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Physical Characteristics of Cilostazol–Hydroxybenzoic Acid Cocrystals Prepared Using a Spray Drying Method

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Abstract: The cocrystal formation of pharmaceuticals can improve the various physical properties of drugs, such as solubility, without the need for chemical modification of the drug substances. In the present study, we prepared cocrystals of cilostazol and additive coformers (derivatives of hydroxybenzoic acid) using a spray drying method. Based on the preparation of the cocrystals of cilostazol and the coformers as reported previously, the characteristics of the cilostazol cocrystals prepared using solvent evaporation, slurry, and spray drying methods were compared. The physical characterization revealed that the spray drying method successfully produced cilostazol–4-hydroxybenzoic acid and cilostazol–2,4-dihydroxybenzoic acid cocrystals, whereas samples of cocrystals of cilostazol and 2,5-dihydroxybenzoic acid produced via the spray drying process appeared to contain coformer polymorphs. The dissolution of cilostazol was improved using the spray-dried cocrystal samples composed of coformers compared to samples prepared using cilostazol alone or a physical mixture. The present results provide useful information regarding the manufacture of cilostazol cocrystals and pharmaceutical cocrystals via spray drying in large-batch production.

Keywords: cocrystal; coformer; spray drying; cilostazol; hydroxybenzoic acid

1. Introduction

Cocrystals are novel forms of crystals composed of active pharmaceutical ingredients (APIs) and cocrystal coformers (coformers) and are formed through non-ionic interactions [1]. The generation of cocrystals improves not only the physical and mechanical properties of drugs, such as solubility and stability, but also enhances taste masking and intellectual property development [2]. As many poorly water-soluble compounds have been discovered, improving solubility is an important issue in new drug development. Pharmaceutical techniques such as pulverization of APIs, amorphous solid dispersion (ASD), the addition of salts, and the formation of cocrystals have been vigorously investigated as a means of improving solubility. For example, ASD improves both the dissolution and intestinal absorption of poorly water-soluble compounds [3]. However, controlling crystallization in ASD remains a challenging issue, as the physicochemical stability of materials generated with this technique is low. In contrast, crystalline materials such as salts and cocrystals are often physicochemically stable, and a wide variety of coformers are available to use in forming cocrystals, irrespective of the presence or absence of dissociating groups.

Cocrystals can be prepared by several methods, such as crystallization from a solution [4,5], spray drying, freeze drying [6], liquid-assisted grinding [7], hot-melt extrusion [8,9], and others,

such as the microwave heating of supercritical fluids [10]. These methods for preparing cocrystals were extensively reviewed by Izutsu et al. [11]. The spray drying method is one of the unit operations used to make powders during the production of pharmaceuticals and is also a general-purpose technology for industrial production. Scalability is a major advantage of the spray drying method. While crystallization in aqueous or organic solvents is commonly used, the application of cocrystal generation during drug production using the spray drying method remains limited, as quality control issues such, such as ensuring purity, present potential challenges. Pure cocrystals can be obtained using the spray drying method, even with an incongruent system; if there is a significant difference in the solubility of the API and coformer in the solvent used, the solutes with low solubility will precipitate first as their concentration increases under the drying process [12]. In spray drying, the solvent of the raw material evaporates immediately, and, therefore, the concentration and temperature of the solid component change rapidly. This dramatically shortens the crystal growth time, which promotes the precipitation of metastable crystals and amorphous solids. Alhalaweh et al. reported the use of spray drying to prepare pharmaceutical cocrystals by evaporating several solvents containing APIs and/or coformers [13]. It is presumed that this feature has a positive effect on the formation of cocrystals, as the API and coformer become supersaturated as they are rapidly concentrated in the sprayed droplets, causing the nucleation and growth of the cocrystals. However, there are relatively few reports describing the production of cocrystals by the spray drying method [14–17].

In the current study, we used the spray drying method to prepare cilostazol (CLZ) cocrystals. CLZ is an antiplatelet drug that exhibits vasodilatory effects. CLZ is categorized as a Biopharmaceutics Classification System Class II compound [18] and has no dissociating groups in its molecular structure (Figure 1a). As such, its low water solubility is a detriment to oral absorption. Jinno et al. investigated the effect of the size of CLZ particles prepared as a nanocrystalline powder and found that reducing the size of CLZ particles improved their dissolution following the Noyes–Whitney equation [19]. In our previous study, we screened the CLZ cocrystals produced using the slurry method with 61 candidate coformers, including various carboxylic acids, saccharides, and amino acids [20]. Cocrystals were prepared for three types of hydroxybenzoic acid derivatives, as shown in Figure 1b–d. In order to extend this research, CLZ-cocrystals were prepared using a spray dryer in the current study, and the effect of spray drying on CLZ-cocrystal generation was investigated by varying the spray drying conditions.

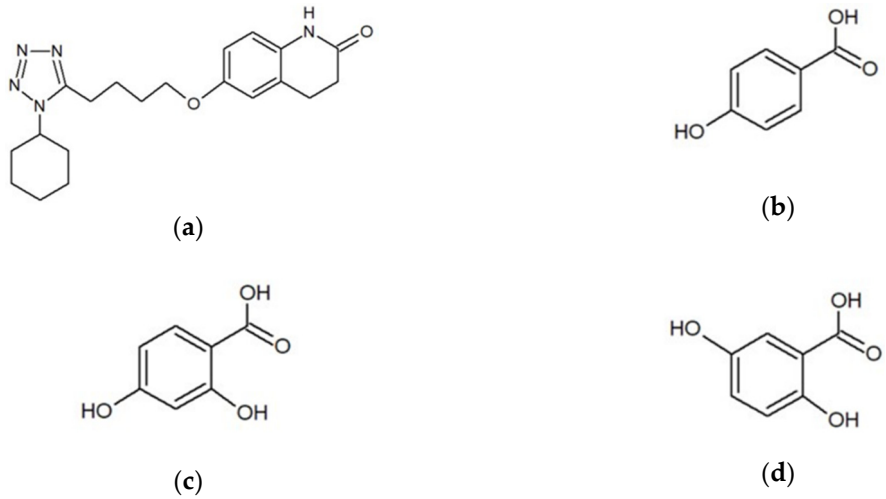

Figure 1. Chemical structures of (**a**) cilostazol (CLZ), (**b**) 4-hydroxybenzoic acid (4HBA), (**c**) 2,4-dihydroxybenzoic acid (2,4DHBA), and (**d**) 2,5-dihydroxybenzoic acid (2,5DHBA).

2. Materials and Methods

2.1. Reagents

CLZ was synthesized and hammer-milled at Otsuka Pharmaceutical Co., Ltd. (Tokushima, Japan). 4-Hydroxybenzoic acid (4HBA) was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), and 2,4-dihydroxybenzoic acid (2,4DHBA) and 2,5-dihydroxybenzoic acid (2,5DHBA) (as the coformers) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Hypromellose, type 2910 grade TC-5E, was used for kinetic dissolution and obtained from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Lactose monohydrate was obtained from DFE Pharma Ltd. (Goch, Germany). Colloidal silicon dioxide was obtained from Otsuka Pharmaceutical Co., Ltd.

2.2. Sample Preparation

To enable comparison to samples produced by the spray drying method, in the present study, we also prepared samples by physical mixing and the solvent evaporation and slurry methods, which are widely used for the preparation of cocrystals.

2.2.1. Preparation of Samples by Physical Mixing

CLZ and each coformer were weighed at a stoichiometric ratio of 1:2 (for CLZ and 4HBA), 1:2 (for CLZ and 2,4DHBA), or 1:1.6 (for CLZ and 2,5DHBA). The CLZ and coformer were physically mixed with a mortar and pestle. For the preliminary analysis of various compositions, CLZ and 4HBA were prepared at a stoichiometric ratio of 1:1, as shown in Supplementary Materials Table S1.

2.2.2. Preparation of Samples Using the Solvent Evaporation Method

CLZ and the coformer were dissolved in an organic solvent, and the solvent was distilled using an evaporator to prepare the sample. CLZ-4HBA was prepared at a stoichiometric ratio of 1:1 for preliminary analysis of the various compositions, as shown in Table S1, and then investigated at a stoichiometric ratio of 1:2. CLZ-2,4DHBA was prepared at a stoichiometric ratio of 1:2, and CLZ-2,5DHBA was prepared at a stoichiometric ratio of 1:1.6.

2.2.3. Preparation of Samples Using the Slurry Method

In the slurry method, CLZ and 4HBA (or 2,4DHBA) were combined in a glass tube at a stoichiometric ratio of 1:2. Then, 4 mL of acetone (against 1.0 g of CLZ) was added to the tube, and the sample mixture was stirred at room temperature for 7 days. The resulting suspension was subjected to suction filtration to collect the residue, which was further dried under a vacuum at room temperature. For 2,5DHBA, the CLZ and coformer mixture was prepared in a glass tube at a stoichiometric ratio of 1:1.6, and 1.5 mL of acetone (against 1.0 g of CLZ) was added to the tube. The viscous mixture was then suspended and dispersed in a warm bath at 40 °C for 24 hours. Thereafter, the sample mixture was stirred at room temperature for 6 days. The resulting suspension was subjected to suction filtration to collect the residue, which was then dried under a vacuum at room temperature.

2.2.4. Preparation of Spray Dried Samples

CLZ and coformer were dissolved in acetone/methanol (1/1 [*v*/*v*]) at a stoichiometric ratio of 1:1, and the solvent was spray dried using a CNL-3 spray dryer (Ohkawara Kakohki Co. Ltd., Yokohama, Japan) under closed conditions. The spray drying conditions were as follows: inlet temperature, 80–140 °C; flow rate, 1 kg/h. The resulting spray-dried powder was further dried under a vacuum.

2.3. Powder X-Ray Diffraction (PXRD)

The CLZ samples were analyzed by PXRD using a Rint-Ultima instrument (Rigaku Co., Ltd., Tokyo, Japan) via irradiation with Cu-Kα X-rays. The tube voltage and amperage were 44 kV and 40 mA, respectively. The samples were scanned between 2θ of 3 to 35°.

2.4. Differential Scanning Calorimetry (DSC)

The thermodynamic properties of the CLZ cocrystals and host crystals were evaluated by DSC using a DSC-60 instrument (Shimadzu Corp., Kyoto, Japan) equipped with a refrigerated cooling system. A total of 2–3 mg of sample was heated at a rate of 10 °C/min under a nitrogen purge (continuous purging at a flow rate of 20 mL/min) in a crimped aluminum pan.

2.5. Fourier-Transform Infrared Spectroscopy (FT-IR)

KBr tablets (101 mg) composed of 100 mg of KBr and 1 mg of the sample were prepared using a press machine (Mini Press, MP-1; JASCO Co., Tokyo, Japan) to obtain samples for FT-IR. The FT-IR analysis was performed using an FT-IR-8400S spectrometer (Shimadzu Corp.).

2.6. Scanning Electron Microscopy (SEM)

Samples were observed by SEM (S-4300, Hitachi, Tokyo, Japan) after coating with Pt-Pd using an ion sputtering apparatus (E-102; Hitachi). The D_{50} median particle diameter was calculated from the cumulative distribution of the diameters of particles in SEM images of each sample using the ImageJ®software (public-domain).

2.7. Dissolution Test

Dissolution testing was conducted as described previously, with minor modifications [20]. To prepare the dissolution medium as in a typical experiment, Japanese Pharmacopoeia 1st fluid (pH 1.2) was used. Hypromellose (1%) was then added to the dissolution medium to prevent recrystallization of CLZ. The dissolution medium (100 mL) was then placed in a beaker and stirred (500 rpm) at 37 °C. Each CLZ sample was mixed with lactose and light anhydrous silicic acid (49:1 [*w*/*w*]) to promote the rapid dispersion of the water-repellent CLZ bulk powder in the dissolution test. The resulting powder sample containing 10 mg of CLZ was added to the beaker. A 2-mL volume of the dissolution medium was then sampled at 5, 10, 15, 30, 45, 60, 90, and 120 min. Each sample solution was filtered through a 0.20 μm membrane filter and quantified by high-performance liquid chromatography (LC-10Ai, Shimadzu Corp.) under the following conditions: column, Inertsil ODS-80A (5 μm, 2.1 × 150 mm; GL Sciences Inc., Tokyo, Japan); mobile phase, water/acetonitrile/methanol (10:7:3 [*v*/*v*/*v*]); flow rate, 0.2 mL/min; detection wavelength, 257 nm.

3. Results and Discussion

3.1. Cocrystals of CLZ and Hydroxybenzoic Acid Derivatives

CLZ, an antiplatelet agent, is a poorly water-soluble drug (Figure 1a). Improving the dissolution and intestinal absorption of CLZ is thus necessary to expand its use as a medicine. Several options are possible to accomplish this, such as size reduction, solid dispersion to preserve the amorphous state of the drug, and cocrystallization. Yoshimura et al. reported the formation of CLZ cocrystals using hydroxybenzoic acid derivatives (Figure 1b–d) as coformers [20]. In order to extend that study, various combinations of APIs and coformers were subjected to spray drying, a common unit operation in pharmaceutical manufacturing.

The results of the crystal structure analyses (Mercury®) [20] shown in Figure 2 and Supplementary Materials Figure S1 indicate that the CLZ-4HBA and CLZ-2,4DHBA cocrystals exhibit similar crystal packing. Three hydrogen bonds were confirmed: those between the tetrazole skeleton amine of CLZ and

the carboxyl group of hydroxybenzoic acid (N˙˙˙HO-C), between the carbostyril skeleton amine and carboxyl group of hydroxybenzoic acid (NH˙˙˙O=C), and between the carbostyril carbonyl group and para- or meta-hydroxyl group of hydroxybenzoic acid (C=O˙˙˙HO-C). The CLZ-2,5DHBA cocrystals exhibited different crystal structures, with hydrogen bonds between the CLZ tetrazole skeleton amine and 2,5DHBA meta-hydroxyl group (N˙˙˙HO-C) and between the CLZ carbostyril skeleton carbonyl group and the 2,5DHBA carboxyl group (C=O˙˙˙HO-C). In addition, it was confirmed that the carbostyril skeleton of CLZ forms hydrogen bonds with two molecules. We hypothesized that such crystals could be formed not only by the slurry method, as demonstrated in previous reports, but also by the spray drying method, as used in the present study. Therefore, we evaluated the physicochemical properties of the resulting CLZ cocrystals.

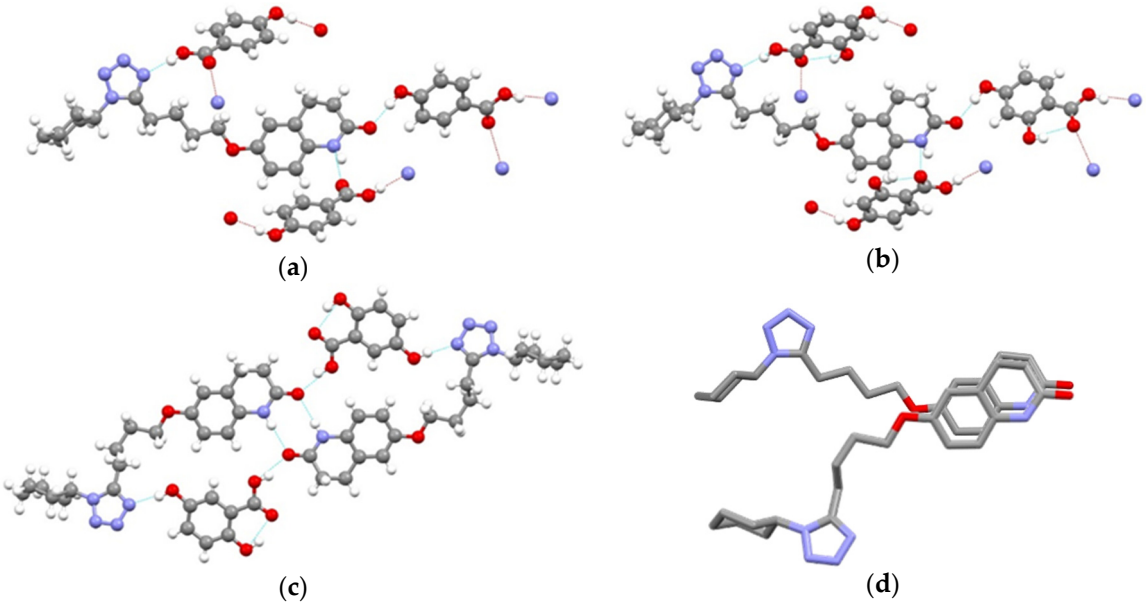

Figure 2. Crystal structures of the CLZ cocrystals; (**a**) CLZ-4HBA cocrystal, (**b**) CLZ-2,4DHBA cocrystal, (**c**) CLZ-2,5DHBA cocrystal, and (**d**) overlaid CLZ conformations in the CLZ-4HBA and CLZ-2,5DHBA cocrystals. Images were produced using Mercury® based on a previous study [20].

3.2. Characteristics of the CLZ-4HBA Cocrystals Prepared Using the Solvent Evaporation, Slurry, and Spray Drying Methods

Various CLZ and 4HBA concentrations and solvent compositions were screened in the present study. As shown in Table S1, two different solvent compositions (acetone or acetone/methanol) and two drug concentrations were compared. In the previous study, acetone alone was used for the preparation of CLZ cocrystals using the slurry method [20]. By contrast, in the current study, a mixture of acetone and methanol was used to generate CLZ cocrystals via the spray drying method to enhance the efficiency of the spray drying during formulation.

The results of the PXRD analysis of the samples prepared according to the solvent evaporation method are shown in Supplementary Materials Figure S2. Results for CLZ and 4HBA standards, the physical mixture (PM), and the CLZ cocrystals generated using the solvent evaporation methods are shown (the simulated ['SIM'] PXRD result shows the diffraction pattern calculated from the expected crystal structure, and the same applies hereafter). In the PXRD analyses, the samples prepared by the solvent evaporation method exhibited new diffraction peaks at $2\theta = 17°$ and 20°, which were not observed in the CLZ or 4HBA patterns. As this diffraction pattern was very similar to the simulated pattern, it was considered indicative of cocrystal formation. This pattern of the PXRD peaks was generally consistent despite differences in drug concentration and organic solvent used; varying these factors had minimal influence on cocrystal formation under the solvent evaporation method.

We next investigated the characteristics of the CLZ-4HBA cocrystals generated using the three different methods (Figure 3), comparing the results of the PXRD, FT-IR, and DSC analyses of samples prepared via the solvent evaporation, slurry, and spray drying methods. As shown in Figure 3a, the samples prepared using the solvent evaporation, slurry, and spray drying methods exhibited new PXRD diffraction peaks near 2θ = 17° and 20°; these peaks were not observed when analyzing samples of the CLZ and 4HBA standards or the PM. Samples were prepared by the spray drying method at different inlet temperatures (80, 100, or 120 °C). The new diffraction peaks near 2θ = 17° and 20° were present irrespective of spray drying inlet temperature.

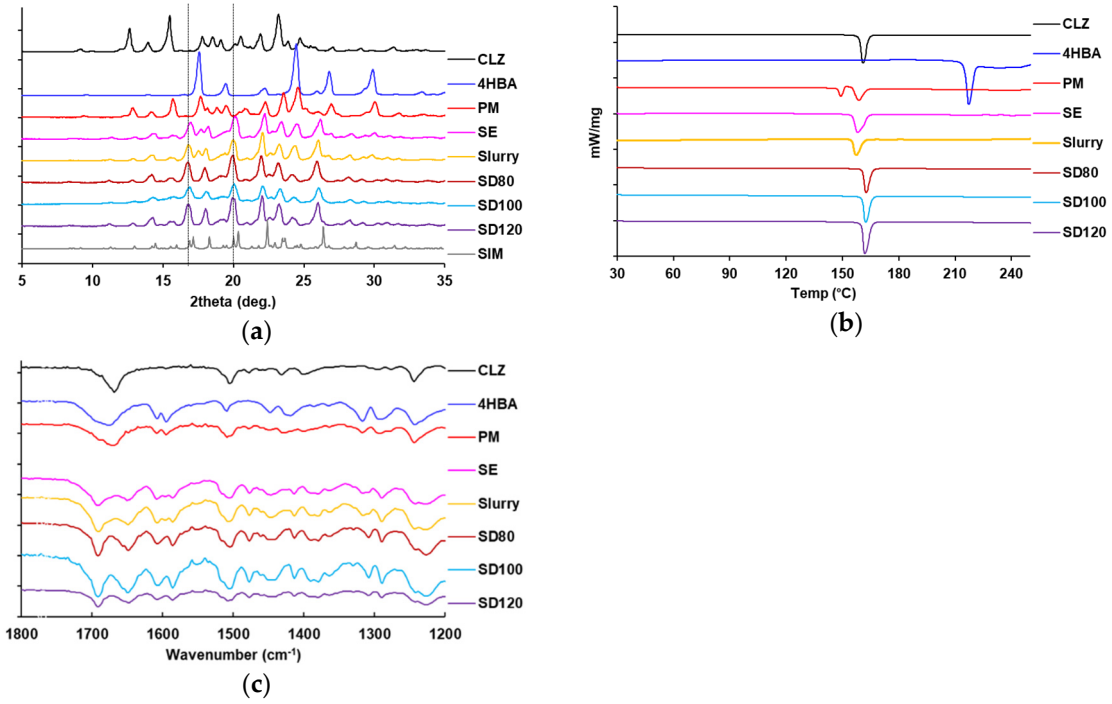

Figure 3. (**a**) PXRD, (**b**) DSC, and (**c**) FT-IR analysis of the CLZ-4HBA cocrystals prepared using the solvent evaporation method, slurry method, or spray drying method at 80, 100, and 120 °C.

As reported in the literature [20], the melting point of CLZ-4HBA cocrystals is 161.7 °C. As shown in Figure 3b, the DSC analysis revealed similar melting points around 160 °C for the cocrystal samples prepared using the various methods. Furthermore, exothermicity was observed in the PM sample after eutectic formation at 149 °C, suggesting that the cocrystal was formed by melting a sample of the physical mixture. As a result, under this DSC condition, an endothermic peak similar to that observed in the solvent evaporation and slurry method samples was observed at 158 °C.

In the FT-IR spectroscopy results shown in Figure 3c, a peak was observed at around 1700 cm^{-1} in the samples prepared using the three methods that differed in shape from a similar peak observed in the spectra of the CLZ drug substance, 4HBA, and PM. This is probably the result of the peak of the carbonyl group shifting due to the effect of intermolecular hydrogen bonding. Collectively, the above data confirm that CLZ-4HBA cocrystals can be prepared by the solvent evaporation, slurry, or spray drying methods at different temperatures.

3.3. Characteristics of CLZ-2,4DHBA Cocrystals Prepared Using the Solvent Evaporation, Slurry, and Spray Drying Methods

Next, the characteristics of the CLZ-2,4DHBA cocrystals prepared using the three different methods were investigated. Figure 4 shows the results of the PXRD, FT-IR, and DSC analyses of the cocrystals prepared using the solvent evaporation, slurry, and spray drying methods. Cocrystals prepared using the solvent evaporation, slurry, and spray drying methods exhibited new PXRD

diffraction peaks at 2θ = 11°, 18°, and 26° that were not observed in analyses of the CLZ drug substance, 2,4DHBA, or the PM (Figure 4a). In the samples prepared according to the spray drying method, the presence of these peaks was not affected by the different spray drying temperatures used. As reported in the literature [20], the melting point of CLZ-2,4DHBA cocrystals is 152.9 °C, and similar values were observed in the DSC analyses (Figure 4b) of the cocrystals prepared using the different methods. Furthermore, exothermicity was observed in the PM sample after eutectic formation at 142 °C, suggesting that the cocrystal was formed by melting a sample of the physical mixture. As a result, under these DSC conditions, an endothermic peak similar to that observed for the cocrystals prepared using the solvent evaporation or slurry method was observed at 153 °C. In the FT-IR spectroscopy results shown in Figure 4c, no peak shift different from that of the CLZ drug substance, 2,5DHBA, or PM was observed. Collectively, the above data further confirm that CLZ-2,4DHBA cocrystals can be prepared by the solvent evaporation, slurry, or spray drying methods at different temperatures.

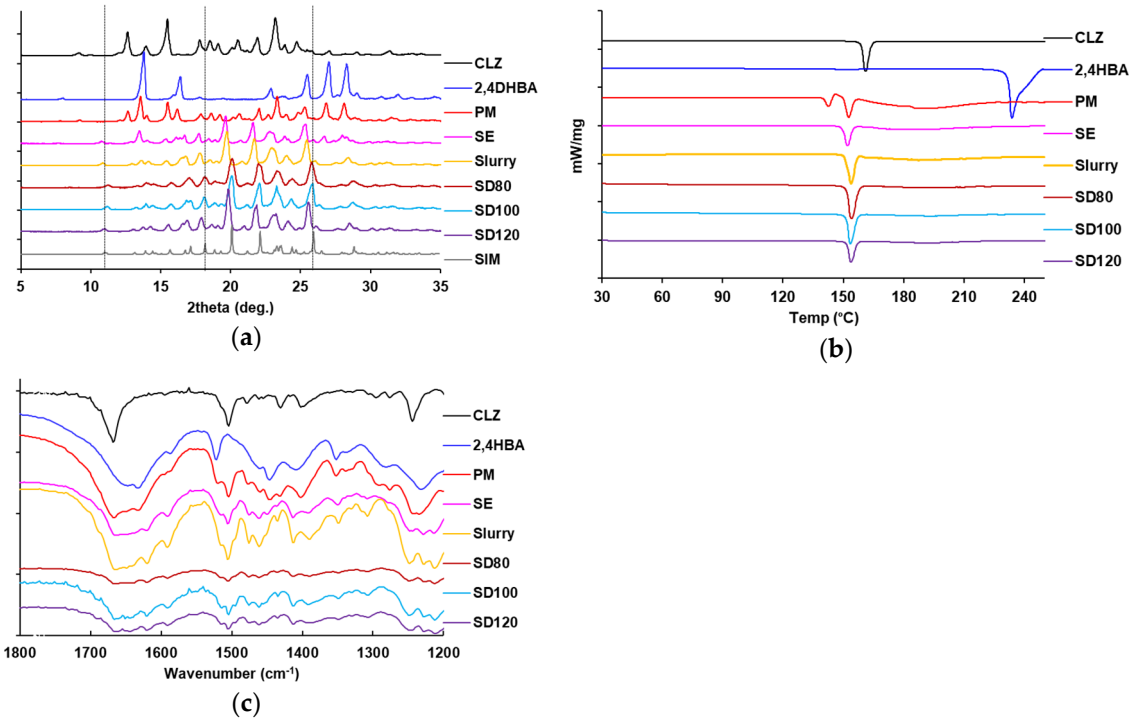

Figure 4. (**a**) PXRD, (**b**) DSC, and (**c**) FT-IR analysis of the CLZ-2,4DHBA cocrystals prepared using the solvent evaporation method, slurry method, or spray drying method.

3.4. Characteristics of CLZ-2,5DHBA Cocrystals Prepared Using the Solvent Evaporation, Slurry, and Spray Drying Methods

The characteristics of the CLZ-2,5DHBA cocrystals prepared using the three different methods were investigated by PXRD, FT-IR, and DSC, and the results are shown in Figure 5. Cocrystals prepared using the slurry method exhibited new PXRD diffraction peaks at 2θ = 10.5° and 12°, which were not observed with the CLZ drug substance, 2,5DHBA, or the PM (Figure 5a). In the spray drying method, spray drying was conducted at a higher temperature (140 °C) to enhance efficiency, which resulted in new diffraction peaks at 2θ = 10.5°, 17.5°, and 28°. The peaks observed in the samples of the cocrystals prepared using the slurry and spray drying methods did not match the peaks of the simulated sample. In contrast, the peak pattern of the sample obtained using the solvent evaporation method was similar to that of the PM sample. As reported in the literature [20], the melting point of CLZ-2,5DHBA cocrystals is 120.1 °C, which is consistent with that observed in the DSC analysis of the samples of cocrystals prepared using the solvent evaporation, slurry, and spray drying methods (Figure 5b). The samples prepared by different methods exhibited comparable results in the DSC analysis but exhibited different

results in the PXRD analysis. Possibly, the heating process of DSC can change the state of material samples, resulting in similar endothermic peaks corresponding to the samples of the physical mixture. In the FT-IR results shown in Figure 5c, no peak shift different from that of the CLZ drug substance, 2,5DHBA, or PM was observed. These results indicate that CLZ-2,5DHBA cocrystals can be prepared using the slurry method but that they are not generated in purified form; in contrast, CLZ-2,5DHBA cocrystals are not produced using the solvent evaporation method.

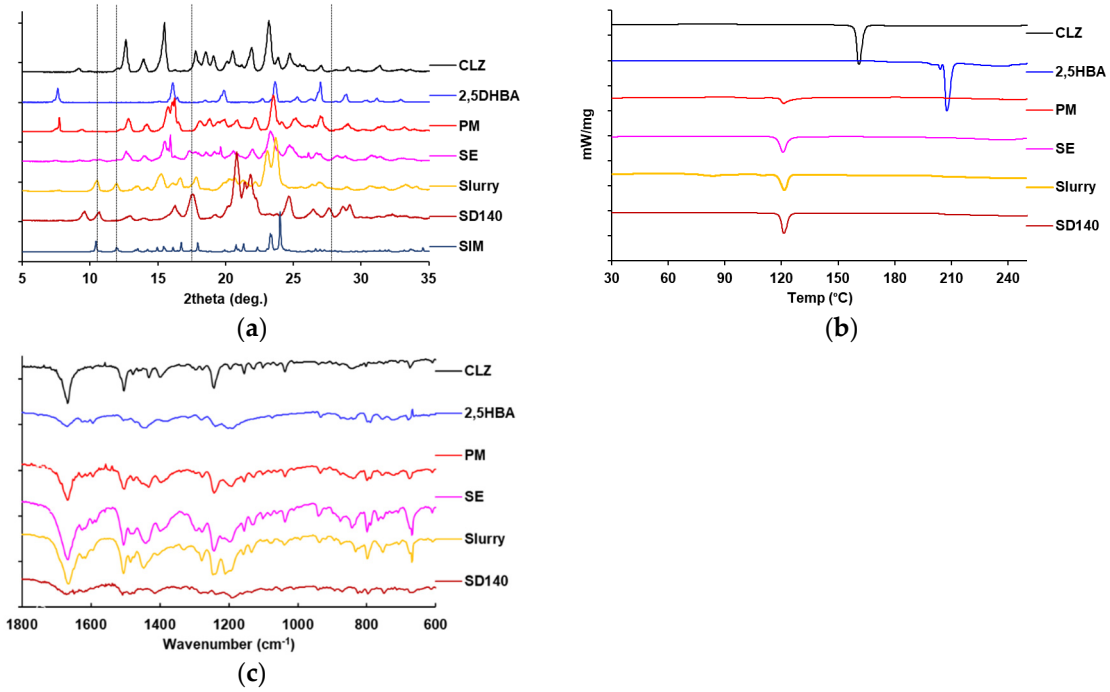

Figure 5. (**a**) PXRD, (**b**) DSC, and (**c**) FT-IR analysis of the CLZ-2,5DHBA cocrystals prepared using the solvent evaporation method, slurry method, or spray drying method.

In order to better understand the different characteristics of spray-dried CLZ-2,5DHBA cocrystals versus CLZ-4HBA and CLZ-2,4DHBA cocrystals, the following experiments were conducted. As shown in Supplementary Materials Figure S3a, CLZ-2,5DHBA samples were prepared at 80 °C by spray drying. No peak characteristic of these cocrystals was observed at this temperature, but new diffraction peaks that were not observed with CLZ, 2,5DHBA, or the PM were observed at 2θ = 10.5°, 17.5°, and 28°. Considering the possibility of a polymorphic transition of the cocrystals or coformer, spray drying of 2,5DHBA alone was conducted. The PXRD results before and after spray drying revealed that the form of the 2,5DHBA crystals changed. According to the crystal structure analysis (Mercury®), there are two types of 2,5DHBA polymorphs. As shown in Figure S3b,c, two types of polymorphs, type I (disordered) and type II (ordered), were present. Each PXRD peak is shown in Figure S3a, indicating that 2,5DHBA existed as type II before spray drying and changed to type I as a result of spray drying. When the peaks were compared to those of the spray-dried sample of CLZ-2,5DHBA, the peaks at 2θ = 10.5° and 17.5° of type II 2,5DHBA matched those of the spray-dried samples. Eventually, we expect that the spray drying of CLZ-2,5DHBA may include CLZ, CLZ cocrystals, 2,5DHBA, and its polymorph.

3.5. Physical Characterization of Spray-Dried CLZ–Hydroxybenzoic Acids Cocrystals

Figure 6 shows SEM images of the samples prepared using the spray drying method. The form of the CLZ-4HBA cocrystals spray dried at 80 °C was similar to that of 4HBA, which was a rod type, while the samples spray dried at 100, and 120 °C were spherical. The D_{50} median diameters of the CLZ-4HBA cocrystals spray dried at 80, 100, and 120 °C were 78, 53, and 91 μm, respectively. In addition, CLZ-2,4DHBA exhibited a spherical crystal form, with D_{50} median diameters of the

spray-dried CLZ-4HBA cocrystals of 63, 70, and 85 µm at spray drying temperatures of 80, 100, and 120 °C, respectively. We did not find the influence of spray drying temperature on the size of the resulting particles between the results of the CLZ-4HBA cocrystals and the CLZ-2,4HBA cocrystals. In contrast, the samples of the CLZ-2,5DHBA cocrystals prepared by spray drying at 140 °C exhibited a fragmented structure; for example, 2,5DHBA assumed a mica-like form. The D_{50} median diameter was 27 µm smaller than that of the CLZ-HBA and CLZ-2,5DHBA cocrystals. The physical properties of hydroxybenzoic acid derivatives and their interaction with CLZ may affect the size of the resulting CLZ cocrystals.

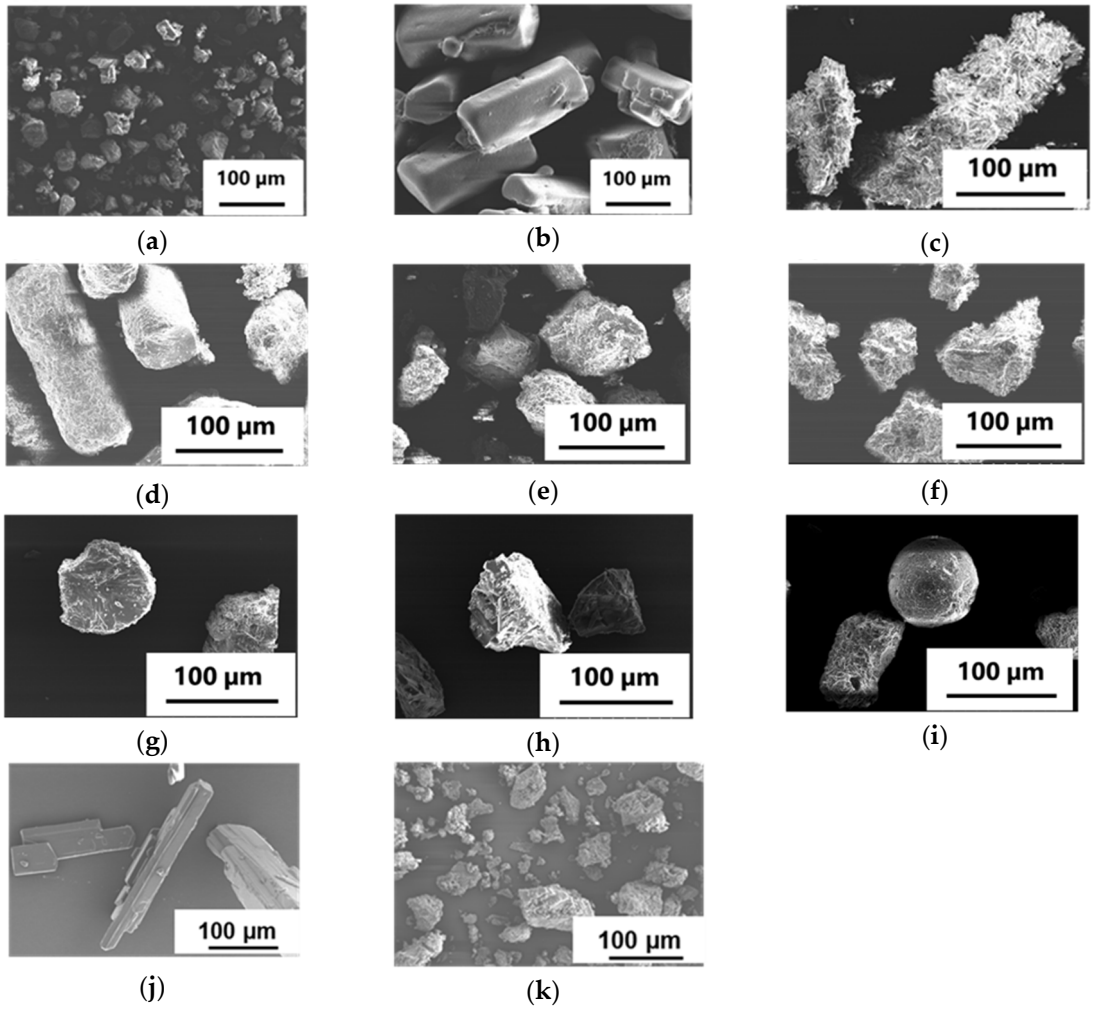

Figure 6. SEM images of CLZ-cocrystals prepared using the spray drying method. (**a**) CLZ, (**b**) 4HBA, (**c**) 2,4DHBA, (**d**) CLZ-4HBA SD80, (**e**) CLZ -4HBA SD100, (**f**) CLZ -4HBA SD120, (**g**) CLZ-2,4DHBA SD80, (**h**) CLZ-2,4DHBA SD100, (**i**) CLZ -2,4DHBA SD120, (**j**) 2,5DHBA, (**k**) CLZ -2,5DHBA SD140.

3.6. Dissolution Behavior of Spray-Dried CLZ–Hydroxybenzoic Acids Particles

Figure 7 shows the results of the dissolution testing of the spray-dried cocrystals. Cocrystals prepared at each spray drying temperature dissolved at about twice the amount of the CLZ standard or the PM. The error range was large for cocrystals prepared by the spray drying method. However, because CLZ cocrystals have a high dissolution rate, and CLZ tends to readily recrystallize, the recrystallization process was very rapid, with supersaturation occurring at an apparent dissolution rate of about 20% to 25%.

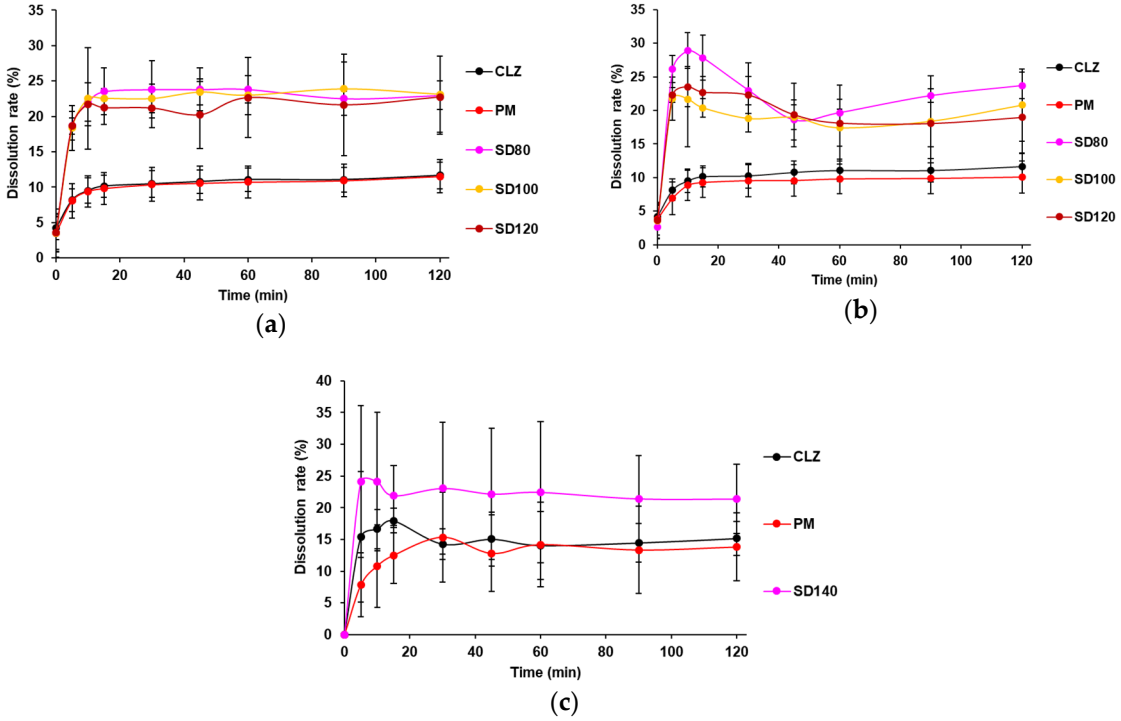

Figure 7. Dissolution behavior of CLZ-cocrystals. (**a**) CLZ-4HBA cocrystals, (**b**) CLZ-2,4DHBA cocrystals, and (**c**) CLZ-2,5DHBA cocrystals. Data are presented as the mean ± standard deviation (n = 3).

4. Conclusions

The characteristics of CLZ-HBA cocrystals prepared using the spray drying method were investigated in the current study. PXRD, DSC, and FT-IR analyses confirmed that the spray drying method could be used to generate CLZ-HBA cocrystals. CLZ-4HBA and CLZ-2,4DHBA cocrystals prepared by the spray drying method exhibited similar characteristics to the samples of cocrystals prepared using the solvent evaporation and slurry methods. In contrast, the characteristics of the CLZ-2,5DHBA cocrystals prepared by the spray drying method differed from those of the samples prepared using the other two methods. Our results suggest that the preparation method used can affect the physical properties and quality of cocrystals composed of CLZ and APIs. Our results also indicate that spray drying enhances the dissolution of CLZ and coformers. This suggests that poorly water-soluble drug cocrystals could be successfully prepared by the spray drying method because a large amount of cocrystals with a high dissolution capacity can be prepared at one time, although additional quality control measures for API cocrystals during manufacturing should be considered.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4352/10/4/313/s1. Figure S1. Molecular arrangement in the crystal structures of the CLZ cocrystals; (a) CLZ-4HBA cocrystal, (b) CLZ-2,4DHBA cocrystal (c) CLZ-2,5DHBA cocrystal. Images were produced using Mercury®based on a previous study [20]. Figure S2. The PXRD of CLZ-4HBA cocrystals prepared using the solvent evaporation method. The composition of the sample solutions is described in Table S1. Figure S3. (a) PXRD analysis of spray-dried CLZ-2,5DHBA cocrystals and spray-dried 2,5DHBA crystals. (b) Type I (disordered) 2,5-DHBA and (c) Type II (ordered) 2,5-DHBA images acquired using the Mercury®software. Table S1. Screening of compositions for the preparation of CLZ-4HBA cocrystals using the solvent evaporation methods. CLZ and 4HBA were mixed at a stoichiometric ratio of 1:1, and samples were further prepared as described in the Materials and Methods section.

Author Contributions: Conceptualization, T.F.; methodology, E.G. and T.F.; validation, M.K.; investigation, M.U., M.K., K.K., and E.G.; resources, T.O.; data curation, M.U., M.K., and T.T.; writing—original draft preparation, M.U.; writing—review and editing, T.T. and T.F.; visualization, M.U., T.T., and T.F.; supervision, T.F. and T.O.; project administration, T.F. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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