

Stability of Pharmaceutical Cocrystal During Milling: A Case Study of 1:1 Caffeine-Glutaric Acid

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ABSTRACT: Despite the rising interest in pharmaceutical cocrystals in the past decade, there is a lack of research in the solid processing of cocrystals downstream to crystallization. Mechanical stress induced by unit operations such as milling could affect the integrity of the

material. The purpose of this study is to investigate the effect of milling on pharmaceutical cocrystal and compare the performance of ball mill and jet mill, using caffeine-glutaric acid (1:1) cocrystal as the model compound. Our results show that ball milling induced polymorphic transformation from the stable Form II to the metastable Form I; whereas Form II remained intact after jet milling. Jet milling was found to be effective in reducing particle size but ball milling was unable to reduce the particle beyond certain limit even with increasing milling intensity. Heating effect during ball milling was proposed as a possible explanation for the difference in the performance of the two types of mill. The local increase in temperature beyond the polymorphic transformation temperature may lead to the conversion from stable to metastable form. At longer ball milling duration, the local temperature could exceed the melting point of Form I, leading to surface melting and subsequent recrystallization of Form I from the melt and agglomeration of the crystals. The findings in this study have broader implications on the selection of mill and interpretation of milling results for not only pharmaceutical cocrystals but pharmaceutical compounds in general.

Keywords: Mechanical stress; Planetary ball milling; Jet milling; Polymorphic transformation; Pharmaceutical cocrystal

▪ INTRODUCTION

Pharmaceutical cocrystal has been considered as a new class of drug compound with great potential. This is primarily because the physicochemical properties of an active pharmaceutical ingredient (API), such as solubility, dissolution rate, stability and hygroscopicity,

can be altered by forming cocrystal with a suitable coformer.¹⁻¹¹ As each cocrystal is considered as a new molecular entity, cocrystal also offers new avenues for generating patents and intellectual property that could create huge economic benefit.¹² It was once thought that cocrystals have a lesser tendency to form polymorphs.¹³ However, the number of solid forms known for a given compound is proportional to the time and money spent in research on that compound.^{14, 15} With the rising interest in cocrystals in the past decade, polymorphs of many cocrystals have been reported according to a database analysis in 2014.¹⁶ Cocrystals are just as likely to exhibit polymorphism as single component crystals.¹⁷

With pharmaceutical cocrystal gaining prominence, research in cocrystal has been actively pursued by many research groups. Most of the literature reports focus on the discovery of novel cocrystals and their enhancement in physicochemical properties. Recently, there has been major progress in the development of cocrystallisation processes that are amenable to industrial production.¹⁸⁻²² However, research in the solid processing unit operations downstream to crystallization is lacking. Solid processing such as milling, granulation and tableting all induce mechanical stress and involve solvent exposure that could lead to solid form changes (polymorph, solvate).^{23, 24} Dissociation into the constituent components could be an additional concern for pharmaceutical cocrystal. Milling has been known to induce form changes to API due to the high mechanical energy introduced.²⁵⁻³² Boldyreva has provided a comprehensive review on the various views and concepts regarding mechanochemistry of inorganic and organic systems.³³ De Gusseme et al.²⁶ has shown that the outcome of milling depends on the temperature at which the milling was performed: amorphization occurred at temperature below glass transition temperature (T_g) while polymorphic transformation took place at temperature above T_g . In this work, we aim to study the effect of milling on the stability of pharmaceutical

cocrystal. The performance of two types of mill typically used in the industry, ball mill and jet mill, is also compared.

Caffeine-glutaric acid (1:1) cocrystal (CA-GA) is chosen as the model compound in this study. Caffeine (1,3,7-trimethyl-2,6-purinedione) is known to exhibit instability toward moisture, with the formation of non-stoichiometric hydrate.³⁴ Trask et al. demonstrated that CA-GA could be a remedy for caffeine hydration problem.⁹ Two polymorphs have been identified for CA-GA (Forms I and II)^{9, 35} and their relative thermodynamic stability has recently been thoroughly investigated.³⁶ Form I is needle-shaped or rod-shaped while Form II appears as blocks.^{9, 36}

▪ EXPERIMENTAL SECTION

Materials. Anhydrous caffeine (99% purity) was obtained from Fluka and glutaric acid (99%) from Alfa Aesar were used as received. The solvents were of analytical or chromatographic grade. Form II of caffeine-glutaric acid cocrystal was obtained by seeded cooling solution cocrystallization following the procedure described in Yu et al.²² Only sieved fraction between 355 and 600 μm was used in the milling experiments. The sieved crystals were divided into equal portions using a rotary sample divider to ensure that the particle size distribution (PSD) of the crystals used in each milling experiment was as similar as possible. Each portion was placed in a small covered glass vial and stored at < 30% RH and room temperature prior to use. Particle size distribution, particle morphology and polymorph of the milled samples were analyzed on the same day as the milling experiments. This was to ensure that any changes incurred by the milling process could be captured.

Planetary Ball Milling. Ball milling was performed using a Fritsch Pulverisette 5 (FRITSCH GmbH, Idar-Oberstein, Germany), a planetary ball mill equipped with stainless steel jar and balls (10 mm diameter). The mass ratio of ball to sample was kept at 20:1 and the rotation speed was set at 100 rpm for all the runs. 2 g of sample was used in each ball milling run.

Jet Milling. Jet milling was performed using an Alpine spiral jet mill 50 AS (Hosokawa Alpine, Germany). Samples were fed at 1 g/s and the injection and grinding pressures were varied to investigate the effect of milling conditions. 5 g of sample was used in each jet milling run.

Powder X-ray Diffraction (PXRD). The powder diffraction data were collected in Bragg-Brentano geometry with a Bruker D8 Advance (Bruker AXS GmbH, Germany) X-ray powder diffractometer equipped with a Cu-K α radiation ($\lambda = 1.54056 \text{ \AA}$) source, a Nickel-filter, 0.3° divergence slit and a linear position sensitive detector (Vantec-1). The diffractometer was operated at 35 kV and 40 mA. The sample was loaded onto a glass circular sample holder of 1 mm thickness and 1.5 cm diameter. The data were collected over an angle range of 5 to $50^\circ 2\theta$ at a scanning speed of $2^\circ 2\theta$ per minute.

Particle Size Analysis. The particle size distribution was measured using laser diffraction (Malvern Mastersizer MS-2000, UK) with n-decane as the wet dispersion medium and at a pump rate of 2000 rpm. Measurements were done in triplicate.

Scanning Electron Microscopy. The particle morphology was examined by high resolution scanning electron microscopy (SEM, JSM-6700F, JEOL, Japan) operating at 5 kV. The samples were coated with platinum for 1 min by a sputter coater (Cressington Sputter Coater 208HR, UK) prior to analysis.

RESULTS AND DISCUSSION

Characterization of Unmilled Cocrystals

Before the milling experiments, the CA-GA cocrystals obtained by seeded cooling crystallization²² were analyzed by PXRD to confirm that they belonged to Form II. As shown in Figure 1, the PXRD pattern of the unmilled crystals corresponded to that of Form II. Differential Scanning Calorimetry (DSC) was also performed to confirm that the unmilled crystals corresponded to Form II (Figure S1, Supplementary information, SI).

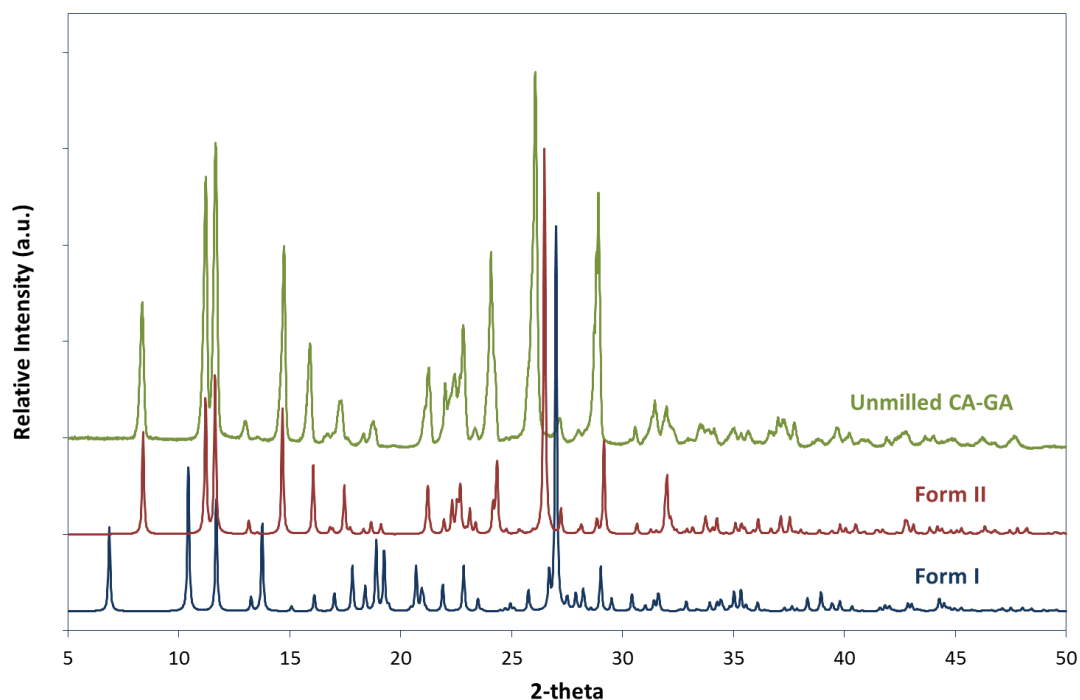


Figure 1. Powder X-ray diffraction pattern of unmilled caffeine-glutaric acid cocrystals confirmed that the raw crystals belonged to Form II.

Since only 1-5 g of crystals were used in each milling experiment, it was difficult to obtain reliable PSD by mechanical sieving. Therefore, PSDs measured by Malvern Mastersizer were used as basis of comparison in this work. The PSD of the unmilled crystal is shown in Figure 2. d_{50} of the raw crystal was 217 μm .

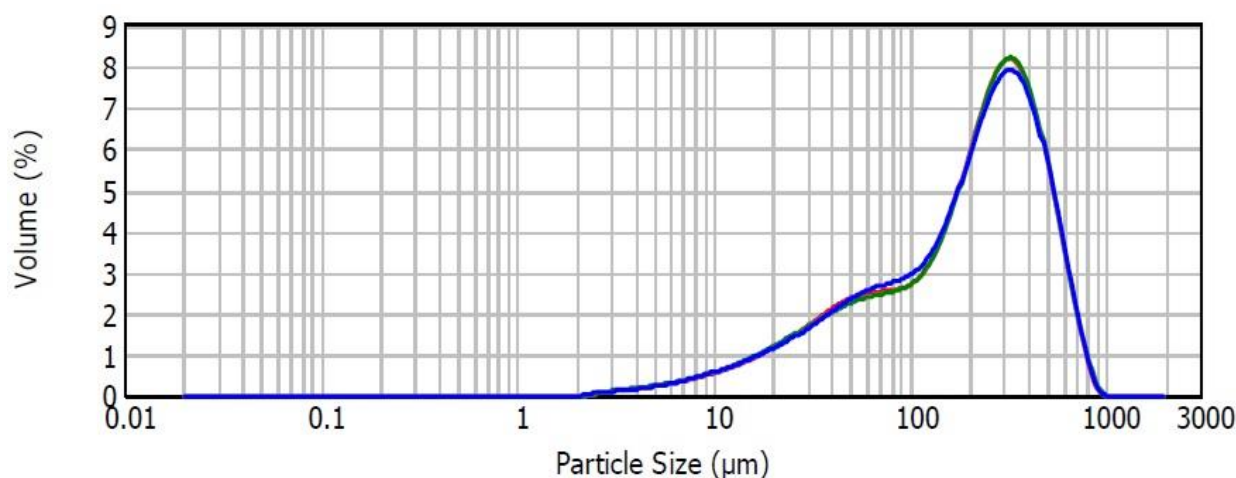


Figure 2. Particle size distribution of unmilled CA-GA cocrystals. $d_{50} = 217 \mu\text{m}$.

Ball Milling

Form II of CA-GA cocrystals were subjected to ball milling for 5, 15 and 25 min. The PXRD patterns of the milled crystals are shown in Figure 3 together with the simulated PXRD patterns for Form I and Form II CA-GA. The signature peaks of Form I at 6.8 and 10.4 2-theta are evident in all the milled samples. This suggests ball milling did not result in any dissociation of the cocrystal into its constituent components as caffeine and glutaric acid but partial transformation from the thermodynamically stable Form II to the metastable Form I occurred even after only 5 min of ball milling. Quantitative analysis of the phase transformation was performed by Rietveld refinements using Topas v4.2 (Bruker-AXS GmbH, Karlsruhe, Germany)

following the same procedure as described in our previous report.³⁶ Rietveld refinements show that the amount of Form I increased with ball milling time (Table 1).

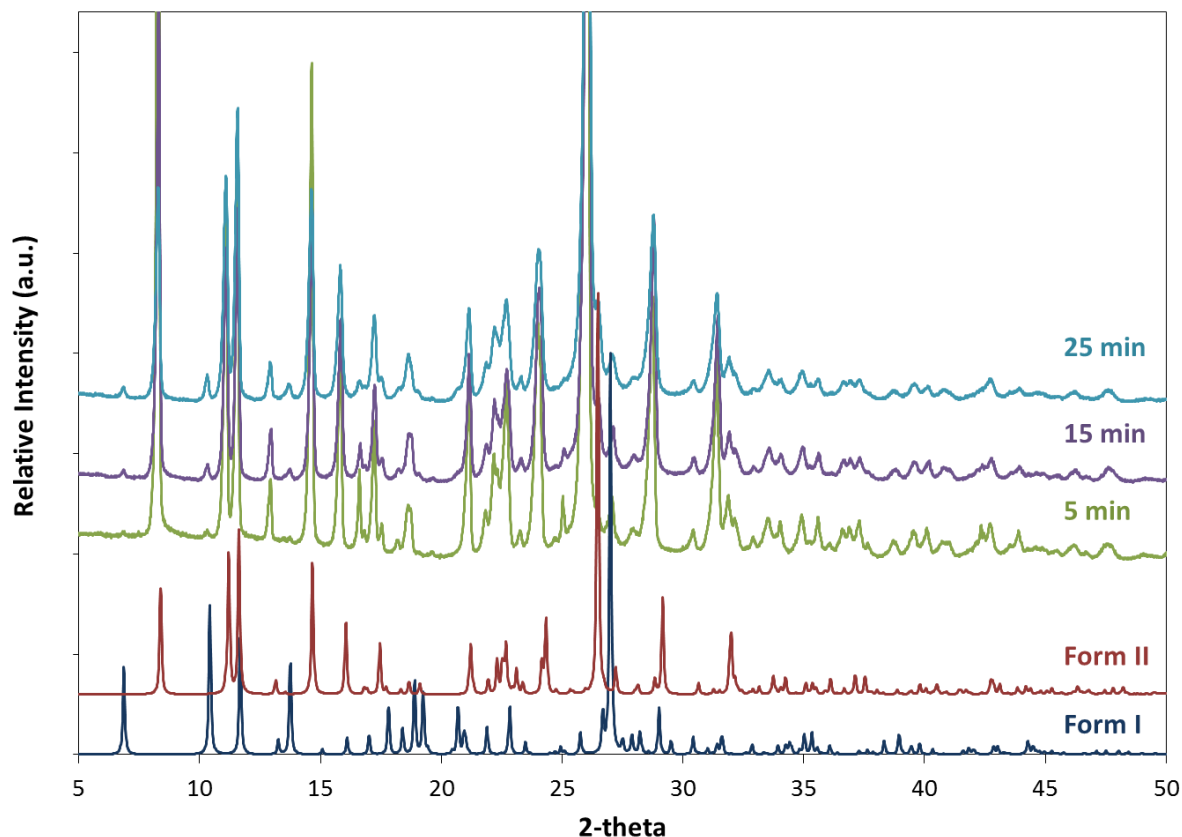


Figure 3. PXRD patterns of CA-GA after ball-milled for 5, 15 and 25 minutes.

Table 1. Form I content obtained from Rietveld refinements.

Milling time (min)	Form I (wt %)
5	2.20
15	5.97
25	9.15

The presence of Form I in the milled samples can also be clearly observed from the SEM images (Figure 4). Needle-shaped Form I can be seen amidst the prismatic Form II.

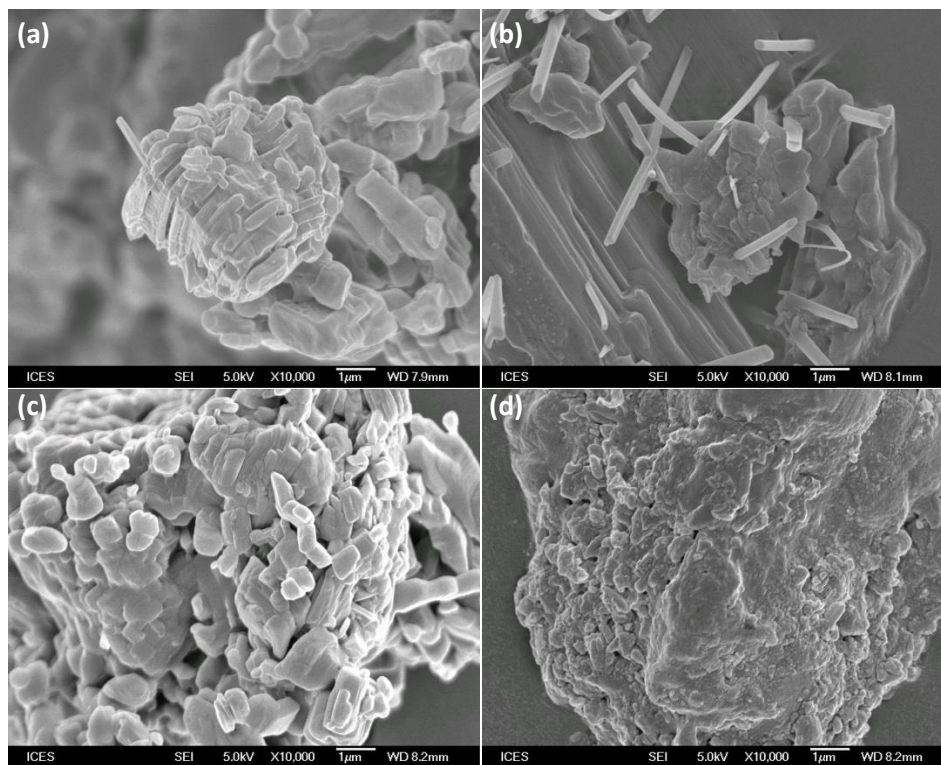


Figure 4. SEM images of CA-GA after ball-milled for (a) 5, (b) 15 and (c,d) 25 minutes.

From the d_{50} of the milled samples (Table 2), ball milling was able to reduce the particle size from d_{50} of 217 μm to 69 μm after 5 min of milling. However, increased milling duration did not result in further reduction in d_{50} and instead an increase in d_{50} was observed. The increase in size with milling time is described as “the negative grinding phenomenon”³⁷ which is generally attributed to the aggregation and agglomeration of particles.³⁸ This appeared to be the case in our experiments as larger extent of agglomeration with increase in milling time can be clearly seen from the SEM images in Figure 4. From the PSD (Figure S2, SI), there is a clear shift of

particle size toward the coarser fraction and it can be seen that fines below 10 μm have almost all disappeared after 25 min of milling.

Table 2. d_{50} of ball-milled samples measured by Malvern Mastersizer.*

Milling time (min)	d_{50} (μm)	SPAN
0	217	2.185
5	69	2.334
15	72	2.787
25	204	2.658

* PSDs are included in Figure S2 in Supplementary Information

Jet Milling

Jet milling was performed on CA-GA Form II at the conditions listed in Table 3. Regardless of the conditions employed, Form II remained intact during jet milling and no Form I was detectable from the PXRD patterns (Figure 5). SEM images (Figure 6) of the jet-milled samples showed no needle-shaped Form I crystals and agglomeration of crystals appeared minimal. More SEM images are included in Figure S3 in the SI. Since the optimization of milling conditions was not the objective of this work, PSD of the jet-milled samples were only measured for three runs to illustrate the particle size reduction after jet milling as shown in Table 3. As expected, intensifying the milling condition by increasing the grinding pressure during jet milling resulted in further reduction of d_{50} from 88 to 29 μm . The width of the PSD (SPAN) also decreased with increasing grinding pressure.

Table 3. Jet milling Conditions and d_{50} Measured by Malvern Mastersizer.*

No.	Injection pressure (bar)	Grinding pressure (bar)	d_{50} (μm)	SPAN
J1	4	1	88	3.430
J2	4	2	29	1.757
J3	4	3	19	1.379
J4	2.5	2	-	
J5	3.0	2	-	
J6	3.5	2	-	

* PSDs are included in Figure S4 in supporting information

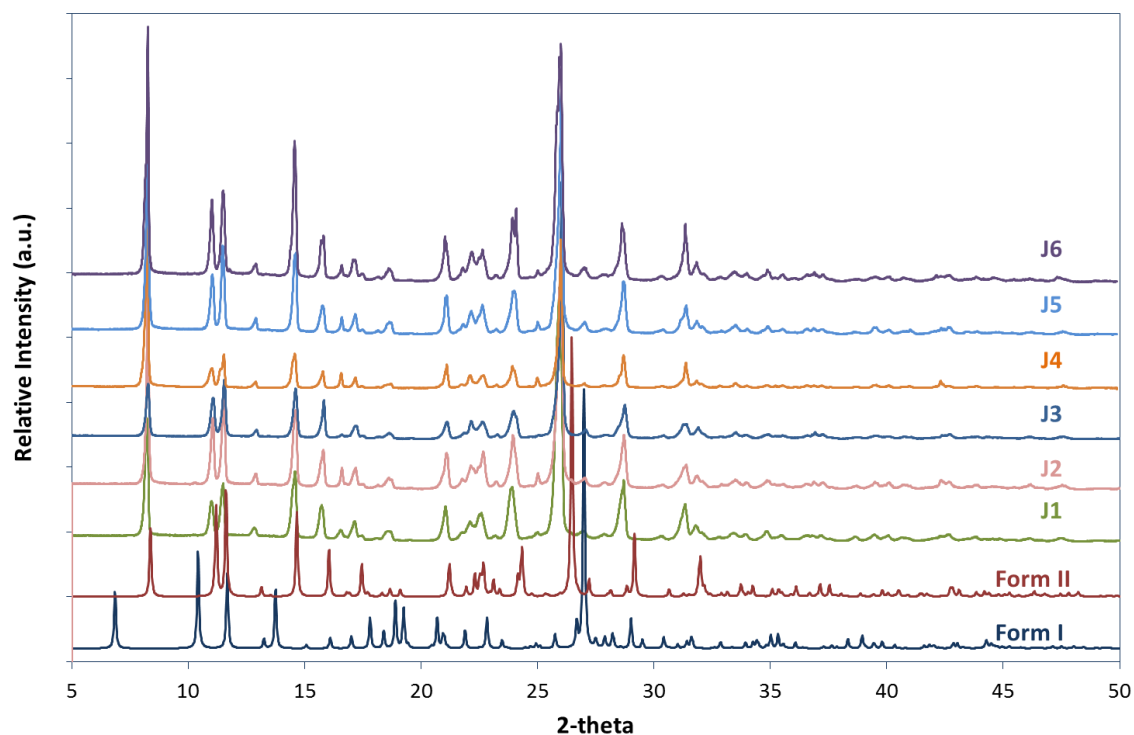


Figure 5. PXRD patterns of CA-GA after being jet-milled under different conditions. No Form I could be detected.

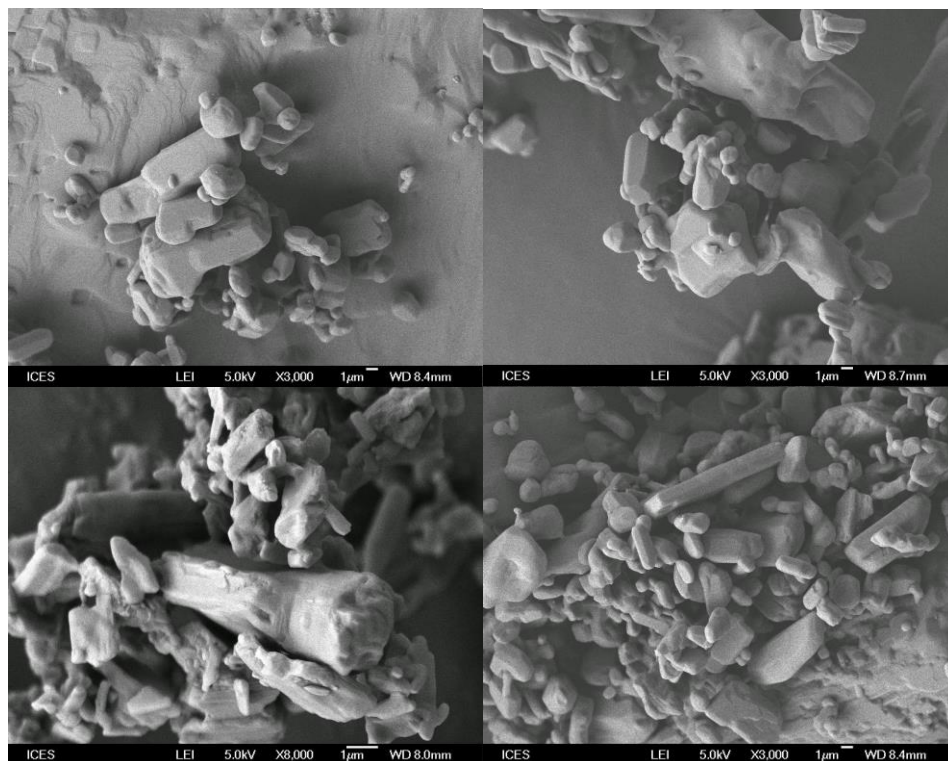


Figure 6. Representative SEM images of jet milled samples.

Post-milling Stability

Milled samples were stored in a desiccator containing P_2O_5 ($\sim 0\%$ RH) at 22°C to investigate the post-milling stability. Figure 7 showed the PXRD of CA-GA after ball milling for 5 min. The signature peaks of Form I at 6.8 and 10.4 $2\text{-}\theta$ can be seen disappearing from day 4 onwards. Trask et al.⁹ have shown that Form I is stable at 0% RH for as long as 7 weeks. The shorter conversion time to Form II observed in our experiment is likely due to the presence of vast excess of Form II that may accelerate the conversion as well as the intermittent exposure to ambient humidity ($>70\%$ RH) during sample withdrawal before each PXRD analysis. The reported conversion time is shorter than a day at humidity of 75% RH.⁹

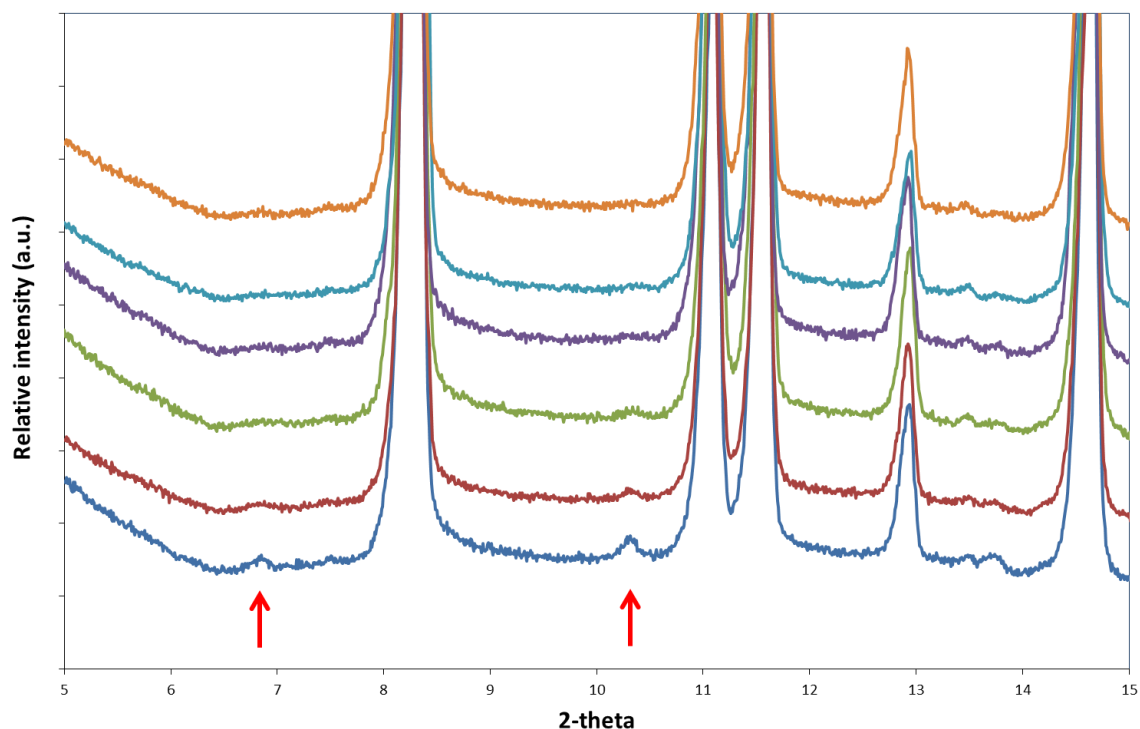


Figure 7. PXRD patterns of ball-milled samples upon storage at 0% RH and room temperature. From bottom: Immediately, 1, 2, 3, 4 and 7 days after ball milling for 5 min. The arrows indicate the signature peaks of Form I.

All jet milled samples belonged to Form II after milling. Post-milled PXRD analysis showed that the samples remained as Form II, as expected (results not shown).

Comparison between Ball Milling and Jet Milling

Ball milling and jet milling both rely on the particle-particle collision and particle-wall (milling tool) collision to effect size reduction. The mechanisms by which particle size is reduced follow the same principles – existing cracks on the micro- or nanoscale present in the particle are

activated when the particle experiences stress and absorb elastic strain energy.³⁹ However, the different modes of operation of these two mill types lead to significant differences to the properties of the milled products. Our experimental findings have shown that jet milling effectively reduced the particle size without incurring any changes to the solid state of the samples. On the other hand, ball milling induced much damage to the samples and size reduction was much less effective than jet milling. Negative-grinding phenomenon was also observed as ball milling duration increased. These observations could be explained by the intensive conditions that the particles experienced during ball milling. During planetary ball milling, the collision process between the particles and between particles and the milling parts (milling balls and wall of the milling jar) over a much longer duration could lead to significant temperature increase inside the milling jar. When particles are subjected to impact and friction forces in the ball mill, mechanical forces result in cracks in the crystals. As the crack propagates at high speed (in the order of 10^2 m/s), crack tip temperature can rise to a temperature much higher than the bulk temperature.⁴⁰ While the temperature surrounding a crack in ductile metals ranges from 450 to 1400 °C,⁴¹ significant heating was also observed for soft polymer material, e.g. 80 °C for PMMA. With such a temperature increase, it is clear that damages to the powder are possible. It has been suggested that during milling, the intense mechanical energy can lead to local heating such that small crystalline regions start to melt.⁴² If the milled material is subsequently quench cooled to below the glass transition temperature (T_g), e.g. in cryomilling, amorphous regions can be obtained from the melt. At temperature higher than T_g , the transiently formed amorphous state will transform to the stable crystal phase.³² Since our experiments were not performed at temperature below T_g , the possibility of amorphous formation can be ruled out.

218 In the case of CA-GA, polymorphic conversion and agglomeration of crystals were observed
219 under the milling conditions used. To understand why such changes were induced, it is
220 necessary to revisit the polymorphism of CA-GA that we have studied previously.³⁶ From the
221 VTXRD results, Form II begins to transform to Form I at around 69 °C. Further heating results
222 in melting at 98 °C. Upon cooling to 78 °C, Form I nucleated and remained to be the only phase
223 observed at the end of the cooling process at 25 °C. As discussed before, the temperature of the
224 powder could easily surpass the transformation temperature of 69 °C during ball milling. This
225 explains why the stable Form II was partially transformed to the metastable Form I. As the
226 milling time increased, the surface of some of the crystals may increase to beyond the melting
227 point of Form I, i.e. 98 °C, in which case small amount of crystals surface may melt giving rise
228 to melted regions on the crystal surface. As the crystals continue to collide with each other, the
229 tiny melt regions on the crystal surface start to coalesce to form liquid bridges between the
230 crystals. The liquid bridges then recrystallize to Form I upon cooling to below 78 °C by the
231 dissipation of energy through contact with air inside the milling jar. Once recrystallized, Form I
232 remains till the end of the experiment. The formation and solidification of liquid bridges could
233 explain the observed agglomeration and appearance of Form I at longer milling time. This
234 melting of the crystal surface is evident in Figure 4d as the crystal edges look fused, in contrast
235 to the sharp edge of crystals obtained from jet milling (Figure 6). In summary, we propose two
236 different mechanisms for the observations in ball milling experiments. At short milling time, the
237 local temperature of the crystals increased to above the polymorphic transformation of 69 °C,
238 leading to the partial transformation of stable Form II to metastable Form I. At longer milling
239 time, the local temperature of the crystals increased to above the melting point of Form I at 98
240 °C. Surface melting occurred, giving rise to tiny melt regions on the crystal surface which then

coalesce to form liquid bridges between crystals upon collision between crystals. The liquid bridges then solidified and recrystallization of Form I took place, resulting in the appearance of Form I and crystals agglomeration. Therefore, at longer milling time, increase in d_{50} and width of distribution were observed.

In a typical jet mill, powders are fed into the grinding chamber via a vibrating feeder that controls the feed rate. The powders are accelerated to a high velocity by an air jet prior to entering the grinding chamber. The pressure of the feeding stream is called the injection pressure. Another air jet enters the grinding chamber through specifically designed and spatially orientated grinding nozzles which accelerate the powder to supersonic speeds and create extreme turbulence inside the grinding chamber. The turbulence and orbital nature of the grinding chamber facilitates multiple particle-particle and particle-wall collisions at a higher frequency and induces particle fracture and size reduction. Unlike ball milling, no heating effect is generated during jet milling.⁴³ This is because of the countering cooling arising from the Joule-Thompson effect when compressed gas rapidly expands to atmospheric pressure when passing through the grinding nozzle. Therefore, jet milling is often the method of choice for heat sensitive material. This also explains why jet milling was effective in reducing the particle size of CA-GA without inducing any change to the solid state of the crystals. Moreover, owing to the design of the spiral jet mill, size reduction and classification are accomplished simultaneously. Within the grinding chamber, two dominant forces are acting on the particles: the inertia centrifugal force and the fluid drag force. The fluid drag force is caused by the gas flow towards the exit at the center of the mill. If the drag force is larger than the centrifugal force, the particle will exit the mill; otherwise, it will stay in the grinding chamber and continue to fracture until it is small enough to exit the chamber. The cut size, size at which the particle exits the mill, can be

controlled by the operating parameters such as feed rate and grinding pressure. Therefore, in our case, the particle size of CA-GA could be continually reduced by intensifying the milling conditions, e.g. increasing grinding pressure (Table 3).

Practical Implications

In this work, jet milling was found to be an effective and suitable micronization method for CA-GA cocrystal. Ball milling, on the other hand, was not effective in reducing particle size and much damage was incurred on the samples in terms of both polymorphic purity and agglomeration. For pharmaceutical compounds, the thermal effects of ball milling could be a major issue since the API generally has a polymorphic transformation temperature and melting point within the range of possible temperature rise during ball milling as discussed earlier on. CA-GA polymorphic transformation during ball milling can be explained by the thermal effect experienced by the material. However, the effect of ball milling on other chemicals can be more complicated and unpredictable. Hedoux et al.²⁸ found that ball milling induced transformation of each form of anhydrous caffeine toward the other, and given long enough grinding, an equilibrium state composed 30% of Form II was attained. Detailed explanation of the observed phenomenon was not given but the authors proposed that it was probably related to the nature of the disorder-disorder transformation and stability conditions of caffeine Form I at room temperature. Therefore, care should be exercised in ball milling of co-crystals for the purpose of particle size reduction at the final stage of pharmaceuticals manufacturing. Nevertheless, ball milling is a valuable tool for small-scale solid-form screening as demonstrated by Jones and coworkers³⁵ as well as chemical synthesis by mechanochemical reactions.⁴⁴⁻⁴⁷

Given the potential stability problem associated with the exposure to water or solvent, it can be foreseen that unit operations utilizing water or solvent such as wet milling and granulation could be problematic for cocrystal and perhaps best avoided unless the phase diagram of the cocrystal with the said solvent is thoroughly investigated to identify the safe region of operation, if any. This is especially important for cocrystals of hydrate forming compound as such as CA-GA. In addition to polymorphic transformation when subject to mechanical stress and heating, these cocrystals may undergo dissociation and subsequent hydrate recrystallization on exposure to water. Eddeleston et al.⁴⁸ demonstrated that even exposure to high humidity condition is sufficient to induce significant levels of cocrystal dissociation for caffeine cocrystals. During wet granulation, the combination of granulating solvent and drying conditions also provide a suitable environment for polymorphic conversion and solvate formation. Crystal form conversion during wet granulation has been reported for several pharmaceutical compounds but such study has yet to be performed on cocrystal system.

▪ CONCLUSIONS

The results from this investigation show that jet milling is a more suitable size reduction method than ball milling for caffeine-glutaric cocrystals. Ball milling induced polymorphic transformation of CA-GA from the stable Form II to the metastable Form I and the particle size was not reduced but increased with increasing milling time. On the other hand, jet milling did not alter the solid state integrity of CA-GA and the particle size was reduced effectively. The difference in the performance of the two mill types was explained by the heating effect during ball milling. Depending on the ball milling time, we propose that the local temperature of

crystals could increase to above the polymorphic transformation temperature of 69 °C or even the melting point of Form I at 98 °C, leading to partial transformation of stable Form II to metastable Form I or even surface melting and subsequent recrystallization of Form I from melt. The plausible formation of liquid bridges between crystals and subsequent recrystallization also result in crystals agglomeration and thus explains the “negative” grinding phenomenon observed with increasing ball milling time. Due to the Joule-Thomson effect, the cocrystals did not experience any net heating during jet milling and thus the solid-state integrity of the cocrystals was preserved. The findings from this study have broader implication to the selection of mill type for not only pharmaceutical cocrystal but pharmaceutical compounds in general.

▪ ASSOCIATED CONTENT

Supporting Information. It contains figures of DSC of CA-GA (Form II) cocrystal, PSDs of ball-milled samples, SEM images of jet-milled samples and PSDs of jet-milled samples. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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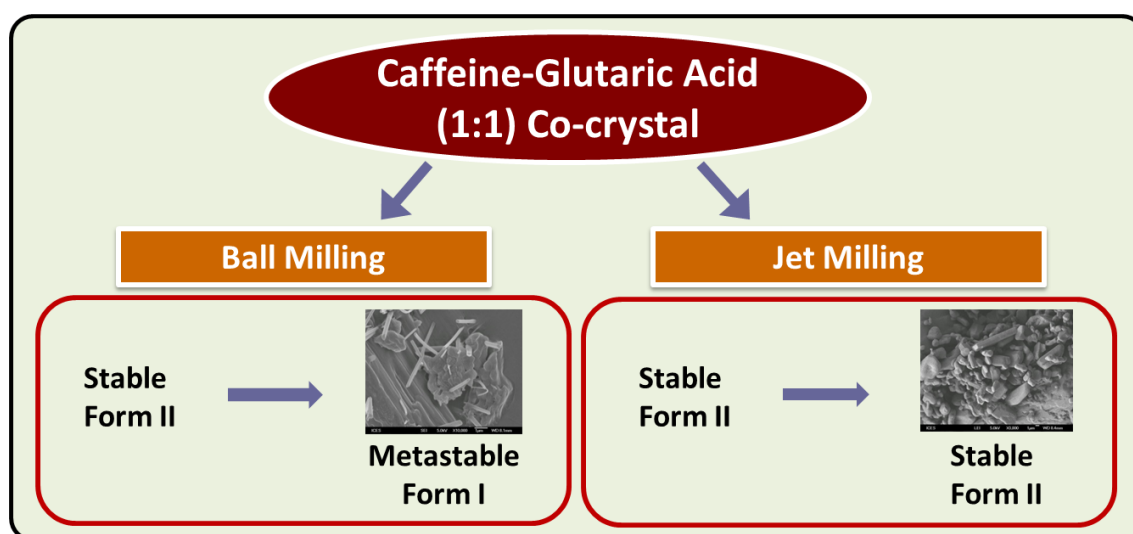
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457 Stability of Pharmaceutical Cocrystal During
458 Milling: A Case Study of 1:1 Caffeine-Glutaric Acid

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462 Despite the rising interest in pharmaceutical cocrystals, there is a lack of research in the solid
463 processing of cocrystals downstream to crystallization. The purpose of this study is to investigate
464 the effect of milling on dimorphic caffeine-glutaric acid cocrystal using ball/ jet mill. It reveals
465 that ball milling induced polymorphic transformation from stable Form II to metastable Form I;
466 whereas Form II remained intact after jet milling. Aside, jet mill was found to be effective in
467 reducing particle size than ball mill. The difference in the performance of the two types of mill

468 was attributed to the localized heating effect during ball milling and Joule-Thompson countering
469 cooling effect during jet milling.

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