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The influence of spiral jet-milling on the physicochemical properties of carbamazepine form III crystals: Quality by design approach

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ABSTRACT

The purpose of this study was to investigate the influence of spiral jet-milling process on the physicochemical characteristics of α polymorphic active pharmaceutical ingredient, using Carbamazepine form III as a model drug, and taking into consideration Quality by Design (QbD) approach to pharmaceutical development. A $2^{(4\text{-}1)}$ factorial screening design was implemented to identify the spiral jet-milling process variables that significantly affect the particle size distribution of milled samples. Diameter of injector nozzles, diameter of ring nozzles and air pressure were selected for further analysis using a $2^{(3\text{-}1)}$ factorial experimental design. Particle size distribution of additional samples was determined, while physicochemical properties were examined by differential scanning calorimetry (DSC), hot-stage polarized microscopy (HSPM), attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR), and compared to those of un-milled drug. The gathered results shown that applied experimental design approach is capable to predict material behavior and could help in better understanding of material behavior during jet-milling process. Created design space (DS) provides assurance of product quality, expressed as the powder particle sizes lower than 5 μm, as well as, in initial polymorph form existence after jet-milling through combination and interaction of input variables.

Keywords: Jet-milling; Carbamazepine; Factorial screening design; Particle size; Polymorphism; Quality by design

1. Introduction

Spiral jet-milling is a process suitable for fine and ultrafine size reduction of pharmaceutical powders and involves acceleration of particles so that grinding occurs by particle-to-particle impact or impact against a solid surface (Joshi, 2011). The high energy delivered by the spiral jet-mill onto the particles leads to structural changes at the surface where the solids come into contact besides size reduction (Palaniandy, 2008).

Advantages of jet-milling are the absence of contamination due to autogenously grinding mechanism, low wear rate, small footprint, low noise and the ability of grinding heat sensitive materials (Berthiaux et al., 1999; Midoux et al., 1999; Kolacz, 2004; Müller et al., 1996). In jet-mill, the main breakage mechanism is destructive breakage due to impact and abrasion effected by attrition between particles (Berthiaux and Dodds, 1999; Frances et al., 2001).

Pharmaceutical industry demands very stringent fine particle specifications in terms of particle size and its distribution, therefore the main objective is to obtain a certain particle size, without causing physical or chemical changes such as amorphous or polymorphic transitions (EMEA, 1999). The rate and extent of these phase transitions will depend on characteristics of the original solid phase, the type of mill and the milling conditions (Zhanga et al., 2004). Based upon the potential for such conversion, the most stable crystalline form is

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often selected and controlled during the entire manufacturing process (US Department of Human Services, FDA, 2007).

It is well known that many organic substances for pharmaceutical applications exist in different crystalline forms or as solvates (Byrn et al., 1995). In the last two decades, the importance of characterization and control of the crystalline forms of active pharmaceutical substances is emphasized because different polymorphs may exhibit different physicochemical properties such as solubility, dissolution, stability, hygroscopicity, and the physiological parameters such as bioavailability, efficacy, and toxicity (Byrn et al., 1995; US Department of Human Services, FDA, 2004). Therefore, it is important to prevent amorphisation or polymorphic transformations during air jet-milling.

Physicochemical characterization takes place when batch milling is carried out for longer milling period in high intensity grinding mills (Chieng et al., 2006). In spiral jet-mills the retention time of particles in the milling chamber is very short because the particles will be out as soon as they reach the desired size. Although the milling occurs instantaneously and the retention time of the particles seems to be very short, the energy delivered to the particle is high, which may result in the modification of crystal structure in short milling period. It was reported that silicium dioxide milled in jet-mill undergoes severe changes in its crystal structure induced by high velocity impact (Juhasz and Opoczky, 1990). On the contrary, it has been reported that no significant structural changes take place during ursodeoxycholic acid grinding in jet-mill, where the reduction of crystallinity is only 2% (Choi et al., 2004; Chung et al., 2003).

The main features affecting the grinding ratio in spiral jet mills, can be classified into two types: geometrical parameters which concern the mill design such as diameter of the grinding chamber, shape, number and angle of grinding nozzles and operational conditions, e.g., solid feed rate, grinding pressure, injector pressure and, of course, material to grind (Midoux et al., 1999). The grind pressure was of utmost importance with respect to particle size distribution and the physical powder stability (Brodka-Pfeiffer et al., 2003). Tasirin and Geldart examined two configurations: a single jet with a target plate and jets from two opposing horizontal nozzles. More specifically, the effect of the separation distance between the jet and target or between the opposing nozzles on the grinding rate was investigated (Tasirin and Geldart, 1999).

Quality by design approach could be used to understand the correlation between process parameters and their influence on the outcome of material processing. Identifying the influence of critical process variables on the product quality attributes is decisive to successful implementation of a QbD approach to product development (Lionberger et al., 2008; Center for Drug Evaluation and Research, FDA, 2006).

Therefore, QbD development process may include identification of the Critical Process Parameters (CPP) and Input (raw) Material Attributes (IMA) that must be controlled to achieve Critical Material Attributes (CMA) of the final product (Lionberger et al., 2008). Jet-milling process parameters present CPPs as measurable input of a process step that must be controlled. The key critical quality attribute (CQA) of micronised material is particle size and polymorphic form.

The purpose of this study is to use the principles of quality by design along with appropriate design of experiments to obtain a comprehensive knowledge about the process of particle size reduction as it applies to jet-milling in order to identify and estimate various critical process parameters. Considering the importance of powder particle size for further pharmaceutical use, another aspect of this study is to investigate possible changes of carbamazepine form III crystals during jet-milling by different analytical methods.

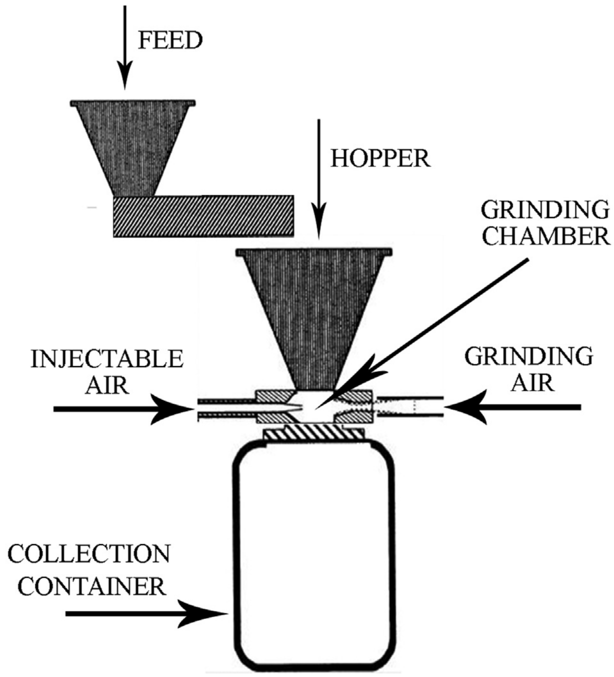

Fig. 1 – Schematic diagram of Hosokawa 50 AS jet mill.

2. Materials and methods

2.1. *Materials*

Carbamazepine (Batches No. CAR/1102B/0021) was supplied by Amoli Organics Pvt. Ltd. (Mumbai, India).

2.2. *Preparation of micronized samples by jet milling*

In order to create design space and compare physicochemical characteristics before and after milling process, carbamazepine was processed in a spiral air jet-mill Hosokawa 50 AS (Hosokawa Micron Ltd., Cheshire, England), illustrated in Fig. 1. The spiral jet-mill consists of a vertical grinding chamber with separated jets for injectable and grinding compressed air. Schematic diagram of the grinding region is illustrated in Fig. 2.

Particles contained in the hopper were continuously fed by screw feeder into the grinding chamber where they were ground at the meeting point of the two concurrent air jets formed by injector nozzle for injectable air and ring nozzle for grinding air, supplied with compressed air. The fine particles were collected in a container below grinding chamber. The operating conditions of the jet mill were controlled by adjusting the following four operating parameters: (1) diameter of injector nozzle for injectable air, (2) diameter of ring nozzle for grinding air, (3) distance between the injector nozzle and chamber for grinding (inclusion of additional rings) and (4) air pressure for milling. The influence strength of all adjustable parameters of spiral jet-mill were investigated, except constant feed rate (10 g/min) that provide thin layer of powder in a feeder. In order to define a range of the process parameters set by the operator that provide the desired quality of product-particle size distribution and preservation