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Stability Orders of Acetaminophen and Theophylline Co-crystals Determined by Co-crystal Former Exchange Reactions and Their Correlation With *In Silico* and Thermal ParametersMakoto Mukaida<sup>1,\*</sup>, Haruna Sato<sup>2</sup>, Kiyohiko Sugano<sup>2</sup>, Katsuhide Terada<sup>3</sup><sup>1</sup> Asahi Kasei Pharma Corporation, Shizuoka 410-2321, Japan<sup>2</sup> Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Toho University, Funabashi, Chiba 274-8510, Japan<sup>3</sup> Laboratory of Molecular Pharmaceutics and Technology, Faculty of Pharmacy, Takasaki University of Health and Welfare, Takasaki-shi, Gunma 370-0033, Japan

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## ABSTRACT

The aim of this study was to determine the thermodynamic stability order of co-crystals using co-crystal former exchange reactions and to validate 2 *in silico* parameters for predicting co-crystal formation. Co-crystal former exchange reactions were performed using acetaminophen (AC) co-crystals of oxalic acid (OX), maleic acid (MA), and theophylline (TH). The addition of TH to an AC-MA co-crystal (AC-MA) afforded AC-TH, suggesting that AC-TH was more stable than AC-MA. The stability order among the other co-crystals was determined in the same manner. The stability order of the AC co-crystals was determined to be AC-TH > AC-MA ≈ AC-OX. Interestingly, the addition of TH to AC-OX afforded TH-OX. The stability order of the TH co-crystals was also determined (OX-TH > AC-TH ≈ MA-TH). Although the stability order of the AC co-crystals was consistent with the differences in their hydrogen bond energy ( $\Delta E$ ), an *in silico* parameter for predicting co-crystal formation, it showed no relationship to the excess enthalpy ( $H_{ex}$ ). These results suggest that co-crystal formation can be predicted with greater accuracy using  $\Delta E$  rather than  $H_{ex}$  for AC co-crystals. The stability orders of the AC and TH co-crystals also correlated well with their melting points and disintegration temperatures.

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## Introduction

Co-crystals can be used to improve the physicochemical properties of active pharmaceutical ingredients (APIs).<sup>1-12</sup> However, there are hundreds of possible co-crystal former (CCF) candidates, making it difficult to determine the best combination for a specific API. The development of new tools for the *in silico* prediction of co-crystal formation based on the chemical structures of APIs and CCFs could therefore improve the efficiency of the CCF selection process in drug discovery. Some *in silico* parameters for CCF selection have been reported by several researchers.<sup>13-20</sup> For example, the difference in the hydrogen bond energy ( $\Delta E$ ) and the excess enthalpy ( $H_{ex}$ ) was reported by the research groups of

Musumeci<sup>16</sup> and Abramov,<sup>20</sup> respectively, as useful *in silico* parameters for predicting co-crystal formation.  $\Delta E$  represents the difference between the hydrogen bond energy of a co-crystal and each component. The hydrogen bond energy is the sum of the products of the hydrogen bond acceptors and donors calculated from the gas-phase molecular electrostatic potential surface.  $H_{ex}$  is the difference between the excess enthalpy of a mixture of co-crystal components and that of each component. It is generally expected that the probability of finding a co-crystal increases as these parameters increase in size. We previously reported that the stability order of co-crystals determined using CCF exchange reactions could be used to validate these parameters.<sup>21</sup> We found that the stability order of 5 caffeine co-crystals determined by the CCF exchange reaction correlated well with the order of the  $\Delta E$  values. However, the number of model drugs was not sufficient to thoroughly validate the use of  $\Delta E$  as a predictive parameter in this context. In this study, we have used acetaminophen (AC) as a model compound to increase the level of confidence in this *in silico* prediction. AC has a simple chemical structure with a hydroxyl group and an amide group (Fig. 1). AC can form

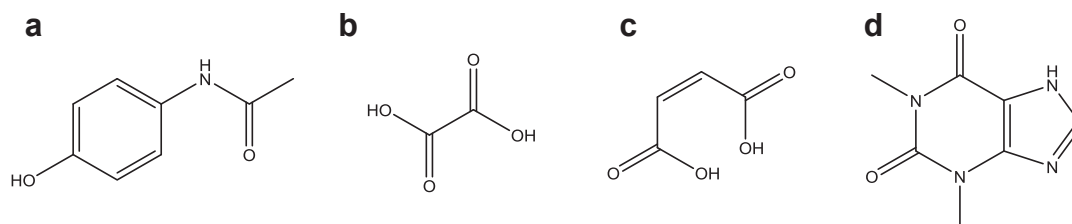
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**Figure 1.** Structures of AC and CCFs. (a) AC, (b) OX, (c) MA, and (d) TH.

co-crystals with various CCFs, making it suitable for the validation of  $\Delta E$  as a predictive parameter.<sup>22-26</sup> In this study, the stability order of the AC co-crystals of oxalic acid (OX), maleic acid (MA), and theophylline (TH) was determined by CCF exchange reactions (Fig. 1). The stability order was then compared with that of the *in silico* parameters.

## Experimental

### Materials

AC and TH were purchased from Tokyo Chemical Industry Company Ltd. (Tokyo, Japan). OX and MA were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan).

### Preparation of Co-crystals

Co-crystals were prepared by liquid-assisted grinding (LAG) using ethanol. AC (50 mg, 0.33 mmol) was mixed with each CCF and ethanol (5  $\mu$ L) in a 1-mL glass vial with four 2.4-mm tungsten balls. The mixture was shaken in a TMS 200 shaker (Hangzhou Allsheng Instruments Company, Ltd., Zhejiang, China) at 1800 rpm for 1-24 h at ambient temperature. The ethanol solvent was then evaporated in a fume hood to give the co-crystals. All of the conditions used for the preparation of the crystals are shown in Table 1.

### CCF Exchange Reaction

An equimolar amount of CCF was added to each co-crystal in a 1-mL glass vial with two 2.4-mm tungsten balls. Ethanol (15  $\mu$ L, except for the MA cases) was then added to the vial, which was then shaken in a BMS-TMS 200 shaker at 1800 rpm for 22 h at ambient temperature. When MA and OX were added to the AC-OX and AC-MA co-crystals, respectively, the volume of ethanol was reduced from 15 to 2  $\mu$ L on account of the high solubilities of OX and MA. The ethanol solvent was subsequently evaporated in a fume hood.

### Powder X-Ray Diffraction

Powder X-ray diffraction (PXRD) patterns were measured on a Bruker D8 Discover diffractometer (Bruker AXS GmbH, Karlsruhe,

Germany) in the reflectance mode (Cu K $\alpha$  radiation [40 kV and 40 mA]). Samples were mounted on a glass plate and the diffraction patterns were collected from  $2\theta = 3.8^\circ$  to  $26.3^\circ$  with a step size of  $0.02^\circ$  for 3 min.

### Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analyses were performed on a TA DSC Q2000 system (TA Instruments, New Castle, DE). Samples (2.5 to 3.1 mg) were loaded into aluminum pans, which were subsequently sealed and heated from  $40^\circ\text{C}$  to  $200^\circ\text{C}$  or  $300^\circ\text{C}$  at a rate of  $5^\circ\text{C}/\text{min}$  under a steady stream of nitrogen (flow rate, 50 mL/min).

## Results and Discussion

### Determination of the Stability Order of Co-crystals Using CCF Exchange Reactions

Three AC co-crystals were prepared by LAG using ethanol. The AC-MA co-crystal (AC-MA) was isolated as a yellow powder, whereas the other co-crystals were all white powders. The PXRD patterns of these co-crystals and their components are shown in Figure 2. These patterns were identical to those previously reported, except for AC-MA, the PXRD pattern of which has been reported for the first time in this study.<sup>26</sup> CCF exchange reactions were performed by LAG using ethanol. The results of a preliminary study revealed that a CCF exchange reaction time of 22 h was sufficient in most cases, and all of the subsequent reactions were performed over this time period. The results for these reactions are shown in Figure 3 and Supplementary Figures 1 and 2 and summarized in Table 2. The addition of TH to AC-MA afforded an AC-TH co-crystal (AC-TH). In contrast, the addition of MA to AC-TH did not afford AC-MA. These results therefore suggested that AC-TH was more stable than AC-MA (Fig. 3). Interestingly, MA-TH was obtained as a side product in both reactions. When MA and OX were added to AC-OX and AC-MA co-crystals, we obtained a mixture of AC-OX and AC-MA, respectively (Supplementary Fig. 1), suggesting that the stabilities of these co-crystals were similar. When TH was added to AC-OX, we obtained an OX-TH co-crystal (OX-TH) instead of AC-TH (Supplementary Fig. 2). Similarly, the addition of OX to AC-TH afforded OX-TH (Supplementary Fig. 2). These results suggested that it is possible for a co-crystal of an API to lose its CCF and be converted to free API when it is treated with another molecule capable of forming a more stable co-crystal with the CCF.

Co-crystals of OX, MA, and TH were prepared to confirm the relationship between the AC co-crystals and several other co-crystals. The OX-TH and MA-TH co-crystals were obtained by LAG with ethanol. However, this technique failed to afford any OX-MA co-crystal (OX-MA). The PXRD patterns of OX-TH and MA-TH (Supplementary Fig. 3) were consistent with previous reports from the literature.<sup>27</sup> The CCF exchange reactions using

**Table 1**  
Conditions for the Preparation of the Different Co-crystals

Co-crystal	Amount of CCF (mg)	Molar Ratio of the Components	Reaction Time (h)
AC-OX	30	1:1	1
AC-MA	38	1:1	2
AC-TH	59	1:1	24
OX-TH	30 (OX), 119 (TH)	1:2	2
MA-TH	38 (MA), 59 (TH)	1:1	2

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