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# Dry mechanochemical synthesis of caffeine / oxalic acid cocrystals and their evaluation by powder X-ray diffraction and chemometrics

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## Abstract

We report the effects of dry mechanochemical synthesis conditions on the crystallization of caffeine and oxalic acid 2:1 cocrystal. Caffeine anhydrate (CA) and oxalic acid (OX) dihydrate were grinded at various temperatures, rotation speeds and grinding time. The cocrystal was also synthesized by an organic solvent evaporation method, as a reference. The produced samples were measured by a powder X-ray diffraction (PXRD) analysis. The PXRD spectra suggest that the grinded cocrystal has a lower crystallinity than the evaporated one. The diffractograms for the cocrystals synthesized by two kind of methods were further evaluated by multivariate curve resolution - alternating least squares method. Sources of the mathematical models constructed were assigned to the cocrystal and unreacted mixture of CA and OX dihydrate. The present approach is concluded to be useful for the improvement of pharmaceutical property because cocrystallization is closely relating to the solubility characteristics, bioavailability, stability, and so on of drugs.

## 1. Introduction

Solubility and dissolution rate of active pharmaceutical ingredient (API) are important factors for the development of pharmaceutical preparation [1-3]. In order to improve solubility characteristics, various basic approaches, such as cocrystallization, salt formation, complexation, encapsulation and so on, have been studied [4-7]. Vishweshwar *et al.* and Bathchelor *et al.* described that cocrystallization would gain a broader foothold in drug formulation [8,9]. Cocrystallization has attracted a lot of interest because of its potential for improving the physicochemical properties of drugs [10,11,48]. In general, pharmaceutical cocrystal consists of an active pharmaceutical ingredient (API) and coformer(s). There are many reports regarding the effect of cocrystallization on the physicochemical and pharmaceutical properties of API [12-15]. Moradiya *et al.* reported that carbamazepine (CBZ) dissolution rate was improved through its cocrystal formation with saccharin (SAC) [16]. Nehm *et al.* developed a mathematical model that describes the solubility of CBZ/nicotinamide cocrystal [17]. However they did not examined mechanochemical synthesis condition in detail.

A lot of cocrystallization methods, such as cocrystallization in supercritical fluid, slurry solution method, ultrasound-assisted crystallization and organic solvent evaporation