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Short communication

Cocrystal production method reducing deposition risk of undesired single component crystals in anti-solvent cocrystallization

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ABSTRACT

The cocrystallization operation has the deposition risk of undesired crystals. In this study, the strategy of cocrystal production method considering the risk reduction of undesired single component crystal deposition was investigated. The anti-solvent cocrystallization was carried out in four-component system of carbamazepine (CBZ), saccharin (SAC), methanol and water. The undesired single component crystals precipitated depending on the solution addition sequences. Considering the driving force for each component, a domain without the deposition risk of the undesired crystals was determined on the phase diagram. It is important to keep the operation point in this domain for production of desired cocrystals.

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Introduction

Cocrystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts [1]. Cocrystals can have properties that are distinct from the solid forms of each component. For example, specific cocrystals are reported to have improved the solubility of poor soluble active pharmaceutical ingredients in order to enhance the bioavailability [2–4].

Solution crystallization is one of the production methods of cocrystal. Cocrystallization operations in the liquid phase are unique separation techniques that produce multicomponent solid phase from admixture systems. Furthermore, the solid phase must have a desired stoichiometric composition. Therefore, it is important for cocrystallization operation to control the deposition with the stoichiometric composition.

Various production methods of cocrystal from multicomponent solution have been developed, including cooling crystallization [5], evaporation crystallization [6], reaction crystallization [7], anti-solvent crystallization [8] and gas anti-solvent crystallization [9]. Especially, for CBZ-SAC cocrystal, solutions mixing methods for cocrystal production have been reported in congruent system (methanol or methanol–water solvent system). These production methods are achieved by mixing of predetermined solutions. One of the solutions mixing method is mixing two polysaturated solution based on ternary phase diagram (two polysaturated solution mixing method) [10]. In this previous method, the driving force for cocrystallization could be determined by using phase diagram. The other solution mixing method for production of cocrystals is anti-solvent cocrystallization method. A recent study reports that anti-solvent cocrystallization is an appropriate method for preparing CBZ-SAC cocrystalline particles. The effect of initial concentration was investigated with phase diagram, and the SAC/CBZ ratio was the important parameter for cocrystal quality (purity and solid yield) [11]. However, there is a possibility of the undesired crystals deposition during anti-solvent cocrystallization.

In the previous studies of cocrystallization, the practical use of phase diagram has attracted attention. Actually, several studies have discussed the condition for production of cocrystal by using phase diagram [4,7,10,11]. For crystallization operation from multicomponent solution, the use of phase diagram is efficient [12].

According to these previous studies, the possibility of integration of both two polysaturated solution mixing method and anti-solvent crystallization method is worthy of discussion in order to produce cocrystals without the deposition risk of undesired crystal. The purpose of this present study is to investigate the strategy of cocrystal production considering the risk reduction of undesired single component crystal deposition in order to produce only cocrystals with the desired stoichiometric composition in the

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integrated cocrystallization method by using multicomponent phase diagram. The anti-solvent cocrystallization was carried out in four-component system of carbamazepine (CBZ), saccharin (SAC), methanol (MeOH) and water at 303 K as a model system. Water is anti-solvent, and the desired cocrystal is CBZ-SAC (1:1) cocrystal Form I.

Materials

CBZ (>97.0%) was purchased from Tokyo Chemical Industry Co., Ltd., SAC (>98.0%) and MeOH (>99.8%) were purchased from Wako Pure Chemical Industries, Ltd. All these chemicals were used without further purification. Water was purified by using a deionizer (ORGANO Corporation) prior to using as the anti-solvent.

Experimental

Experiments were carried out to examine the existence of deposition risk of undesired crystals in the integrated cocrystallization method. Two polysaturated solutions (CBZ rich polysaturated solution named Feed A, and SAC rich polysaturated solution named Feed B) and pure water as anti-solvent were used in this study. Two polysaturated solutions were prepared in the same way of the previous study [10]. In this method, at least three kinds of solutions which are two solutions and anti-solvent should be mixed together. So the addition sequences of these three kinds of solutions were considered in this anti-solvent cocrystallization operation. A 100 mL glass vessel was used as a crystallizer. The solution in the crystallizer was agitated at 300 rpm by a marine type impeller. The volume of Feed A, Feed B and pure water were 20 mL, 20 mL and 40 mL, respectively.

There are six kinds of addition sequence to produce cocrystalline particles by using the integrated method. Typical two kinds of sequence were chosen and examined as follows:

Sequence 1: First, Feed A was fed into the crystallizer, second, Feed B was added into Feed A, third, water was added into the solution. After 120 min from addition of second solution Feed B, crystalline particles were sampled (Sample 1-1st). After 120 min from the addition of third solution water, crystalline particles were sampled (Sample 1-2nd).

Sequence 2: First, Feed A was fed into the crystallizer, second, water was added into Feed A, third, Feed B was added into the solution. After 120 min from addition of second solution water, crystalline particles were sampled (Sample 2-1st). After 120 min from the addition of third solution Feed B, crystalline particles were sampled (Sample 2-2nd).

Each crystalline sample was characterized by X-ray diffraction (XRD) analysis (Rigaku, Ultima IV, Cu$K\alpha$ radiation was used).

Results and discussion

Deposition risk of undesired crystals

XRD patterns of obtained crystals in the experiments are shown in Fig. 1 with the XRD patterns of references from the literatures [13,14,15]. From the comparison among Sample 1-1st (a), Sample 1-2nd (b) and the reference (A), XRD pattern of samples were in good agreement with the reference, so Sample 1-1st, 1-2nd were identified as CBZ-SAC (1:1) cocrystal Form I. Therefore, the success of cocrystallization was achieved by using proposed integrated cocrystallization method.

The XRD pattern of Sample 2-1st (c) was different from the XRD pattern of cocrystal (A), and the pattern of Sample 2-2nd (d) was consistent with the XRD pattern of reference cocrystal (A) [13]. According to the results of XRD analysis, undesired crystals had been precipitated depending on the addition sequence of solutions. Therefore, the existence of latent risk which was the deposition of undesired crystals was confirmed.

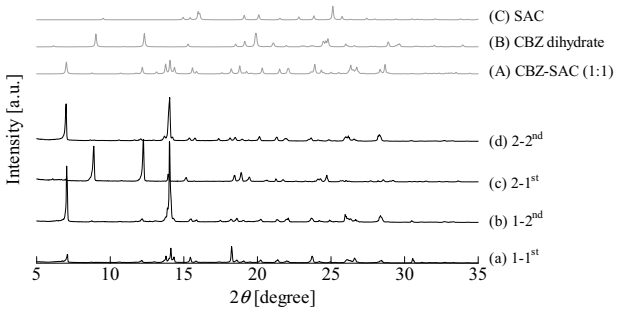

Fig. 1. XRD patterns of obtained crystals in Sequence 1 and Sequence 2 with the XRD patterns of references; (a) Sample 1-1st, (b) Sample 1-2nd, (c) Sample 2-1st, (d) Sample 2-2nd, (A) CBZ-SAC (1:1) cocrystal Form I as Ref. [13], (B) CBZ dihydrate as Ref. [14], and (C) SAC as Ref. [15].

In order to reduce the deposition risk of undesired crystals in this proposed integrated cocrystallization method, the driving force for crystallization of each component was considered with the multicomponent phase diagram. Fig. 2 shows a schematic phase diagram for CBZ-SAC in mixed solvent of MeOH as good-solvent and water as anti-solvent. The thick lines (x), (y) and (z) are the solubility curves of CBZ, SAC and cocrystal, respectively. Based on the previous study of preferential crystallization of organic molecules [16], each solubility curve is extrapolated as metastable solubility curve in the phase diagram. These solubility curves are also shown as dashed lines in Fig. 2.

In this present integrated cocrystallization method, when the predetermined solution is added into the crystallizer, the apparent solution composition as the operation point is determined on multicomponent phase diagram such as Fig. 2. If the apparent solution composition is located in upper side area of the CBZ metastable solubility curve including solubility curve, driving force for deposition of CBZ crystal exists. In the same way, there is the driving force for deposition of SAC crystal when the apparent composition of solution is located in right side area of the SAC metastable solubility curve including solubility curve. Therefore, these two areas have deposition risks of undesired single component crystals in the integrated cocrystallization method.

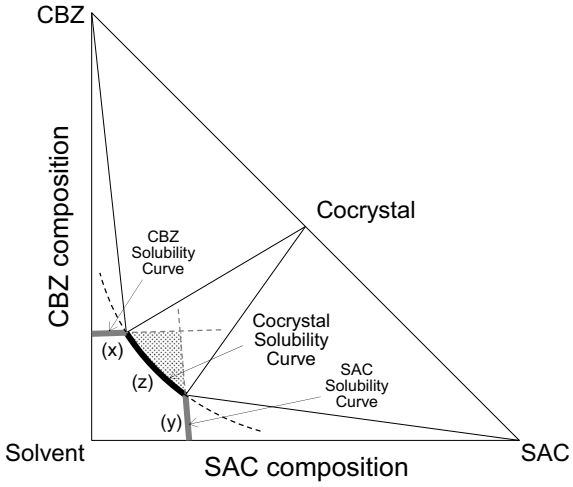

Fig. 2. The schematic phase diagram for CBZ and SAC in mixed solvent of MeOH and water as triangle coordinate. The thick lines are the solubility curves of (x) CBZ; (y) SAC; and (z) cocrystal. The dashed lines are metastable solubility curves extrapolated from each solubility curve. Deposition risk of undesired single component crystals is reduced in the hashed domain.

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