mold was pressed with 2 tons of force for 5 min to form a tablet with a diameter of 1 cm. After that, the THz-TDS spectrum of the sample was measured with a Teraview TeraPulse 4000 terahertz spectrometer (Cambridge, UK). The THz-TDS signals were converted to the THz absorption spectrum in the frequency domain using fast Fourier transformation. Similarly, Origin (ver. 8.5) software was used to plot the THz absorption spectrum and to perform the peak analysis.

2.5. Identification of Co-Crystals by Fourier Transform Infrared Spectroscopy (FT-IR)

Amounts of 1–2 mg of samples and 100 mg of KBr powder were mixed uniformly in an agate mortar. KBr allows infrared radiation to pass through it without absorbing or interfering with the signal. After ingot hydraulic pressing, the ingot was placed on the stage. Furthermore, the infrared absorption spectrum of the sample was obtained via Perkin Elmer Spectrum 100 FT-IR (Shelton, CT, USA). The absorption wavenumber was in the range of 450~4000 cm^{-1}, and the resolution was set to 1 cm^{-1}. Likewise, Origin (ver. 8.5) software was implemented to plot the FT-IR spectrum and to identify the position of the signal peak.

2.6. Solubility Determination of Various Indomethacin Co-Crystals in Phosphate-Buffered Saline (pH 6.8)

An excessive amount of sample was dissolved in 10 mL of phosphate-buffered saline solution and stirred with a stirring bar for 30 min, and then the sample solution was placed in a rotary shaking incubator at 200 rpm and 37 °C for 24 h. Afterwards, it was filtered to obtain a saturated clear solution. After the proper dilution of the saturated solution by 25 to 50 times, a ChromTech CT-2800 UV/VIS spectrophotometer (Singapore) was utilized to measure the absorbance. The calibration line of the absorbance versus concentration of indomethacin was then used to determine the concentration. Ultimately, the original

concentration of the saturated solution could be obtained by multiplying the dilution factor. Group measurements were averaged from three samples.

3. Results

In this study, five different kinds of co-crystals, formed by indomethacin (IND) with saccharin (SAC), nicotine amide (NIC), urea (U), L-lysine (LYS), and L-histidine (HIS), were prepared through the solvent evaporation method. After that, these co-crystals (CCs), as well as physical mixtures (PMs) and individual raw materials, were identified via powder X-ray diffraction (XRD) spectrum, terahertz time-domain spectroscopy (THz-TDS), Fourier transform infrared absorption spectroscopy (FT-IR), and solubility tests. The spectroscopic analyses were performed on the following five groups: the IND/SAC group (Figure 1), IND/NIC group (Figure 2), IND/U group (Figure 3), IND/LYS group (Figure 4), and IND/HIS group (Figure 5). The results of the solubility tests are shown in Table 1.

Table 1. Solubility of indomethacin (IND) and various indomethacin/co-former co-crystals (CC) in phosphate-buffered solution, pH 6.8. Group measurement values were averaged from three samples (mean ± SD).

Substance	Solubility (mg/L)
IND	247 ± 33
IND/SAC CC	756 ± 34
IND/NIC CC	696 ± 15
IND/U CC	575 ± 23
IND/LYS CC	742 ± 10
IND/HIS CC	451 ± 14

3.1. Indomethacin/Saccharin (IND/SAC) Co-Crystal Preparation and Characterization

The powder XRD patterns, THz spectra, and FT-IR spectra of the indomethacin/saccharin co-crystal (IND/SAC CC) and the indomethacin/saccharin physical mixture (IND/SAC PM) as well as pure indomethacin (IND) and pure saccharin (SAC) are shown in Figure 1. It can be observed in Figure 1a that the XRD pattern of the physical mixture of indomethacin and saccharin (IND/SAC PM) has characteristic peaks at 15.84°, 16.56°, 18.90°, and 21.80°, showing the superposition of the characteristic peaks of both indomethacin (IND) and saccharin (SAC). In contrast, the co-crystal of indomethacin and saccharin (IND/SAC CC) has new characteristic peaks at 14.28°, 21.06°, and 27.27°, which is consistent with the XRD patterns of the indomethacin–saccharin co-crystal simulated by using a molecular modeling technique in the literature [13]. It is obvious that the characteristic peak patterns of IND/SAC PM and IND/SAC CC are significantly different, indicating that the two have their own crystal structures, and XRD can be used to determine whether the co-crystal drug is successfully formed.

For the similar characterization of the indomethacin/saccharin co-crystal (IND/SAC CC) and indomethacin/saccharin physical mixture (IND/SAC PM), as well as pure indomethacin (IND) and pure saccharin (SAC), performed by THz-TDS, the results are shown in Figure 1b. Indomethacin has absorption peaks at 1.24 and 1.99 THz, and saccharin has absorption peaks at 1.13 and 2.03 THz. IND/SAC PM has absorption peaks at 1.22 and 2.00 THz, which are formed by the superposition of the spectra of indomethacin and saccharin. As for IND/SAC CC, there are new absorption peaks at 1.10 and 1.34 THz, which shows that if the co-crystal is successfully formed, the change in the hydrogen bond vibration mode will make the signal of the absorption peak different from that of the original drug (indomethacin) and the original co-former (saccharin). These results are consistent with THz spectrum results reported by Xu et al. [26], showing that THz-TDS can also be utilized for drug and co-crystal identification.

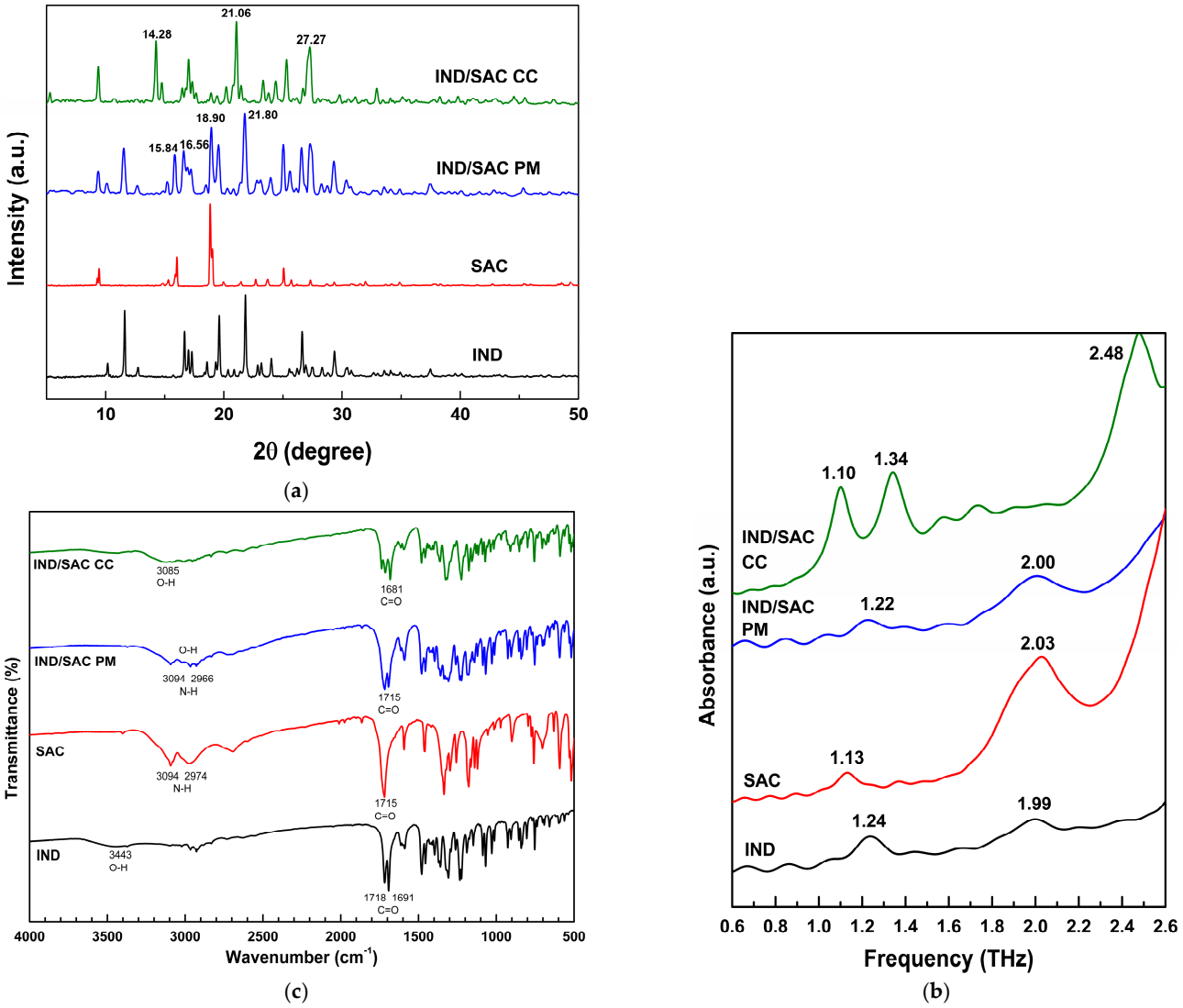

Figure 1. Indomethacin/saccharin (IND/SAC) system. (**a**) Powder XRD patterns, (**b**) terahertz (THz) absorption spectra, and (**c**) FT-IR absorption spectra of co-crystals of indomethacin/saccharin prepared by solvent evaporation (IND/SAC CC), physical mixture of indomethacin/saccharin (IND/SAC PM), saccharin (SAC), and indomethacin (IND).

Similarly, for the characterization of the indomethacin/saccharin co-crystal (IND/SAC CC) and indomethacin/saccharin physical mixture (IND/SAC PM), as well as pure indomethacin (IND) and pure saccharin (SAC), performed by FT-IR, the results are shown in Figure 1c. The FT-IR spectrum of the indomethacin/saccharin co-crystal has been reported [27]. Figure 1c shows that the hydroxyl group (at 3443 cm^{-1}) of pure indomethacin, the amino group (at 2974 and 3094 cm^{-1}) of pure saccharin, and the acyl group (around 1700 cm^{-1}) of both exist in the IND/SAC PM, and there is no shift in the position of the characteristic peak, while for IND in the IND/SAC CC, the position of the acyl group (at 1681 cm^{-1}) shifts to red, the intensity of the characteristic peak of the hydroxyl group (at 3085 cm^{-1}) becomes stronger, and the two characteristic peaks of the amine group overlap, making it unnoticeable. These phenomena are caused by the formation of hydrogen bonds (formation of co-crystal) that affect the vibration mode of chemical bonds, triggering the characteristic peak intensity to become stronger or causing the peak position to shift.

3.2. Indomethacin/Nicotine Amide (IND/NIC) Co-Crystal Preparation and Characterization

While nicotine amide (NIC) is used as a co-former, the results of the powder XRD, THz, and FT-IR analyses of the indomethacin/nicotine amide co-crystal (IND/NIC CC) and indomethacin/nicotine amide physical mixture (IND/NIC PM) as well as indomethacin (IND) and nicotine amide (NIC) are shown in Figure 2. The XRD patterns displayed in Figure 2a reveal that the IND/NIC PM has characteristic peaks at 16.70°, 21.88°, and 25.76°, while the IND/NIC CC has characteristic peaks at 13.55° and 15.75° that indomethacin and nicotine amide do not have. The XRD patterns of the IND/NIC CC are consistent with that simulated by Majumder et al. using a molecular modeling technique [28], which indicates that indomethacin and nicotine amide successfully formed co-crystals through solvent evaporation.

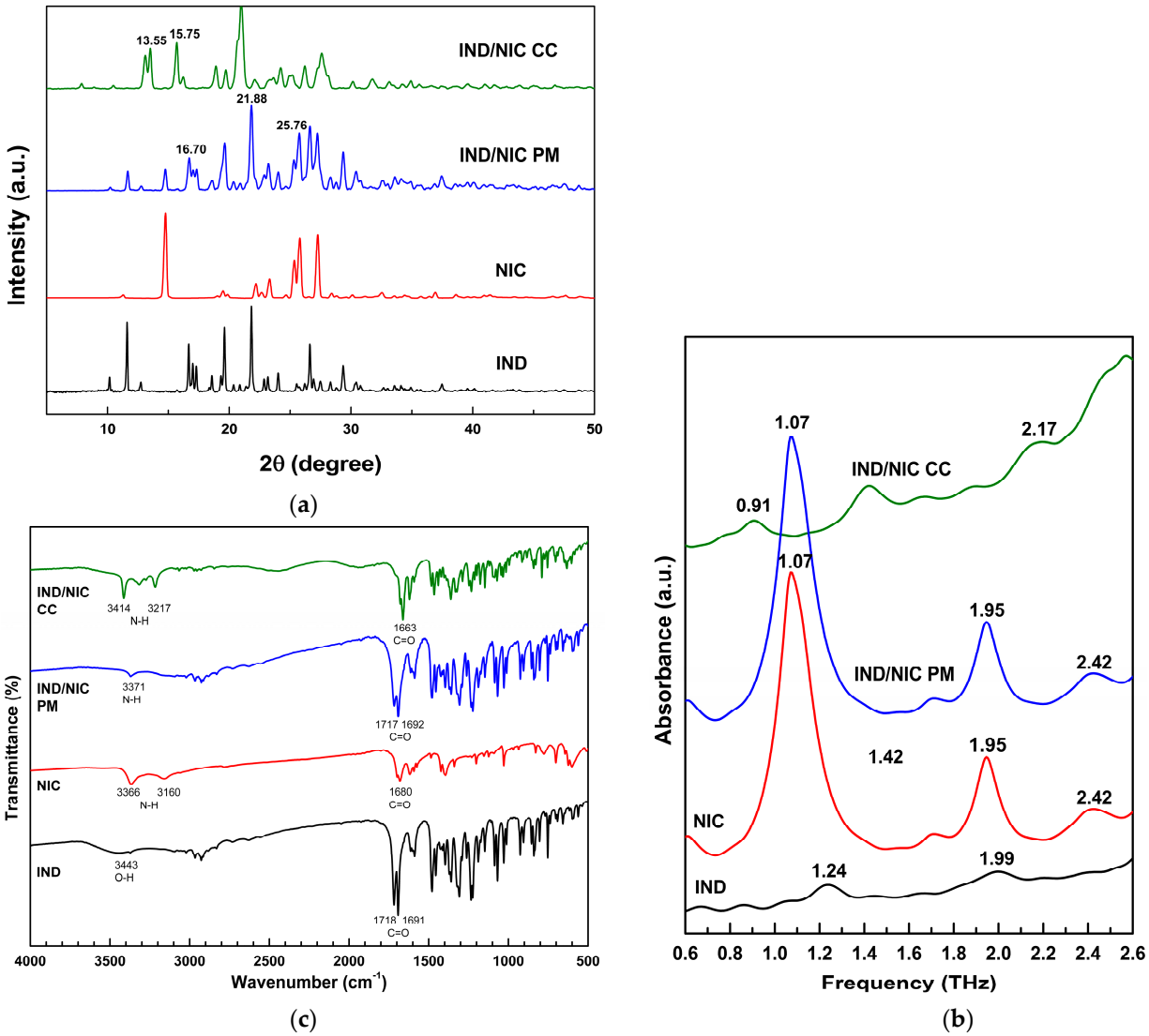

Figure 2. Indomethacin/nicotinamide (IND/NIC) system. (**a**) Powder XRD patterns, (**b**) terahertz (THz) absorption spectra, and (**c**) FT-IR absorption spectra of co-crystals of indomethacin/nicotinamide prepared by solvent evaporation (IND/NIC CC), physical mixture of indomethacin/nicotinamide (IND/NIC PM), nicotinamide (NIC), and indomethacin (IND).

For similar characterization performed by THz-TDS instead, the results are shown in Figure 2b. IND-NIC PM has obvious absorption peaks at 1.07, 1.95, and 2.42 THz, which are very similar to the nicotine amide. The main reason is that the THz absorption peaks of indomethacin are much smaller than those of nicotine amide, so the IND/NIC PM peaks

are like those of nicotine amide even after the superposition of the absorption peaks of indomethacin and nicotine amide. In contrast, the formation of co-crystals (IND/NIC CC) generates new absorption peaks at 0.91 and 2.17 THz, which is consistent with the literature [26].

Figure 2c shows the FT-IR spectra of IND/NIC PM and IND/NIC CC. In the IND/NIC PM spectrum, the acyl group (at 1692 and 1717 cm^{-1}) of indomethacin and the amine group (at 3371 cm^{-1}) of nicotinamide can be observed, and there is no shift in the position of these characteristic peaks. However, in the IND/NIC CC spectrum, the position of the acyl group (at 1663 cm^{-1}) is red-shifted, and the position of the amine group (at 3414 cm^{-1}) is blue-shifted, and the peak intensity becomes higher, indicating that the hydrogen bond formation between the acyl group and the amine group affects the vibration mode of the chemical bond, thus altering the position and intensity of the characteristic peaks, which is similar to the study by Lin et al. [29].

3.3. Indomethacin/Urea (IND/U) Co-Crystal Preparation and Characterization

In the case that urea (U) is used as a co-former, Figure 3 presents the powder XRD, THz, and FT-IR results of the indomethacin/urea co-crystal (IND/U CC) and indomethacin/urea physical mixture (IND/U PM) as well as indomethacin (IND) and urea (U). In the XRD patterns shown in Figure 3a, the IND/U CC produces characteristic peaks at 8.52° and 14.90°, which neither IND nor U have, indicating that the IND/U CC is formed successfully.

Looking at the THz spectra in Figure 3b, the absorption spectrum of IND/U PM has strong absorption peaks around 1.22 and 2.00 THz, which is very similar to the superpositions of the absorption peaks of indomethacin and urea (there is no obvious peak for urea, which is consistent with the literature [30]). In contrast, the IND/U CC has a new absorption peak at 1.49 THz, which also indicates the formation of a co-crystal that changes the hydrogen bond vibration mode, resulting in a change in the position of the absorption peak.

Figure 3c is the FT-IR spectra, which shows the characteristic peaks of the hydroxyl (at 3450 cm^{-1}) and acyl (at 1689 and 1715 cm^{-1}) groups of the indomethacin and amine groups (around 3450 cm^{-1}) of urea in the IND/U PM, with no shift in the positions of these characteristic peaks. However, in the FT-IR spectrum of the co-crystal (IND/U CC), the characteristic peak intensity of the hydroxyl, amine (both at 3448 cm^{-1}), and acyl groups (at 1692 cm^{-1}) becomes greater, indicating that the hydrogen bond formation between the hydroxyl, amine, and acyl groups affects the vibration mode of the chemical bond. Nevertheless, the FT-IR spectra of the IND/U PM and IND/U CC groups are not significantly different from each other.

It is noteworthy that the formation and spectra of the IND/U CC are novel, and these important findings have not been reported yet. Thus, we offer a new opportunity for indomethacin co-crystals to be developed further.

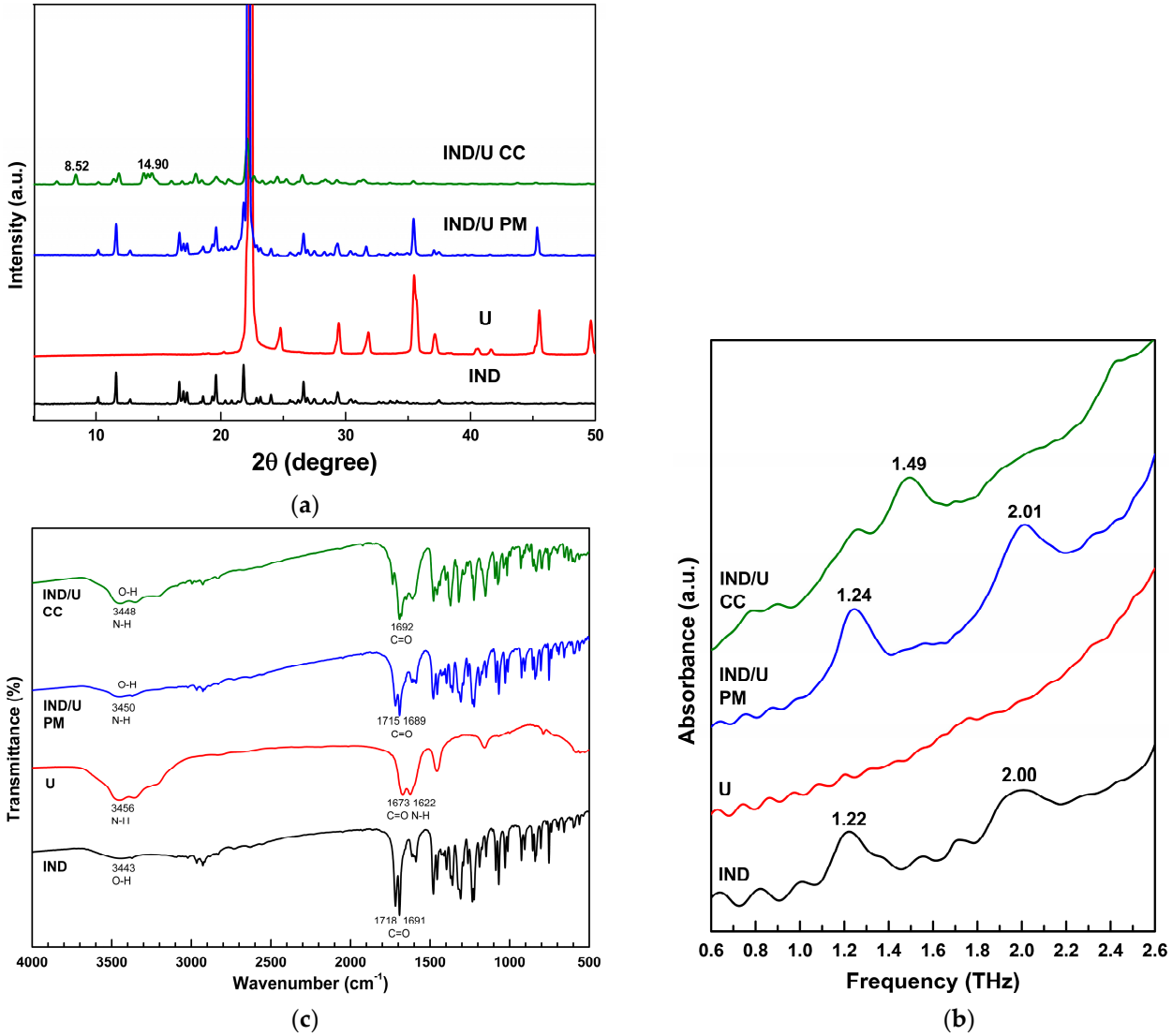

Figure 3. Indomethacin/urea (IND/U) system. (**a**) Powder XRD patterns, (**b**) terahertz (THz) absorption spectra, and (**c**) FT-IR absorption spectra of co-crystals of indomethacin/urea prepared by solvent evaporation (IND/U CC), physical mixture of indomethacin/urea (IND/U PM), urea (U), and indomethacin (IND).

3.4. Indomethacin/Lysine (IND/LYS) Co-Crystal Preparation and Characterization

Figure 4 shows the results of the powder XRD, THz, and FT-IR analyses of the indomethacin/lysine co-crystal (IND/LYS CC) and indomethacin/lysine physical mixture (IND/LYS PM) as well as indomethacin (IND) and lysine (LYS) if L-lysine (LYS) is used as a co-former. In the XRD patterns shown in Figure 4a, the IND/LYS PM has the characteristic peaks of both indomethacin and lysine, such as 16.70° and 18.53°, indicating that the physical mixture retains two individual crystals of pure components. In contrast, the IND/LYS CC has characteristic peaks at 17.95° and 28.20°, which are quite different from those of the two pure components, and the XRD pattern is consistent with the XRD characteristic peaks of the indomethacin-L-lysine co-crystal reported by Kasten et al. [31], also confirming the successful preparation of a co-crystal.

As for the THz spectra in Figure 4b, L-lysine has signal peaks at 0.95 and 2.21 THz, which are consistent with the experimental values in the literature [32], while the absorption spectrum of the IND/LYS PM is mainly the superposition of the absorption spectra of indomethacin and lysine, with absorption peaks at 1.24 and 1.70 THz. In contrast, the

IND/LYS CC has new absorption peaks at 1.43 THz, so the THz spectrum analysis can easily distinguish co-crystals from physical mixtures.

Figure 4c shows the FT-IR spectra. The overlapping characteristic peaks of the hydroxyl (at 3434 cm^{-1}), acyl (around 1700 cm^{-1}), and amine (at 1565 cm^{-1}) groups of lysine and indomethacin are present in the IND/LYS PM but less obvious. However, in the spectrum of the IND/LYS CC, the peak of the hydroxyl (at 3450 cm^{-1}) has shifted to a higher wavenumber. In addition, the peaks of the amine (at 1637 cm^{-1}) and acyl (at 1678 cm^{-1}) groups have changed their positions as well, indicating the successful formation of hydrogen bonds between indomethacin and L-lysine molecules.

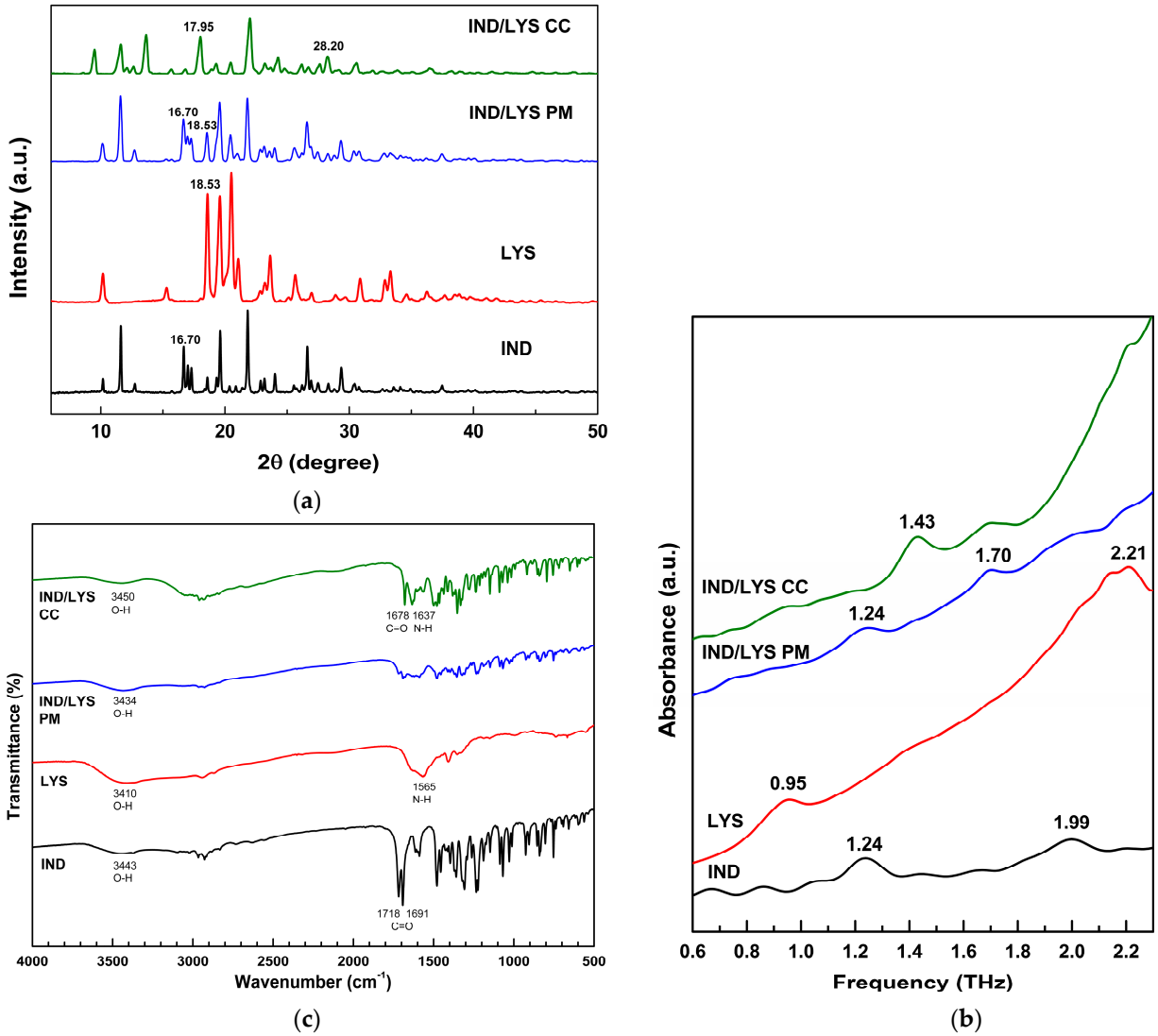

Figure 4. Indomethacin/lysine (IND/LYS) system. (**a**) Powder XRD patterns, (**b**) terahertz (THz) absorption spectra, and (**c**) FT-IR absorption spectra of co-crystals of indomethacin/lysine prepared by solvent evaporation (IND/LYS CC), physical mixture of indomethacin/lysine (IND/LYS PM), L-lysine (LYS), and indomethacin (IND).

3.5. Indomethacin/Histidine (IND/HIS) Co-Crystal Preparation and Characterization

Figure 5 shows the results of the powder XRD, THz, and FT-IR spectra of the indomethacin/histidine co-crystal (IND/HIS CC) and indomethacin/histidine physical mixture (IND/HIS PM) as well as indomethacin (IND) and histidine (HIS) for when L-histidine (HIS) is used as a co-former. In the XRD patterns shown in Figure 5a, the IND/HIS PM has characteristic peaks at 9.45° and 19.00°, and these characteristic peaks also appear in

pure components, indicating that the physical mixture constituting the two components still retains the characteristics of the individual components. In contrast, the IND/HIS CC has characteristic peaks at 7.03°, 8.55°, and 13.99°, which are different from those of the IND/HIS PM, indicating that the IND/HIS CC is produced successfully.

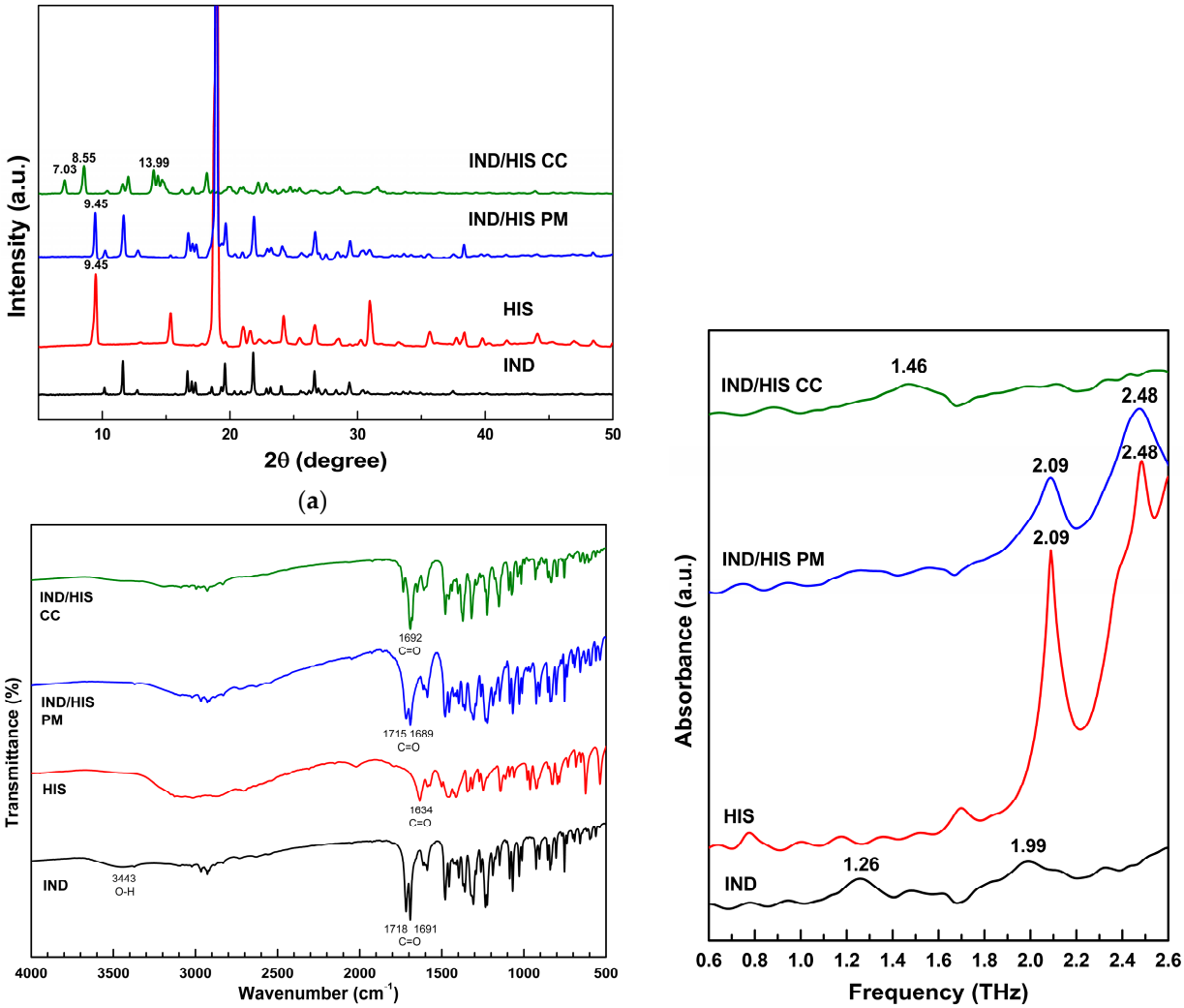

Figure 5. Indomethacin/histidine (IND/HIS) system. (**a**) Powder XRD patterns, (**b**) terahertz (THz) absorption spectra, and (**c**) FT-IR absorption spectra of co-crystals of indomethacin/histidine prepared by solvent evaporation (IND/HIS CC), physical mixture of indomethacin/histidine (IND/HIS PM), L-histidine (HIS), and indomethacin (IND).

As for the THz spectra in Figure 5b, the absorption spectrum of the IND/HIS PM is mainly the superposition of the absorption spectra of indomethacin and histidine. L-histidine has absorption peaks at 2.09 and 2.48 THz, which is consistent with the literature [33]. Because the absorption peaks of histidine are much stronger than those of indomethacin, the IND/HIS PM also has absorption peaks at 2.09 and 2.48 THz. In contrast, the IND/HIS CC group has a new absorption peak at 1.46 THz, and the entire absorption peak curve is obviously different from that of the IND/HIS PM, confirming the formation of the IND/HIS CC. Additionally, this is a new spectrum that has never been reported.

Figure 5c shows the results of the FT-IR spectra of the IND/HIS CC and IND/HIS PM. In the IND/HIS PM spectrum, the characteristic peaks of the acyl groups (at 1689 and 1715 cm^{-1}) of indomethacin and L-histidine are still obvious, while the characteristic peaks of the acyl groups (at 1692 cm^{-1}) in the IND/HIS CC spectrum have changed, indicating

that hydrogen bond formation may affect the acyl groups and the associated vibrational mode of the chemical bond. This phenomenon is similar to the result of a study conducted by Alsalhi et al. [34].

3.6. Solubility Enhancement by Co-Crystallization

One of the purposes of synthesizing drug co-crystals is to increase the solubility of poorly aqueous soluble drugs so as to improve the bioavailability of drugs. Table 1 shows the solubility of indomethacin and the five indomethacin/co-former co-crystals in the phosphate-buffered solution with pH 6.8 at 37 °C. The group measurement values were averaged from three samples (mean ± SD). It can be seen that after the formation of co-crystals, the solubility of indomethacin is enhanced by about two to three times, and the solubilities of the indomethacin/saccharin and indomethacin/lysine co-crystals (IND/SAC CC and IND/LYS CC) increase significantly. This result may be attributed to the "spring and parachute" phenomenon [35]. In other words, a relatively more water-soluble co-former is pulled out of the co-crystals in an aqueous environment, leaving the API (drug) supersaturated, which can be transiently maintained in the presence of other excipients or ingredients. Hence, the solubility enhancement of the drug is achieved owing to the transient drug supersaturation. Therefore, the solubility of poorly soluble drugs such as indomethacin can be successfully improved via the formation of co-crystals.

4. Discussion

The above investigations, including powder XRD, THz-TDS, FT-IR, and the solubility test, were performed on the co-crystals formed by indomethacin together with one of the five co-formers, including three kinds of amides (saccharin, nicotine amide, and urea) and two kinds of amino acids (L-lysine and L-histidine). The formation of co-crystals and the force of hydrogen bonding can be observed in the THz spectra according to the shift in the position of the absorption peak and the change in the shape of the absorption peak. Compared with the XRD pattern, which may have more diffraction peaks, the THz spectrum can clearly identify and distinguish the co-crystals from physical mixtures. Several studies conducted on the preparation and characterization of co-crystals reveal similar results as the aforementioned ones. In the study by Otsuka et al. [36], caffeine and oxalic acid form a co-crystal with a molar ratio of 2:1. In the result of the XRD analysis, while slightly different, the pattern of caffeine highly resembles that of the co-crystal. Hence, it is not easy to determine the successful formation of co-crystals at a glance. In comparison, the patterns of THz display an explicit distinction between caffeine, oxalic acid, and the co-crystal, confirming the existence of the co-crystal. Furthermore, Ouyang et al. [37] also performed XRD and THz analyses on the co-crystal consisting of vanillin and isonicotinamide molecules. Since vanillin has compact peaks in the XRD spectra, especially in the range of 10 to 30 degrees, it is not easy to validate the formation of a co-crystal by XRD solely, whereas the THz pattern of a co-crystal can be distinguished effortlessly from those of pure components. Therefore, it seems that THz is more suitable for identifying co-crystal formation than XRD. Additionally, Heidrich et al. [38] found that THz has a lower detection limit than XRD to identify minor changes in the drug crystallinity. More importantly, THz analysis is a non-destructive and non-ionizing radiative technique that is more convenient and safer to use than XRD analysis because the energy of an X-ray is about a million times stronger than that of terahertz electromagnetic waves.

If comparing the use of THz spectra with the use of FT-IR spectra in distinguishing co-crystals from physical mixtures, the difference between the co-crystal and the physical mixture is relatively small in the FT-IR spectra, usually less than 30 cm^{-1}. For example, as shown in Figure 3b, the difference between the co-crystal (IND/U CC) and the physical mixture (IND/U PM) can be directly observed in the THz spectra. However, as shown in Figure 3c, in the FT-IR spectra, the difference between the IND/U CC and IND/U PM is not very apparent, and the red shift or blue shift of the characteristic peaks is quite inconspicuous. There are several studies that have been performed by researchers to compare

the spectra of the same sample by using the two techniques. In the study conducted by Ying et al. [39], the FT-IR spectra merely changed even though carbamazepine formed a co-crystal with nicotinamide. That is, the spectrum of the co-crystal was approximately identical to that of carbamazepine. However, in the work of Zhou et al. [40], the co-crystal of the two aforementioned components was analyzed by THz-TDS spectroscopy. It was found that the spectrum of the co-crystal was significantly different from those of the two constituents, confirming the formation of the co-crystal. Therefore, it may be said that THz analysis is more suitable than FT-IR analysis for identifying co-crystals and original materials. Furthermore, it was also reported that the signal-to-noise ratio is higher in the case of THz-TDS spectroscopy when compared with FT-IR [41]. In addition, THz spectroscopy can provide the finger-print spectra referring to special molecular structures [42] and further information regarding the weak molecular vibrations and kinds of structural changes in crystalline within the low-frequency region, particularly below 3.0 THz [43,44].

As for the solubility enhancement, since the solubility test methods vary substantially, and the solubility of a drug depends on several conditions, such as the temperature, pH value, sampling time, and nature of the solvent used, it is hard to find the solubility data measured under the same conditions from other studies in the literature. The solubility of indomethacin in water at 25 °C was 0.937 mg/L [16]. In another study, however, the solubility was 18.46 mg/L [45]. In phosphate buffer (pH 6.8), the solubility of indomethacin was found to be enhanced [46], possibly due to its dissociation because the pKa of indomethacin is 4.5 [16]. Moreover, some other relevant studies are also worth mentioning. For example, the solubility of indomethacin was increased by two to four times, depending on the strength of phosphate buffer, in a co-crystal form with saccharin according to the research by Basavoju et al. [13]. This is in agreement with the solubility results obtained in this study. Additionally, Alsalhi and coworkers [34] found that the solubility of indomethacin (IND) increased with an increase in the concentration of amino acids, such as L-lysine (LYS) and L-histidine (HIS), implying that the use of amino acids can improve the solubility of a poorly soluble drug. Additionally, it was found that the interactions between IND and the amino acids comprise both ionic and non-ionic effects [34].

Regarding the expense, the total cost for each of the three analytical methods used in this study includes the cost to procure the instrument and annual maintenance, the cost to prepare various samples (including co-crystals, physical mixtures, and single components), and the personnel cost for instrument operation and management. The XRD instrument used in this study costs about USD 170,000, the THz instrument costs about USD 190,000, and the FT-IR instrument costs about USD 40,000. The annual maintenance fee required for each instrument is about USD 3000–8000, and replacement parts have additional costs. The other costs for using the three analytical methods are similar.

As for the measurement of the samples, XRD measurements take about 10–20 min for each sample and require about 1 g per sample. THz measurements take less than 5 s for each sample and require less than 0.04 g per sample. FT-IR measurements take less than 1 min for each sample and require less than 0.002 g per sample. As for the accuracy of the analysis, XRD is quite accurate. In case a co-crystal forms through intermolecular hydrogen bonds, the change in the crystal lattice structure will lead to the emergence of new XRD peaks or the disappearance of old ones. The THz discrimination of materials is also powerful. The spectrum between 0.6 and 2.6 THz is mainly the vibrational spectrum between molecules; thus, it is capable of detecting weak intermolecular forces, such as hydrogen bonds in a co-crystal. The characteristic THz peaks will shift, as shown in our results. FT-IR spectroscopy is used to identify various functional groups. When a co-crystal forms, the characteristic FT-IR absorption peak of a specific functional group can still be seen, but the position of the peak may shift, or the peak may be broader. However, our results indicate that the intensity change or position shift of the characteristic FT-IR peaks of the specific functional groups due to the formation of the co-crystal is relatively not as obvious as that revealed by the XRD and THz analyses. Therefore, based on the above discussion, even though the costs of purchasing XRD and THz instruments are several times

higher than those of purchasing FT-IR instruments, XRD and THz analyses demonstrate superior discriminating capabilities.

Finally, it is worth mentioning that, in comparison with XRD analysis, THz analysis offers the advantages of non-destructive, non-ionizing radiative, and relatively rapid measurement techniques. It can be expected that the use of THz analysis in the identification of drug co-crystals, raw materials, and physical mixtures, and also the use of co-crystallization in the solubility enhancement of drugs, will be more prevalent in the future.

5. Conclusions

In the present study, five different kinds of indomethacin/co-former co-crystals were successfully prepared by the solvent evaporation method. We provided a comprehensive series of spectra obtained by the three spectroscopy methods that apply electromagnetic waves. Not only did we validate some of the spectra in this study, but we also suggested some novel spectra that have not yet been reported in other relevant studies in the literature. In addition, the use of powder XRD and terahertz (THz) spectra analyses showed that both analyses were more capable of distinguishing co-crystals from physical mixtures for all sets than FT-IR. But precisely, compared with XRD and FT-IR spectra, THz spectra are simpler and clearer with less noise. Hence, when comparing the spectra of co-crystals and physical mixtures, the differences can be clearly distinguished. In addition, THz spectroscopy is a non-destructive, non-ionizing radiative, and relatively rapid measurement technique which is more convenient and safer to use than XRD analysis. It is also confirmed in this study that the terahertz spectrum has good reproducibility. If a sufficient amount of THz-TDS data can be established in the future, they are expected to play an important role in real-time product monitoring and product identification in the pharmaceutical industry. Even though the costs of purchasing XRD and THz instruments are several times higher than those of purchasing FT-IR instruments, XRD and THz analyses demonstrate superior discriminating capabilities. The solubility tests also show that after indomethacin forms co-crystals with one of the five co-formers selected in this study, they all exhibit higher solubility than pure indomethacin, suggesting that drug co-crystallization technology can improve the solubility of poorly soluble drugs. It is thus highly expected that the use of co-crystallization in the solubility enhancement of drugs will be more extensive.

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