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Optimization of the Operating Conditions of a Lab Scale Aljet Mill Using Lactose and Sucrose: A Technical Note

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INTRODUCTION

In pharmaceutical products, the particle size of drugs and components may affect processing and bioavailability.[1-4] An increasing number of compounds that are investigated in industrial drug discovery have low aqueous solubility. For class II compounds (according to the biopharmaceutical classification), dissolution rate is the limiting factor for bioavailability. According to the Noyes-Whitney equation, particle size reduction, resulting in increased surface area, is a very promising approach to enhance dissolution rate and, thus, the bioavailability of poorly water-soluble compounds.[5,6] It has been reported in the literature that amphotericin, fluocinolone acetonide, medroxyprogesterone acetate, bishydroxycoumarin, nitrofurantoin, tolbutamide, and spironolactone have shown increased clinical efficacy following particle size reduction.[7]

There are different kinds of mills available in the pharmaceutical industry for particle size reduction, such as the ball mill, fluid energy mill, cutter mill, hammer mill, pin mill, vibration mill, etc. However, the fluid energy mill and the ball mill are the only 2 that may reduce the particle size to less than 5 μ by dry milling.[8] The fluid energy mill has some advantages over the ball mill, such as its higher milling efficiency and its ability to mill thermolabile, hard, and abrasive compounds.[8,9] The fluid energy mill can be easily sterilized and operated by the use of sterile air. Another advantage of the fluid energy mill is that there is no product contamination caused by wear, as there are no moving parts.[8]

The authors have examined the literature reported on micronization conditions of a lab scale fluid energy mill (Aljet mill), which is very useful in particle size reduction at early stage drug development. None of the reviewed articles indicate that the compound was milled under optimized micronization conditions.[10-12] Therefore, it would be valuable to investigate the optimized micronization conditions using 2 kinds of crystals with different crystal strength and surface hardness, such as lactose and sucrose. The minimum batch size for an Aljet mill is approximately 1 g, which makes it very useful for micronizing compounds at discovery stage to enhance the bioavailability of poorly water-soluble drug candidates.

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MATERIALS AND METHODS

Materials

Lactose monohydrate 310 and sucrose were obtained from Foremost Farms (Milwaukee, WI) and Sigma (St Louis, MO), respectively.

Methods

In an Aljet mill (Model 00-Jet-O-Mizer, Fluid Energy, Telford, PA; see **Figure 1**), the material is fluidized and conveyed at a high velocity by a compressed fluid through extreme turbulence created by the grinding nozzles, causing particle size reduction by interparticular impact and attrition. The compressed gaseous fluid provides the kinetic energy that causes the particles to impact with other particles with sufficient momentum for fracture to occur. Turbulence ensures that the level of particle-particle collision is high enough to produce substantial size reduction by impact and some attrition.

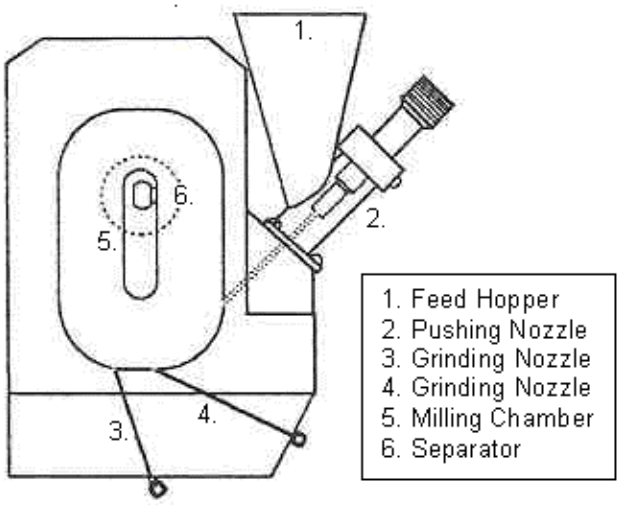

Figure 1. Schematic drawing of a Aljet mill.

Micronization of Lactose and Sucrose

Approximately 3 g of lactose monohydrate or sucrose was micronized at a constant feed rate of approximately 1.8 g/min through the Aljet mill. Initial particle size distributions of lactose, expressed in terms of D50 and D90 were 65 µ and 160 µ, respectively. The D50 and D90 represent the median or the 50th percentile and the 90th percentile of the particle size distribution, respectively, as measured by volume. That is, the D50 (D90) is a value on the distribution such that 50% (90%) of the particles have a volume of this value or less. The sucrose particle size was measured using sieves because of large particle size. The D80 was approximately 850 µ. It was important to keep the feed rate constant because a faster feed rate may produce larger particles. The material was fed into the mill using a vibratory feeder. Two grinding nozzles and 1 pushing nozzle were set at different pressures as indicated in the experimental design. Nitrogen was used as an inert gas during the milling process.

Particle Size Distribution Measurements by Laser Light Diffraction

Particle size analysis was carried out using the Sympatec laser light diffraction particle size analyzer (Sympatec, Clausthal-Zellerfeld, Germany). One measurement of particle size was carried out for each milling condition. The instrument was equipped with a RODOS powder dispenser and an R2 lens, which allowed measurements of a narrow particle size distribution in the range of 0.45 to 87.5 µ. The R4 lens was used to observe aggregation if any was present. The R4 lens could observe large particles that were not detected by an R2 lens. The minimum accuracy of measurements on the Sympatec instrument using the R2 lens, when tested using standards for a particular distribution, was approximately ± 0.19 µ. The inlet pressure on the equipment was set at 3.5 bars, and the evacuation pressure at 100 mbar. A RODOS dispenser (Sympatec) was used for consistent feeding for the powder samples as a stream of gas-solid aerosol. The particle size distribution of sucrose was measured immediately after micronization because micronized sucrose formed aggregates under ambient conditions due to its hygroscopic nature.

Experimental Designs

The lab scale Aljet mill has 2 grinding nozzles and 1 pushing nozzle. In the design of experiments, the 2 grinding nozzles were considered as 1 variable and the same setting was used in each experiment because the grinding nozzles were usually set at the same level to maximize attrition between the particles. The pushing nozzle was considered to be the other variable. The response factor was the particle size distribution, specifically, the D50 and D90. An initial experiment using the soft crystalline structure of lactose was performed to evaluate the effect of the grinding nozzle pressure and the pushing nozzle pressure on the particle size distribution (D50 and D90). Five levels of each nozzle, ranging from 20 psi to 110 psi, were evaluated using a central composite design as shown in **Table 1**. In a separate series of experiments, the tougher crystalline structure of sucrose was evaluated using a full factorial design with 2 center points (**Table 2**). In this design, 3 levels of the grinding nozzle pressure and the pushing nozzle pressure, ranging from 65 psi to 110 psi, were evaluated. The analyses of both designs were carried out using Design Expert 5 (Stat-Ease Corp, Minneapolis, MN).

RESULTS AND DISCUSSION

Results of the central composite design with lactose (**Figure 2**) suggested that runs # 5 and # 6 corresponding to grinding nozzle pressures of 33 and 20 psi, respectively, had D50 and D90 values significantly larger compared with other runs. These values suggested that a very low grinding nozzle pressure was not effective in significantly reducing the particle size of lactose. The pushing nozzle pressure did not seem to affect the particle size as significantly as the grinding nozzle pressure. When the grinding nozzle pressure was at least 65 psi, the D50 and D90 for lactose remained be

Table 1. Central Composite Design for Lactose Monohydrate

Run #	Grinding Nozzle Pressure (psi)	Pushing Nozzle Pressure (psi)
1	110	65
2	65	110
3	65	65
4	65	65
5	33	33
6	20	65
7	33	97
8	97	97
9	97	33
10	65	20

Table 2. Full Factorial Design With 2 Center Points for Sucrose

Run #	Grinding Nozzle Pressure (psi)	Pushing Nozzle Pressure (psi)
1	65	65
2	87	87
3	87	87
4	110	110
5	110	65
6	65	110

low 5 μ and 22 μ, respectively, for the entire studied range of pushing nozzle pressures. At low pushing nozzle pressures, such as 20 to 33 psi, it was observed that a small amount of material was kicked back from the mill, reducing the yield. The pushing nozzle creates a suction vacuum allowing the material to be injected into the reduction chamber. When the pushing nozzle pressure was low, the vacuum created was not enough to retain the material inside the mill, especially at a high grinding nozzle pressure. The smallest particle sizes may be achieved by either setting the grinding nozzle pressure at 110 psi and the pushing nozzle pressure at 65 psi, or vice versa.

This experiment provided evidence that the operating conditions of a lab scale Aljet mill need to be between 65 and 110 psi in order to micronize lactose effectively.

In order to confirm the suitability of the results to a wide range of compounds, with different crystal toughness and surface hardness, and to further optimize the operating conditions of the mill, sucrose was selected as a much harder crystal than lactose monohydrate to study in a full factorial design with 2 center points. The results are summarized in **Figure 3**.

The data indicated that the pattern of the particle size distribution of sucrose was similar to what was observed with lactose. The smallest particle sizes were obtained in runs #5 and #6 corresponding to the grinding nozzle pressure of 110 psi and the pushing nozzle pressure of 65 psi, respectively, or vice versa. Although statistical analysis indicated that changes in the levels studied in this experiment for grinding nozzle pressure and pushing nozzle pressure were not significant ($P > .05$), a smaller particle size was preferred when dealing with poorly water-soluble compounds.

To explain the relationship between grinding and pushing nozzle pressure on D50 and D90 using the results as summarized in **Figure 2**, least squares regression was used to obtain predictions within the design space.

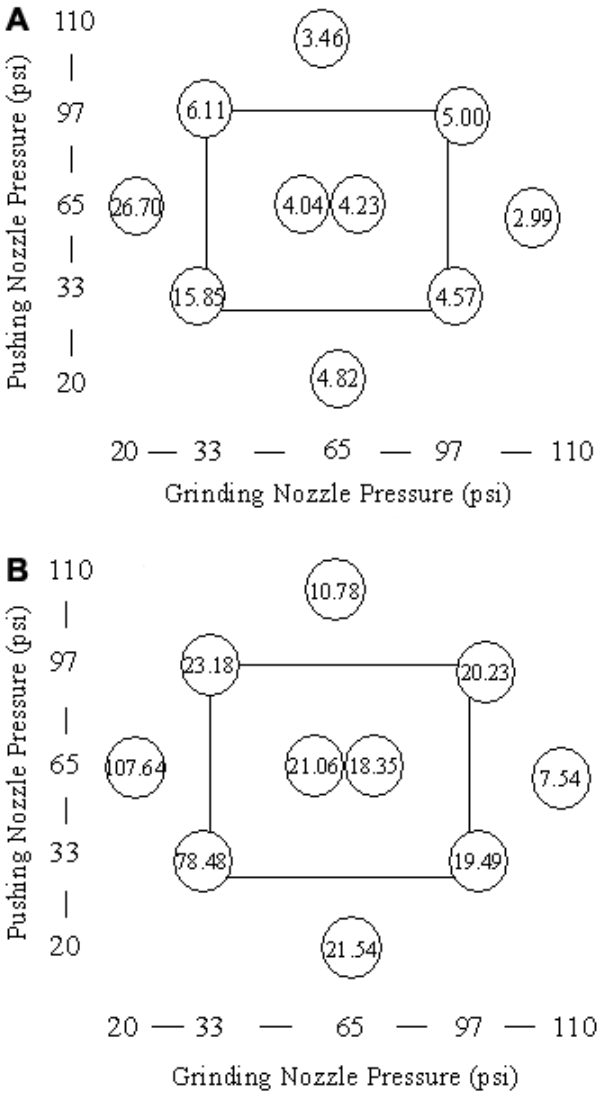

Figure 2. Particle size analysis (n = 1) results and the corresponding pushing and grinding nozzle pressures of micronized lactose monohydrate: (A) D50 of micronized lactose; (B) D90 of micronized lactose.

The models for D50 and D90 are shown in Equations 1 and 2, respectively,

$$D50 = 6.38 + 0.130 * PN - 0.130 * GN - 0.00146 * PN^2 + 0.00120 * PN * GN \quad (1)$$

$$D90 = 10.5 + 0.590 * PN - 0.370 * GN - 0.00540 * PN^2 + 0.00334 * PN * GN \quad (2)$$

where PN and GN are pushing nozzle pressure and grinding nozzle pressure, respectively.

Figure 4 displays contours of the D50 and D90 of micronized sucrose based on the above equations. These contours helped visualize the optimal conditions within the design space. For both responses, at low pushing nozzle pressure (65 psi), particle size was smallest at high grinding nozzle pressure (110 psi). In addition, at high pushing nozzle pressure (110 psi), small particle sizes were observed across all levels of the grinding nozzle pressures within the design space. Although setting both the pushing and grinding nozzles at high pressures produced small particles, it should be noted that more nitrogen would be needed to operate both nozzles at higher pressures. The contours also showed that mid levels of the pushing nozzle pressure resulted in higher particle sizes. The trend indicated that the contour plots may allow one to estimate the milling conditions to operate in order to obtain desired particle size after micronization.

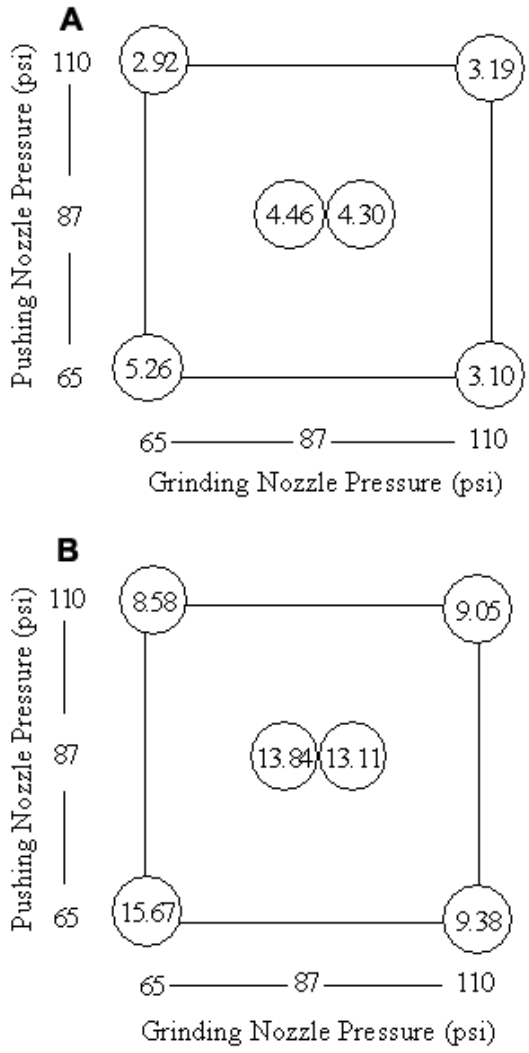

Figure 3. Particle size analysis (n = 1) results and the corresponding pushing and grinding nozzle pressures of micronized sucrose: (A) D50 of micronized sucrose; (B) D90 of micronized sucrose.

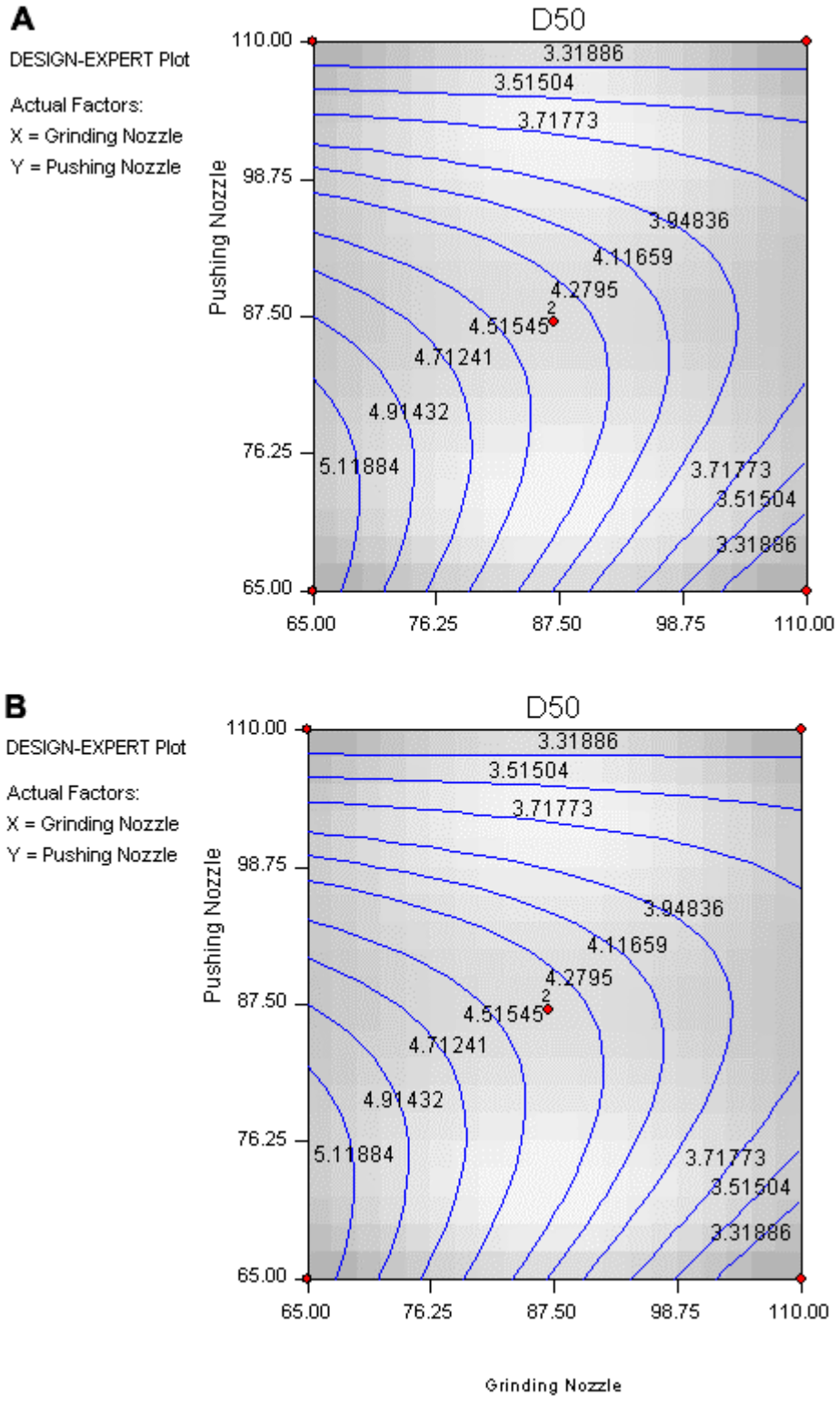

Figure 4. Contour plot of D50 (A) and D90 (B) of micronized sucrose at different pushing and grinding pressures.

CONCLUSION

The results of the experiments have revealed that the optimal operating conditions for a lab scale Aljet mill are at the high level (110 psi) of the pushing nozzle and the low level (65 psi) of both grinding nozzles, or vice versa. Operating the Aljet mill at high pushing and grinding pressures also produces small particle size; however, the high pressures require more gaseous fluid making the process less efficient. At a very low pushing nozzle pressure as compared with the grinding nozzle pressure, the material kicks back from the mill, reducing the yield. Optimization of the lab scale Aljet mill operating conditions will be very useful in particle size reduction of poorly water-soluble compounds and is particularly beneficial at early stages of drug development when the drug quantity is very limited.

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