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Evaluation and scale-up of miniaturized rotor–stator impact mills

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ABSTRACT

Two recently marketed, miniaturized rotor–stator impact mills of 70 mm and 35 mm rotor diameter were evaluated and compared to a conventional small scale model of 110 mm rotor diameter, in order to reduce the minimum batch size while maintaining adequate predictability. The minimum batch size of the conventional scale model is about 1 to 4 kg and far too big to establish rotor–stator impact milling technology at the early-stage of drug development due to limited availability of drug compound, and rather inefficient for the technical processing of costly drug compounds during the drug development cycle. Both miniaturized equipment models show comparable behavior on product particle size by process parameters feed rate and rotor speed in relation to the conventional scale model. The minimum, predictable batch size could be considerably reduced to 400 g and 10 g for the rotor–stator impact mills of 70 mm and 35 mm rotor diameter, respectively. Scale-up could be established between the two miniaturized models and the conventional scale model for process parameter feed rate by a common power factor concept available in literature, and for process parameter rotor speed by the cumulative specific stress energy of the rotating pins. Finally, both miniaturized rotor–stator impact mills enable significant improvements for the application in drug development, with reduced dynamic working range of cumulative specific stress energy, compared to rotor–stator impact mills at pilot and manufacturing scales.

1. Introduction

Rotor impact milling technologies are frequently applied in chemical, food, mineral and pharmaceutical industries in order to manufacture the desired particle size distribution of the related intermediates and products [1–4]. In particular, rotor–stator impact mills of pin disc configuration and radial particle movement between rotor and stator are well distributed in industry since many decades [1,5–9]. Several studies are available in literature with respect to the different applications in industry [10–15]. The main process parameter rotor speed was extensively investigated, demonstrating in principle a decrease in product particle size with increase in rotor speed. However, systematic studies evaluating further process parameters, like feed rate and gas flow or design of rotor and stator pin disc are rarely reported in the literature [12,13,16–18]. The reported studies are typically restricted to the evaluation of a specific material and equipment scale, and performed with limited attention paid to process parameters such as feed rate and gas flow. Interestingly, process parameter feed rate has been shown to provide contradicting results for the processing of rice husk [13] with an observed decrease in product particle size with an increase in feed rate, compared to the processing of a not disclosed compound [12] and limestone [16] with an increase in product particle size observed with an increase in feed rate. In addition, the particle movement and evolution of particle size during the radial transport between rotor and stator pin discs are poorly understood [17]. Basic concepts are available in the literature, but without experimental confirmation [6,16,18]. More recent advancements with respect to particle capture and impact velocity by rotating pins for a different type of rotor impact mill [19,20], and the impact breakage behavior of accelerated particles stressed against rigid surfaces [21–23] have been reported in the literature. However, a profound understanding of the particle movement, capture, stress and size reduction, including impact of process and design parameters as well as material properties at impact stress against rigid pins and against particulate product is currently not available for rotor–stator impact mills of pin disc configuration.

The pharmaceutical industry frequently applies rotor–stator impact mills of pin disc configuration, especially to engineer drug particle size after chemical synthesis [4,24–26]. Interestingly, systematic studies evaluating process relevant aspects are not available in the literature for this field of application. In order to establish rotor–stator impact mills as standard platform technology, it is essential to understand some of the evolving demands during drug development and manufacturing that are highlighted below [27]:

- milling feasibility by experimental trials at a predictable equipment scale with minimum batch size;
- equipment scale according to the needs for process development and product manufacturing across the drug development cycle and during commercial manufacturing, e.g. equipment scale from several gram batch sizes at preclinical/early clinical development stage up to several hundred kilogram batch sizes during commercial manufacturing;

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- process understanding of the impact of process parameters at the specific equipment scale across a broad range of drug compounds;
- scale-up between the different equipment scales by engineering principles.

In the present study, a systematic investigation on a rotor–stator impact mill of pin disc configuration at conventional pilot scale was performed, considering the process parameters rotor speed, feed rate and gas flow. Depending on the applied process conditions, the investigated equipment scale requires about 1 to 4 kg drug compound as minimum batch size. Therefore, two recently launched rotor–stator impact mills of pin disc configuration (both models of strictly smaller equipment scale) were also evaluated, along with a systematic investigation of the related process parameters. The results obtained on each equipment scale were compared and extrapolated to the manufacturing scale in order to establish scale-up criteria by engineering principles with an aim to facilitate the implementation of rotor–stator impact milling as a standard platform technology for drug development.

2. Materials and methods

2.1. Materials

The model compounds selected for this study were α-Lactose-monohydrate and a proprietary drug compound from Novartis Pharma AG. α-Lactose-monohydrate of type CapsuLac® 60 was obtained from Meggle GmbH & Co. KG, Wasserburg, Germany. Particle size of raw α-Lactose-monohydrate was determined by laser light diffraction providing the cumulative undersize volume particle size distribution with characteristic particle size x_{10}, x_{50} and x_{90} of 144 μm, 256 μm and 404 μm, respectively. Fig. 1 shows a scanning electron micrograph (SEM) of the raw α-Lactose-monohydrate. The SEM shows prismatic shaped primary particles up to 300 μm in length, and irregular shaped particles, potentially fragments of prismatic shaped particles. Interestingly, prismatic and irregular shaped particles are frequently attached to aggregates of up to 400 μm in length.

Particle size of the raw drug model compound was determined by laser light diffraction with characteristic particle size x_{10}, x_{50} and x_{90} of 6.4 μm, 31 μm and 349 μm, respectively. Fig. 2 shows a scanning electron micrograph (SEM) of the raw drug model compound. The SEM shows needle shaped primary particles of several microns in diameter and up to 400 μm in length. The primary particles are frequently attached to form complex agglomerates and aggregates of up to 100 μm in minimum Feret diameter and up to 400 μm in maximum Feret diameter, respectively.

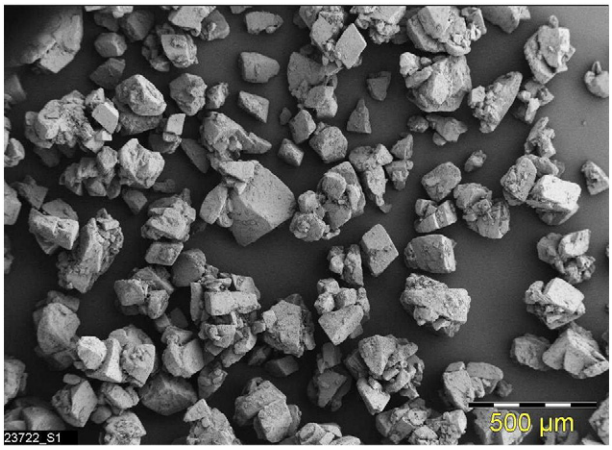

Fig. 1. Scanning electron micrograph (SEM) of raw α-Lactose-monohydrate.

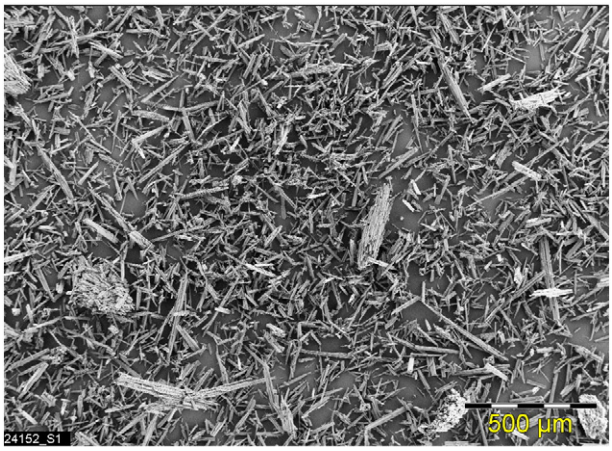

Fig. 2. Scanning electron micrograph (SEM) of raw drug model compound.

2.2. Methods

Rotor–stator impact milling was performed on conventional pilot scale equipment, type 100UPZ, from Hosokawa Alpine AG, Augsburg, Germany. The rotor–stator impact mill was operated with conventional rotor and stator pin disc configuration. Each disc was equipped with a total of 192 pins, each of 3 mm diameter and 8 mm height. The rotor pin disc has a diameter of 110 mm of the outer pin row. The raw material is fed into a vertical pipe by a twin screw feeder and immediately afterwards accelerated by the transport of dry nitrogen gas. The gas flow transports the raw material axially through the stator pin disc into the center between rotor and stator pin disc, and from there, radially between the rotor and stator pin discs. Particle size reduction can take place by impact stress of particles against rotating pins, particles against stationary pins, and particles against particles. The processed product is transported by the gas flow to a filter device, where it is separated from the transport gas by a filter cloth. Finally, the processed product is collected by gravimetric transport into a bulk product container, directly installed below the filter device. The rotor pin disc can be operated at 2000 to 22,000 revolutions per minute, resulting in an operational range of 12 to 125 m/s rotor tip speed. The feed rate of raw material into the rotor–stator impact mill is controlled by a volumetrically controlled twin screw feeder. The flow of the transport gas is independent of the rotor speed and controlled by a frequency inverter directly connected to a blower.

Rotor–stator impact mills, type LPM2-Mikro® and type Picoplex®, both from Hosokawa Alpine AG, Augsburg, Germany, were evaluated within this study for downscaling from the pilot scale equipment. Rotor–stator impact mill, type LPM2-Mikro®, was operated with conventional rotor and stator pin disc, each disc equipped with a total of 120 pins of 2.2 mm diameter and 7 mm height. The rotor pin disc has a diameter of 70 mm of the outer pin row. A further downscale is provided by the rotor–stator impact mill, type Picoplex®. The rotor–stator impact mill was operated with conventional rotor and stator pin disc, each equipped with pins of 1.4 mm diameter and 7 mm height of in total 72 pins on the rotor disc and 54 pins on the stator disc. The rotor pin disc has a diameter of 35 mm of the outer pin row. Both downscale rotor–stator impact mills were operated with appropriate twin screw feeders and filter devices, comparable to the pilot scale equipment described above. Process parameter feed rate was controlled for both downscale equipments by an appropriate twin screw feeder using volumetrical control. Flow of dry nitrogen transport gas was not controlled for both downscale rotor–stator impact mills. Therefore, process parameter gas flow was a consequence of the specific installation and the rotor speed applied. The rotor pin disc of type LPM2-Mikro® can be operated at 1000 to 36,000 revolutions per minute, resulting in an