



## Kinetics of co-crystal formation with caffeine and citric acid via liquid-assisted grinding analyzed using the distinct element method



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### ABSTRACT

The kinetics of co-crystal formation of caffeine (CF) with citric acid (CTA) was evaluated. Ball milling of CF and CTA in molar ratios of 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, and 1:4 was performed by the liquid-assisted grinding (LAG) method. The samples were characterized by powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC). Two types of co-crystals (**co-crystal-1**, a 1:1 CF-CTA co-crystal; and **co-crystal-2**, a new co-crystal form) were obtained. The kinetic characteristics of this new co-crystal formation were assessed by calculating the ball impact energy and force using the distinct element method (DEM) simulations. The results indicated that **co-crystal-2** creation occurred under a condition in which the ball impact force exceeded a certain threshold value. Moreover, the total ball impact energy was positively correlated with co-crystal formation, exhibiting a higher ball impact force than the threshold value. The kinetics of **co-crystal-2** formation was almost consistent with the Jander equation. Consequently, **co-crystal-2** formation could be explained according to a three-dimensional diffusion mechanism.

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## 1. Introduction

Mechanochemistry is a branch of solid state chemistry concerning reactions or synthesis due to the effects of mechanical energy, such as with grinding or ultrasonic technology (Fernández-Bertran, 1990). Mechanochemical synthesis provides minimal solvent (or solvent-free) pathways to produce industrial products (James et al., 2012) and therefore, has gained widespread attention as an eco-friendly means for producing functional materials (Varma, 2007; Carlier et al., 2011). Co-crystallization via grinding methods, including neat grinding and liquid-assisted grinding (LAG), has been recently investigated as a representative application of mechanochemical synthesis (Steed, 2013). According to the US Food and Drug Administration guidelines (2013), co-crystals are

defined as “solids that are crystalline materials composed of two or more molecules in the same crystal lattice.” Co-crystallization via grinding methods is also dependent on mechanical energy.

Specifically, significant improvement in co-crystallization reactions via LAG can be achieved by the addition of an appropriate solvent (Shan et al., 2002), which acts as a lubricant for the reaction or a medium to facilitate molecular diffusion. In other words, an appropriate solvent can have a profound effect on the course of mechanochemical co-crystallization. LAG reactions mostly proceed according to a phase diagram in which the fraction of the solvent is low (Friščić and Jones, 2009). Hence, co-crystallization via grinding is expected to be more efficient for substances that are difficult to prepare from co-crystals in solution (Blagden et al., 2008).

Co-crystallization can also enhance the physical properties of compounds, such as solubility, stability, and compressibility (Steed, 2013; Goyal et al., 2012; Wouters and Quéré, 2011), without disrupting intrinsic structures (Qiao et al., 2011). Co-crystals have been applied in wide range of areas, such as the production of energy materials (Lee et al., 2013), electronics (Yamamura et al., 2012), and pharmaceuticals (Lemmerer et al., 2010). In the pharmaceutical industry, development strategies for drug discovery have evolved in recent years owing to

Abbreviations: CF, caffeine; CTA, citric acid; DEM, distinct element method; DSC, differential scanning calorimetry; DTA, differential thermal analysis; FT-IR, Fourier-transform infrared spectroscopy; IR, infrared; LAG, liquid-assisted grinding; MSDS, material safety data sheet; PXRD, powder X-ray diffraction; SEM, scanning electron microscope.

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improvements in synthesis technologies. However, approximately 70% of new drug candidates have exhibited poor aqueous solubility because of the complexity of structures or increased molecular weights of the candidate compounds (Wairkar and Gaud, 2013).

Poor solubility of drugs is, in most cases, associated with poor bioavailability in humans (Askeröy et al., 2009; Bushrab and Müller, 2003). In response, several studies have investigated a number of techniques to enhance drug solubility (Aldawsari et al., 2013; Charoenchaitrakool et al., 2000; Chen et al., 2015; Fujimori et al., 2015; Sanphui et al., 2011; Serajuddin, 2007; Wang et al., 2010). Nonetheless, a number of compounds have great potential applicability in co-crystallization due to the existence of non-covalent bonds between molecules in co-crystals. For example, improved solubility of megestrol acetate co-crystallization with saccharin was reported by Shiraki et al. (2008). Recently, Astellas Pharma Inc. (Tokyo, Japan) obtained approval to market Suglat® tablets, which are composed of ipragliflozin-L-proline co-crystals, for treatment of type 2 diabetes mellitus (Poole and Dungo, 2014). Thus, co-crystallization may be a key technology for the formulation of poorly soluble drugs.

Caffeine (CF) was selected as a model active pharmaceutical ingredient, because the use of CF co-crystals has been published (Buccar et al., 2007; Sun and Hou, 2008; Trask et al., 2005a). In addition, crystallization of CF from solutions including acetic acid resulted in the formation of pseudo-polymorph composed of CF and acetic acid in a respective 1:2 stoichiometric ratio, whereas the direct grinding method could obtain pseudo-polymorphs composed of these compounds in both 1:2 and 1:1 stoichiometric ratios (Trask et al., 2005b). Since the physical properties of co-crystals are largely attributable to their components, the grinding method can form various co-crystals that benefit from the fine-tuning of the physical properties of the solid (Schultheiss and Newman, 2009). However, prediction of the kinetics of co-crystallization via grinding is difficult due to the unique and significant effects of both the operating parameters and substrates. Here, we elucidated the relationship between co-crystallization and reaction parameters to enable the prediction of co-crystal formation via grinding experiments using a planetary ball mill. The effects of the operating parameters on co-crystal formation were investigated by calculating the fraction in terms of co-crystals in the ground powder. The ball impact energy and force were calculated by stimulation via the distinct element method (DEM). The correlation between co-crystallization and ball impact energy was quantitatively analyzed. Our findings of co-crystallization kinetics provide beneficial information to further elucidate the processes of co-crystal formation through LAG.

## 2. Materials and methods

### 2.1. Materials

CF was purchased from Nacalai Tesque, Inc. (Kyoto, Japan) and citric acid (CTA) from Cosmo Bio Co., Ltd. (Tokyo, Japan). CF and CTA were used as received without further purification. Both compounds have pseudo-polymorphic form as hydrates and anhydrides. To distinguish hydrates from anhydrides, they are denoted by CF hydrate and CTA hydrate.

### 2.2. Grinding experiments

LAG experiments with CF and CTA were performed in aqueous solution using a planetary mill (Pulverisette 7; Fritsch GmbH, Idar-Oberstein, Germany) at room temperature. A mixture of CF and CTA in molar ratios of 4:1 (1.496 g:0.370 g), 3:1 (1.423 g:0.469 g), 2:1 (1.296 g:0.642 g), 1:1 (1.023 g:1.012 g), 1:2

(0.720 g:1.424 g), 1:3 (0.556 g:1.647 g), and 1:4 (0.452 g:1.788 g) with stainless steel balls was performed in a 45-mL stainless steel jar. The LAG experiments were carried out under two experimental conditions: (I) using 12 stainless steel balls with diameters of 9.5 mm and 20 stainless steel balls with diameters of 6.35 mm and (II) using 40 stainless steel balls with diameters of 6.35 mm. Then, 0.30 mL of distilled water was added to the jar. The revolution speed of the jar  $N$  (rpm) and the grinding time  $t$  (min) were varied as the main variables. In addition, the jar itself was rotated in the opposite direction to the revolution at the rate of  $N$ . The grinding time was considered as the accumulated time. The grinding process was stopped every 10 min to cool the jar for 10 min to prevent an excessive increase in temperature during the grinding process (Kim et al., 2004). The ground samples were stored at room temperature with silica gel until further analysis.

### 2.3. Characterization

#### 2.3.1. Powder X-ray diffraction

Powder X-ray diffraction (PXRD) analyses were performed using the SmartLab high-resolution diffraction system (Rigaku Corporation, Tokyo, Japan) with Cu  $K\alpha$  radiation ( $\lambda = 1.5406 \text{ \AA}$ ) at a voltage of 40 kV and a current of 200 mA. About 1 mg of the samples were put on a glass slide and softly pressed to give a flat surface. The samples were scanned with a  $0.004^\circ$  ( $2\theta$ ) step size over a range of  $5\text{--}45^\circ$  ( $2\theta$ ) at a rate of  $4^\circ/\text{min}$ .

Co-crystal stoichiometry was discussed by Job's (continuous variation) plot analysis for CF and CTA in molar ratios of 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, and 1:4 (Job, 1928; Likussar and Boltz, 1971; Hazekamp and Verpoorte, 2006). The fraction in terms of new co-crystal form (**co-crystal-2**) in the solid phase after grinding,  $\alpha$  (i.e., the degree of transition of the starting materials into **co-crystal-2**), was defined and calculated by the following equation (Matsuoka et al., 2010):

$$\alpha = \frac{A_{7.1} + A_{11.4} + A_{25.7}}{A_{7.1} + A_{11.4} + A_{25.7} + A_{13.3} + A_{17.6} + A_{28.0} + A_{8.0} + A_{22.5} + A_{30.9}} \quad (1)$$

where  $A_{2\theta}$  is the peak area at  $2\theta$ , which is specific to each crystal form. In the denominator, the first three angles ( $2\theta = 7.1^\circ$ ,  $11.4^\circ$ , and  $25.7^\circ$ ) belong to **co-crystal-2**, the second three angles ( $2\theta = 13.3^\circ$ ,  $17.6^\circ$ , and  $28.0^\circ$ ) belong to CF-CTA 1:1 co-crystal, while the remaining belong to CF hydrate.

#### 2.3.2. Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FT-IR) spectra were obtained using the FT/IR-6100 spectrometer (JASCO Corporation, Tokyo, Japan) over a range of  $400\text{--}4000 \text{ cm}^{-1}$  with  $4 \text{ cm}^{-1}$  resolution in 30 scans. Before each measurement, the sample was finely ground, mixed with KBr using a mortar and pestle, and pressed into pellets.

#### 2.3.3. Scanning electron microscope

Particle morphology of the samples was observed by scanning electron microscope (SEM) (VE-7800; Keyence Corporation, Osaka, Japan). The samples were sputter-coated with gold before observation using sputtering equipment (E-1045; Hitachi High-Technologies Corporation, Tokyo, Japan). All samples were observed at an operating voltage of 2–2.4 kV.

#### 2.3.4. Differential scanning calorimetry

Differential scanning calorimetry (DSC) curves were obtained using a DSC-60 calorimeter (Shimadzu Co., Ltd., Kyoto, Japan). Approximately 10 mg of sample was packed in a hermetically crimped aluminum pan and heated under dry nitrogen purge at a

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