Itraconazole cocrystallization in fatty acid under high-pressure CO_2

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Abstract

Cocrystal formation is a processing method to improve the solubility of active pharmaceutical ingredients. This work aims to establish cocrystals of itraconazole in liquefied fatty acid under high-pressure CO_2. Itraconazole cocrystals can be formed in fatty acids, such as linoleic acid, oleic acid and stearic acid. On the other hand, they are not formed by the cocrystallization with hydrocarbons, octadecane and 1-octadecene, and without the fatty acid. For the purpose of clarifying the role of fatty acids on this cocrystallization, we also focused on the molecular interaction energies from quantum chemical calculation. The calculated results give that the molecular interaction of the cocrystal compounds with the fatty acid are stronger than those with hydrocarbon. The experimental and calculated results could suggest that the strong molecular interaction with fatty acids achieve the promotion of the itraconazole cocrystallization.

Keywords

cocrystallization, itraconazole, high-pressure CO_2

1. Introduction

Itraconazole (ITZ), which is an antifungal drug with a low solubility, has been known as one of the model molecules in the investigation of processing technologies to improve solubility to human body, such as ITZ-loaded nanostructured lipid carriers, amorphous solid dispersions, salts and cocrystals [1-7]. In particular, cocrystal, which is a new crystal structure composed of active pharmaceutical ingredients (APIs) and other substance called as coformer (CF), has been focused on. Cocrystal has many candidate compounds for APIs and CF because cocrystal which is formed by non-ionic bonds does not require dissociating groups in composed compounds [8]. Hence, many studies have reported cocrystal [4-7].

Some methods for cocrystallization used ITZ for API has already been known. These conventional methods need multi-steps which are dissolving APIs and CF into organic solvents and removing solvents by slow evaporation or using high pressure CO_2 [4-6]. Many kinds of CF were successfully applied to form ITZ-cocrystal with these methods. However, these methods contain the disadvantages using much unsafe organic solvents and multi steps. Therefore, a safety and single-step method to form ITZ-cocrystal is required.

This work aims to establish a single step method for the formation of ITZ-cocrystal in liquefied fatty acids under high pressure CO_2 in terms of their melting point depression by high pressure CO_2 [9-12]. Fatty acids have been focused on because they are harmless and some of them are reported to enhance our health [13, 14]. The experimental results for the method to form cocrystal in liquefied fatty acids under high pressure CO_2 were compared with them for using fatty acid only and them under high pressure CO_2 only. In addition, whether the cocrystals were formed with the different fatty acids was explained by the calculating the molecular interaction energies from COSMO-based quantum calculation [15].

2. Experimental methods

2.1. Materials

Carbon dioxide (purity > 99.5 %) was supplied by Fujii Bussan Co., Ltd. Itraconazole (ITZ, purity > 98.0 %) was supplied by Tokyo Chemical Industry Co., Ltd. Succnic acid (SUC, purity > 99.5 %), octadecane (OD, purity > 97.0 %), 1-octadecene (1-OD, purity > 90.0 %), stearic acid from plants (SA, purity > 95.0 %), Oleic acid from sunflower (OA) and linoleic acid (LA, purity > 88.0 %) were supplied by Fuji Film Wako Pure Chem. Ind.

2.2. Cocrystallization in fatty acid under high pressure CO_2

ITZ (0.2 mmol) as API and SUC (0.1 mmol) as CF and additives as fatty acid or hydrocarbon (0.4 g) were put in the high-pressure vessel with 10 ml. Then the vessel was put under 5.0 MPa at 50 ºC (65 ºC only SA) with stirring at 300 rpm for 2 h. After 2 h, the vessel was depressurized, and then the samples were collected. The experiments were also conducted by varying the amount of fatty acid to 0.4, 0.2, 0.1 and 0.04 g with using LA as additive under the same temperature and pressure conditions.

2.3. Cocrystallization under high pressure CO_2

ITZ (0.2 mmol) and SUC (0.1 mmol) were also put in the high-pressure vessel with 10 ml. Then the vessel was put under 5.0 MPa at 50 ºC with stirring at 300 rpm for 2 h. After 2 h, the vessel was depressurized and the samples were collected.

2.4. Cocrystallization in fatty acid

ITZ (0.2 mmol) and SUC (0.1 mmol) and LA were put in the vessel with 10 ml. Then the vessel was put at 50 °C with stirring at 300 rpm for 2 h.

2.5. Powder X-Ray Diffraction (PXRD)

In order to measure the pattern of crystal structure, PXRD was used for the samples. For all samples, PXRD patterns were collected in the 2 θ range of 2° - 50° with a step size of 0.02 ° and a scanning speed of 0.2 °/min.

3. Modelling methods

In this study, the molecular interaction energies among ITZ, SUC and additive are expressed as the energy difference between the coexistence of ITZ, SUC and additive and the only ITZ or SUC by itself. The molecular interaction energy ΔG_{ITZ}, which is the energy difference between the coexistence of ITZ, SUC and additive and the pure ITZ, is written as

$$\Delta G_{ITZ} = \mu^{c}_{ITZ} - \mu^{p}_{ITZ} = RTln(\gamma^{c}_{ITZ}\, x^{c}_{ITZ}) \quad (1)$$

where γ means the activity coefficient, x means the molar ratio, and each superscript is c for the coexistence and p for the pure. The molecular interaction energy ΔG_{SUC} is calculated similarly. As shown in the following, the activity coefficient γ is calculated by COSMO-SAC [15], which is a method for estimating activity coefficients by combining statistical thermodynamics and quantum chemical calculations using Conductor-like Screening Model (COSMO) [16]. COSMO is a method of calculating the molecular surface charge by quantum chemical calculation. The molecular surface charge density $p(\sigma)$ is expressed as

$$p(\sigma) = \frac{A(\sigma)}{A} \quad (2)$$

where $A(\sigma)$ is the total surface area of segments with the molecular surface charge σ and A is the surface area of the molecule. The activity coefficient of segment $\Gamma(\sigma)$ is represented as

$$\ln\Gamma(\sigma_{\mathrm{m}}) = -\ln\left\{\sum_{\sigma_{\mathrm{n}}} p(\sigma_{\mathrm{n}})\,\Gamma(\sigma_{\mathrm{n}})\exp\left[\frac{-\Delta W(\sigma_{\mathrm{m}},\sigma_{\mathrm{n}})}{RT}\right]\right\} \quad (3)$$

where ΔW is the segment exchange energy [15]. From the activity coefficient of segment $\Gamma(\sigma)$, the activity coefficient γ is provided as follows:

$$\ln\gamma^{c} = \frac{A}{a_{\mathrm{eff}}}\sum_{\sigma} p(\sigma)[\ln\Gamma^{c}_{(\sigma)} - \ln\Gamma^{p}_{(\sigma)}] \quad (4)$$

where a_{eff} is the surface area of a standard surface segment.

4. Results

4.1. Experiments

PXRD patterns of samples composed of ITZ, SUC and additive are indicated in Fig. 1. As shown in Fig. 1, the different peak patterns from ITZ and SUC are confirmed at 2 θ values of 3.02, 6.02, 9.02, 18.12, 22.50, 24.36, and 27.34 with LA, OA and SA as additives under high pressure CO_2. On the other hand, the different peak patterns from ITZ and SUC are not shown with hydrocarbon as additives and without additives under high pressure CO_2 in Fig. 1. Also, the characteristic peak patterns in Fig. 1 are 3.86, 7.86, 11.52 and 15.38 of pure OD and 4.56, 6.70, 11.12, 21.52 and 24.08 of pue SA.

By the results of varying the amount of LA, cocrystals are also formed in the case that the added amount of LA was 0.4 or 0.2 g. However, the small amount of added LA does not promote to form ITZ-cocrystal. Moreover, ITZ-cocrystals are not formed by cocrystallization in fatty acids. Therefore, it means that ITZ-cocrystals are not formed unless ITZ and SUC are contacted with high-pressure CO_2 even in fatty acids.

These results showed that cocrystal formations can be promoted in the media of the fatty acids under high-pressure CO_2.

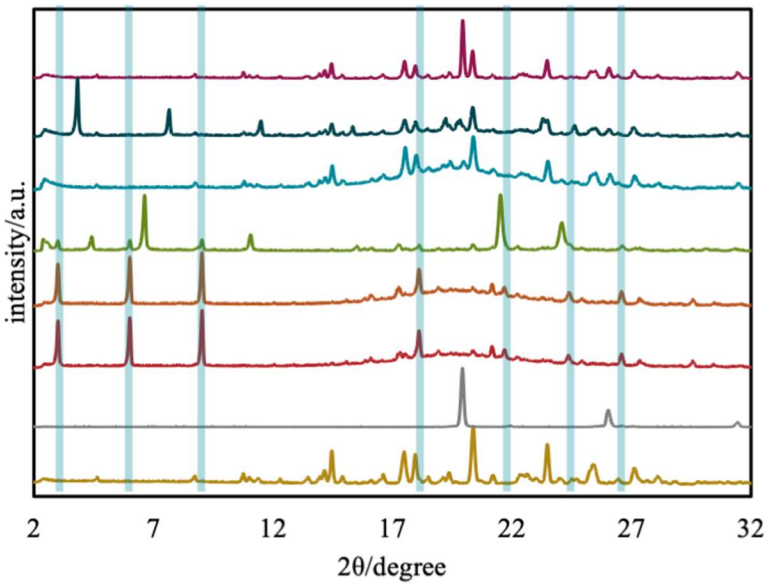

Fig. 1. PXRD pattern of cocrystallization in fatty acids, in hydrocarbons, or without addtives under high pressure CO_2. The cocrystal peaks were shown in light blue lines. From top to bottom, samples without additives (purple), with OD (dark blue), with 1-OD (blue), with SA (green), with OA (orange), with LA (red), only SUC (gray) and only ITZ (light brown).

4.2. Modelling

Figure 2 shows the results for calculating the molecular interaction energies. In Fig. 2,

the molecular interaction energies are stronger with fatty acids than with hydrocarbons. In addition, large molecular interaction energies are calculated along with increasing their number of unsaturation, regardless of the fatty acids and hydrocarbons. In terms of the amounts of added fatty acids, the molecular interaction is also larger with the case that the amount of LA added is higher in Fig. 2.

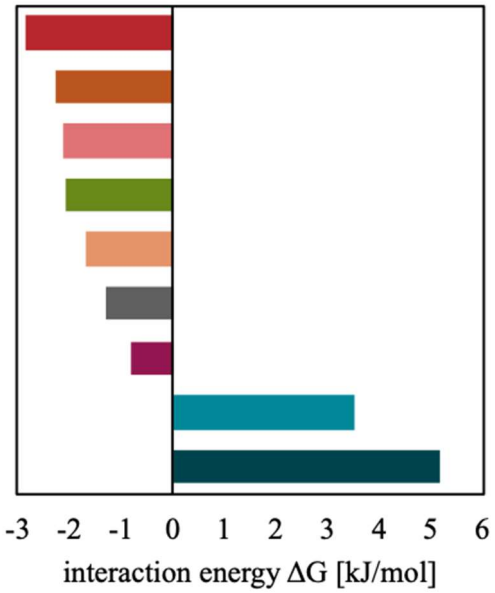

Fig. 2. The comparison of molecular interaction energies among ITZ, SUC and additive under using diffenret kinds and amounts of additives. From top to bottom, additives as 0.4 g of LA (red), 0.4 g of OA (orange), 0.2 g of LA (pink), 0.4 g of SA (green), 0.1 g of LA (pale orange), 0.04 g of LA (gray), without additives (purple), 0.4 g of 1-OD (blue) and 0.4 g of OD (dark blue).

5. Discussion

The experimental results show the cocrystals of ITZ are formed with fatty acids under high-pressure CO_2. On the other hand, the results of modelling give that the environment with fatty acids tends to be stronger molecular interaction energies among ITZ, SUC and fatty acid. Comparing the experimental results with the modelling results indicates that the strong molecular interaction with fatty acids may achieve the promotion of the cocrystallization with ITZ and SUC. The stronger molecular interaction can promote to become unstable on the crystal surface of ITZ and SUC. The stirring promotes to expose their new crystal surface and become unstable. For these reasons, the dissolution of ITZ and SUC into high-pressure CO_2 may be enhanced. The additives of solvent improve solubility into high-pressure CO_2, which is generally reported as co-solvent effect [17-19]. Consequently, the improved solubility into CO_2 may promote cocrystal formation in high pressure CO_2 [19].

In contrast, the stronger molecular interaction implies that the surfaces of ITZ and SUC may become partiality unstable crystal structure. Then cocrystals may be formed by the collision of these amorphous surfaces through stirring. A cocrystal mechanism through amorphous has been reported with methods of grinding and liquid assist grinding [20, 21]. However, in the case of ITZ-cocrystallization in fatty acids, ITZ-cocrystals were not formed in fatty acids only and they were formed using fatty acids and high-pressure CO_2. These results may imply that the process through the reduction of crystal stability is not the main mechanism about ITZ-cocrystallization with fatty acids.

6. Conclusion

We proposed how to form ITZ-cocrystals with a single step. In order to establish it, we focused on melting point depression of fatty acids under high pressure CO_2. As a result of experiments, cocrystallization was promoted in the environment with liquefied fatty acids under high pressure CO_2. Moreover, it was found that the interaction energies among ITZ, SUC and additive were stronger with fatty acids than with hydrocarbons by the modelling results using COSMO-SAC. Both experiments and modelling results showed that fatty acids played a role of cocrystal formation composed of ITZ and SUC under high pressure CO_2.

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