



# Anomalous size evolution of partially amorphized pharmaceutical particles during post-milling storage



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## ABSTRACT

Milling is simple and inexpensive method for particle size reduction. The micronization process such as fluid-energy impact mills (e.g. spiral jet mills and fluidized bed jet mills) is commonly used in the pharmaceutical industries to attain optimal/desire particle size distribution for pharmaceutical powders. However, this process may also cause several undesirable effects on active pharmaceutical ingredients (APIs) such as aggregation of fine particles, induction of electrostatic charges, mechanochemical transformation, defects on the surface of drug particles (amorphization) and changes in other physicochemical properties which may significantly affect the physical stability of API powders.

In this study, the effect of milling-induced amorphization on the properties of APIs jet-milled at different energy-inputs (high (I), medium (II) and optimal (III)) provided from industry was investigated. Dynamic vapor sorption (DVS) technique has been established to quantify the amorphous content of industry milled APIs (I, II and III). A time-course study has been conducted to evaluate the physical stability of X-ray amorphous (generated by in-house cryo-milling as control) and three industrial samples I, II and III under accelerated stability test conditions (A = 40 °C/75%RH and B = 25 °C/55%RH) and any accompanying changes in key physicochemical properties such as crystallinity, agglomerate strength, particle size distribution (PSD) and morphology. In descending order, the amorphous content (%) of industrial API samples (milled different energy-inputs (high (I), medium (II) and optimal (III))) were ranked from I (50.9%), II (31.6%) to III (14.6%).

Re-crystallization of X-ray amorphous and industrial samples was observed under both conditions A and B during storage of 13 weeks. It was observed that there were changes in the particle size of APIs during post-micronization storage. There were reductions in particle size of all industrial samples under conditions A and B after 13 weeks of storage. A possible explanation on the observation of anomalous particle size shift during post-milling storage was attributed to two different phenomena occurring at the same time and competing with each other. These two phenomena are called “surface re-crystallization” and “stress relaxation”. Re-crystallization of amorphous surface (observed from SEM) may lead to enlargement of particle size due to formation of solid bridges during storage. Microcompressor tester (MCT) analysis also suggested that the agglomerate strength increases during storage due to the surface re-crystallization. In case of particle size reduction, PSD analysis suggested that the milled agglomerates exhibited breakage pattern termed as localized disintegration whereby clusters of primary particles broke off from the outer surface of milled agglomerates. This was likely attributed to the energy-intensive micronization process that induces residual stresses, which propagate over time and lead to the breakage of particle agglomerates. Overall, the stress relaxation is more dominant than the re-crystallization and results in overall particle size reduction after storage.

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## 1. Introduction

Amorphous or partially amorphous APIs can be generated or induced from various processing methods such as solvent deposition [1] milling [2,3], melt-extrusion [4,5], spray-drying [6], melt-quenching [7] and supercritical fluids technology [8–12]. It has also been reported that the choice of methods used to generate/induce amorphous form has influences on its physical stability in terms of enthalpic relaxation and crystallization behavior [13,14]. Among the methods, jet-milling is a common unit operation employed for particle

**Abbreviations:** API, active pharmaceutical ingredient; DVS, dynamic vapor sorption; PSD, particle size distribution; SEM, scanning electron microscopy; PXRD, powder X-ray diffractometry; MCT, microcompressor tester; EPG, epi-gallocatechin gallate; RH, relative-humidity; DVS, dynamic vapor sorption; ACN, acetonitrile.

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reduction in pharmaceutical industries which is relatively low-cost and easily scalable manufacturing process [15,16]. The jet-milling process requires high energy input and often leads to disruption/defection within the crystal lattice of micronized powder thus creating disordered regions or amorphous regions. These amorphous regions are anticipated predominantly on the surface of micronized API particles. These amorphous regions/surfaces generated may have lower stability (not in thermodynamically equilibrium) as compared to its crystals due to the higher energy level [17–19] and tended to re-crystallize over time. The presence of amorphous regions in micronized API powder may influence its physical and chemical stability (thus its formulation performance). Besides that, it was demonstrated that the role of glass transition ( $T_g$ ) on the transformation of API upon milling is also important whereas decreasing in milling temperature leads to an increase of the amorphization tendency and milling above  $T_g$  can produce a crystal-to-crystal transformation between polymorphic varieties [20–22].

Moreover, the characterization methods of amorphous form are still lacking as existing methods mainly focused on detecting the presence of crystalline rather than the amorphous state [23,24]. There are many characterization methods used to detect amount of crystalline material in the API such powder X-ray diffraction (PXRD), differential scanning calorimetry [25,26] and spectroscopy [27]. However, the amount of amorphous material is not measured directly but is mostly derived from the amount of crystalline material in the sample [24]. As a result, the derived amorphous content of drug does not provide any information whether the drug is present as amorphous drug or as molecularly dispersed molecules through the assessment of crystallinity characterization method. Therefore, it is critical to be able to accurately quantify amorphous content of material in order to evaluate the effect of amorphization and any other accompanying physicochemical properties changes from a micronization process.

Recently, water vapor sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different [28,29]. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples. Li et al. [30] have studied the physical and chemical stability of amorphous epi-gallocatechin gallate (EPG) stored at selected temperature (25–80 °C) and relative humidity (0–97% RH) conditions. They used moisture sorption measurements to determine the crystallization induction times at these different conditions. The rate of re-crystallization increased when the EPG was exposed to higher RH due to the plasticizing effect of the sorbed water vapor which increased molecular mobility. Young et al. [31] applied organic dynamic vapor sorption (organic-DVS) to characterize amorphous content in known amorphous–crystalline mixtures of lactose and salbutamol sulfate. They used *n*-octane as the apolar probe and DVS experiments were conducted by exposing mixtures of each sample to partial pressures 0–90%  $P/P_o$ . A linear relationship between amorphous content and *n*-octane partial pressure was observed for both lactose and salbutamol sulfate with  $R^2$  values of 0.992 and 0.999, respectively. Sheng et al. [32] also employed dynamic vapor sorption (DVS) to induce the re-crystallization behavior of amorphous etravirine. Buckton and Darcy [28] demonstrated that dynamic vapor sorption technique was capable of measuring amorphous material as low as 1% and showed that the method was more sensitive than other techniques such as PXRD, density and heat of crystallization measured by differential scanning calorimetry. Recently, Sheokand et al. [33] also reviewed that DVS technique is useful in quantification for amorphous content because of the tendency of amorphous material to absorb vapors, and in some cases to subsequently demonstrate phase transition.

Therefore, the aim of this study is to investigate the effect of milling-induced amorphization on the properties of APIs jet-milled at different energy-inputs (high (I), medium (II) and optimal (III)) provided by the industry. The organic-DVS method will be used to quantify the amorphous contents of industrial samples (I, II and III). Physical stability

is the most challenging issue to overcome for solid amorphous or partially amorphous APIs. During long-term storage, the rate-limiting step of crystallization is nucleation [34]. However, the temperature dependence of the nucleation rate is difficult to evaluate, and nucleation occurs in a peculiar manner. An accurate estimation of the crystallization rate during storage can be done only by observing the stability at the same temperature of the storage conditions. Thus, a time-course study also will be conducted to evaluate the physical stability of X-ray amorphous (generated by in-house cryo-milling as control) and three industrial samples I, II and III in the presence of moisture (Condition A = 40 °C/75%RH and Condition B = 25 °C/55%RH) and any accompanying changes in key physicochemical properties such as crystallinity, morphology, agglomerate strength, and particle size distribution (PSD).

## 2. Materials and methods

### 2.1. Materials and storage conditions for time-course study

X-ray amorphous form of industry API was prepared in-house by cryo-milling the API crystal powder. Physical stability stress test of in-house cryo-milled API (X-ray amorphous API) and three other jet-milled industrial samples I, II and III (energy inputs: high (I), medium (II) and optimal (III)) provided by industry (due to confidentiality, the API cannot be reviewed) were conducted under accelerated stability test storage conditions. The amorphous content of industrial samples is unknown. Table 1 shows the storage conditions used in this study. The physicochemical properties of the samples were observed over the durations of 0, 1, 4 and 13 weeks.

### 2.2. Cryo-milling

The cryo-milling was carried out using a Retsch CryoMill. 2 g of crystalline API was placed in 50 ml stainless steel grinding jar and a 10 mm diameter stainless steel grinding ball was used. The cryo-milling is conducted at 20 Hz for 150 min (15 sessions per 10 minute interval). The grinding jar is continually cooled with liquid nitrogen before and during the grinding process. There was no temperature controlled during the milling.

### 2.3. Amorphous content – dynamic vapor sorption (DVS)

The amorphous content of samples during time-course studies was measured using DVS (Advantage, Surface Measurement Systems). The weight change of sample during exposure to a defined condition was measured by a sensitive microbalance. In this study, acetonitrile (ACN) was used as the organic solvent for DVS because the sorption of ACN is highly sensitive to the presence of amorphous content in the industry APIs. As shown in Fig. 1 significant amount of ACN was adsorbed when the API was in X-ray amorphous form. Besides that, the ACN was able to induce re-crystallization of the amorphous API. The required ACN partial pressure ( $P/P_o$ ) was controlled by mixing dry nitrogen and nitrogen saturated with ACN, in the corresponding proportions, using mass flow controllers. Approximately, 80–120 mg of sample was weighed and conducted under 0 to 50% ACN  $P/P_o$  in steps of 10% ACN  $P/P_o$  (1 sorption cycle) for each experiment. The system was considered to be in equilibrium if the rate change of mass was less than 0.002%/min. All samples were pre-conditioned prior to the start of DVS experiment

**Table 1**  
Storage conditions for in-house cryo-milled samples and industrial samples I, II and III.

Storage conditions	Temperature (°C)	Relative humidity (RH%)	Storage period (week)
A	40	75	0, 1, 4 and 13
B	25	55	0, 1, 4 and 13

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