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Pharma & Biotech

Engineering Approaches To Respiratory Drug Delivery: Mannitol Case Study

INTRODUCTION

Spray drying and jet milling are commercially viable engineering processes for the development of respirable drug products. This article presents a case study that explores the material and performance properties of spray-dried and jet-milled mannitol for respiratory delivery of crystalline mannitol. The head-to-head comparison reveals opportunities and risks for designing a product based on each approach. It also explores the pros and cons of spray drying versus jet milling, describes how to use risk assessments to inform engineering technology selection, and illustrates how particle morphology affects aerodynamic performance.

TARGET PRODUCT PROFILE AND FEASIBILITY ASSESSMENT

As an inhaled product, mannitol is used to treat the symptoms of cystic fibrosis, a disease that can cause dehydration of the airways, mucus build-up, obstructed airflow, and infections in the lungs. Mannitol promotes water uptake in airway surfaces, rehydrating it. This improves mucociliary clearance and breathing in patients while reducing infections.

The factors defining product design include the mechanism of action, solubility, permeability, dissolution rate, dose, technology, and deposition location. The exact mechanism of action for mannitol is unknown. Its most likely method of transfer is paracellular. As a BCS Class III compound, mannitol has high aqueous solubility and low permeability. In this case study, the selected dose and technology were a size 3 capsule with a 20-mg fill weight used with a Plastiape size 3, low-resistance dry-powder inhaler.

In the literature, therapeutic effect has been shown at doses above 50 mg, so multiple doses would likely be required at the 20-mg fill weight. As described below, this was explored during a study to assess the impact of capsule fill weight on fine particle dose. While the particle sizes selected for the study have a high probability of reaching the deep lung, the primary target for deposition is the central airways, where the main mechanism of clearance is mucociliary.

For early feasibility screening, the target product profile can be simplified. Whether crystalline or amorphous, the active pharmaceutical ingredient should be stable and soluble. Given that the therapeutic effect is likely at doses above 50 mg, the active loading and dose should be high to minimize the number of capsules per dose. For respiratory delivery, the aerodynamic particle size should be between 2 and 5 µm.

To first assess the feasibility of various engineering approaches, the group used flash differential scanning calorimetry (DSC), a relatively new tool that allows researchers to do a material-sparing analysis of some critical material properties. It also helps determine what material forms are possible. To accomplish this, the degradation onset temperature is first determined in a separate experiment. Next, the material is heated at 1,000 Kelvin per second (K/s) and then cooled at different rates (10, 100, or 1,000 K/s).

The flash DSC plot in Figure 1 shows the exotherm facing down and clear differences between the cooling rates, particularly between 10 K/s and each of the other curves. At 10 K/s, around 38°C, there is no glass-transition temperature (T_g), whereas a T_g is observed when cooling at 100 K/s and 1000 K/s. Since this T_g occurs at approximately 38°C and spray drying would have an outlet temperature above this regardless of the effect of the

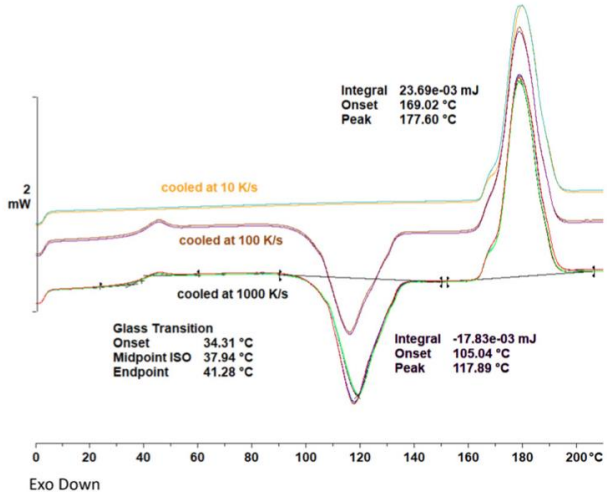

Figure 1
Flash DSC Plot for Mannitol

cooling rate in the spray dryer, the likely result is crystalline material. In addition, amorphous material recrystallizes on heating. The presence of a shoulder on the melt peak indicates that multiple polymorphs may be forming with similar thermal characteristics.

ENGINEERING APPROACH

From the feasibility assessment, an engineering trial comparing spray drying and jet milling was performed using mannitol. For spray drying, a 100% mannitol dry formulation was loaded to 5% by weight in a water solution. Three different atomization pressures (high, medium, and low) were compared to achieve a range of particle sizes. Batch sizes were 15 g, although batches as small as 0.5 g are possible if material is limited.

As shown in Figure 2, the volume-weighted mean particle size ranged from 2.1 µm to 3.5 µm, and the 90th percentile size range was 4.3 to 6.6 µm.

For jet milling, 100% mannitol was milled at three feed/grind pressures (high, medium, and low) with a 15-g batch size. These batches required feeding the material through the jet mill multiple times, which resulted in relatively low yields of 44% to 57%. With a dedicated process design effort, process yield could likely be improved.

These materials ranged in mean volume-weighted particle size from 1.8 µm to 2.7 µm, with the largest particle size exhibiting a 90th percentile size of 6.4 µm. Whether spray drying from solution or jet milling from larger crystals, a significant fraction of particles in the respirable range was achievable. Although both processes generated three batches with particle sizes in the target range, the rest of this study focused on the material made with the medium processing conditions for both the spray-dried and the jet-milled material in a head-to-head comparison.

POWDER CHARACTERIZATION

Although similar particle sizes could be generated, each approach generated significantly different particle morphology. Spray drying generated quasi-perfect spheres in the target respirable size range of less than 5 µm. Jet milling produced angular, slightly elongated particles with less symmetry, but also within the respirable size range of less than 5 µm, as shown in Figure 3.

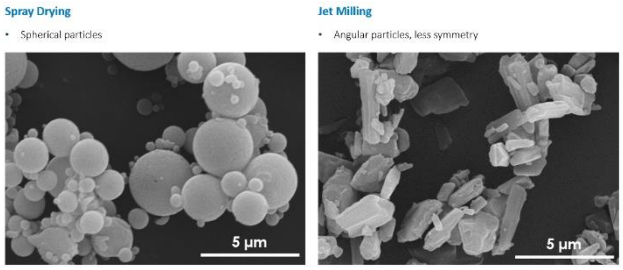

Figure 3
SEM Images Showing Differences in Spray-Dried and Jet-Milled Mannitol

Spray Drying

Formulation	100% Mannitol (dry); Solution: 5wt% in Water		
Atomization Pressure	High	Medium	Low
Batch Size	15.0 g	15.0 g	15.0 g
Yield	13.05 g (87%)	14.44 g (96%)	11.32 g (75%)
D(v 0.1) µm	0.8	0.8	1.2
D(v 0.5) µm	2.1	2.4	3.5
D(v 0.9) µm	4.3	4.8	6.6

Jet Milling

Formulation	100% Mannitol		
Feed/Grind Pressure	High	Medium	Low
Batch Size	15.03 g	15.33 g	15.22 g
Yield	8.59 g (57%)	8.03 g (52%)	6.75 g (44%)
D(v 0.1) µm	0.8	1.0	1.1
D(v 0.5) µm	1.8	2.2	2.7
D(v 0.9) µm	3.7	4.8	6.4

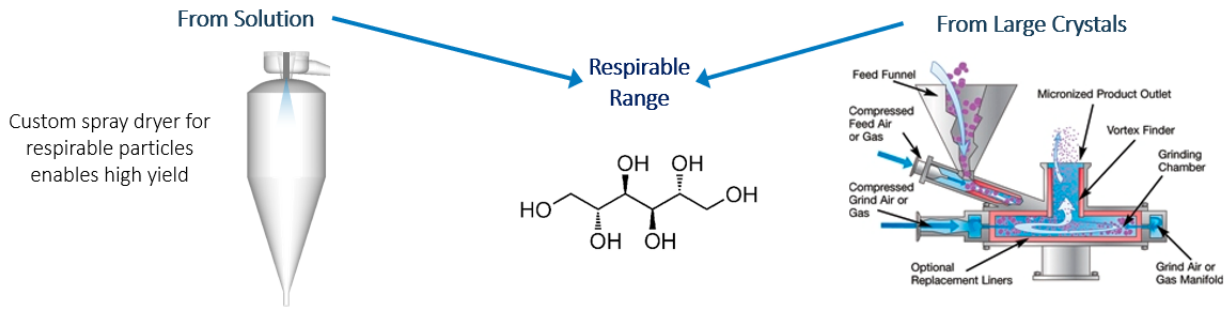

Figure 2
Comparison of Processing Parameters and Particle Size Distribution for Spray-Dried and Jet-Milled Mannitol

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To optimize material for respiratory delivery, it is important to consider the difference between geometric and aerodynamic particle size and how easily each particle changes direction. Although the masses may be the same, the aerodynamic size affects how the particles navigate through the airways. The number one factor driving aerosol performance is geometric size, which has a linear relationship to aerodynamic size. Density and particle shape also impact aerodynamic size to a lesser extent.

Geometric particle size distributions for spray-dried and jet-milled mannitol were similar and considered suitable for inhalation within the 2- to 5-µm range. Time-of-flight aerodynamic particle size distributions appeared to have a higher number of large particles above 5 µm compared to the spray-dried material. This is likely due to differences in density, with large jet-milled particles having higher density than equivalent size spray-dried particles. This may have resulted in longer flight times for large jet-milled particles. For particle sizes below 5 µm, differences in shape factor may have led to shorter flight times and lower aerodynamic diameter for small jet-milled particles compared to equivalent density spray-dried particles.

The jet-milled material had a higher melt temperature and heat of fusion, which indicates that the jet-milled material has higher order crystallinity than the spray-dried material. In addition to slight differences in the thermal performance of these materials, there are also slight differences exhibited in the spray-dried and the jet-milled mannitol mix of beta and alpha phases. These beta and alpha phases are shown in the plots in Figure 5 by characteristic lines on the plot with the beta phase in red and alpha phase in yellow. The spray-dried material exhibits more alpha mannitol content than jet-milled material. The difference in the relative amounts may affect particle performance or stability over time.

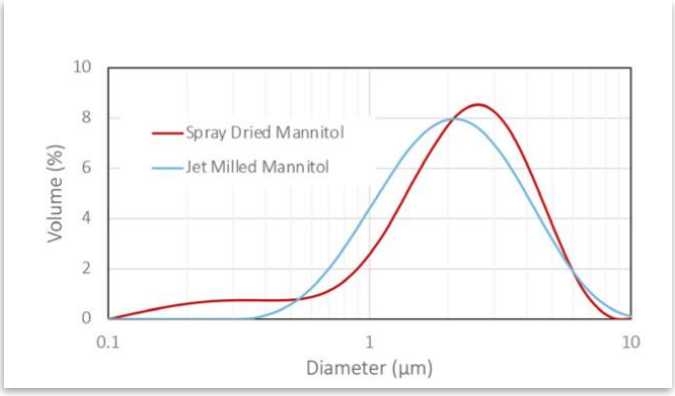

Figure 4
Particle Size Distribution of Spray-Dried and Jet-Milled Mannitol

The water content for the spray-dried mannitol was higher than that of the jet-milled mannitol, and the dynamic vapor sorption data indicated spray-dried mannitol absorbs nearly twice as much water as the jet-milled mannitol. This may be due to the spray-dried material having a higher available surface area. No form changes were observed, which is consistent with the thermal data. Overall, both materials should be considered dry and unlikely to absorb water during storage or handling.

For aerosol performance testing, a Copley fast-screening impactor (FSI) was used. The FSI is a visual combination of the next-generation impactor (NGI) preseparator and external filter. The coarse particle fraction, greater than 5 µm aerodynamic diameter, is captured in the pre-separator and induction port attachments, while the fine particle fraction (less than 5 µm aerodynamic diameter) is captured on the filter insert. The FSI is ideal for fast formulation screening compared to the NGI, which has eight stages to assay whereas the FSI has one. This dramatically reduces the sample preparation time and high-performance liquid chromatography (HPLC) runtime compared to the NGI.

For fine particle dose measurements using the FSI, the filter was weighed before and after actuation for gravimetric analysis. The fine particle dose was defined as particles less than 5 µm, and a Plastiape low-resistance dry powder inhaler was used at 100 L/min. The target fill weight for both materials was 20 mg. Both materials had fine particle doses above 10 mg, or more than 50% of their fill weight. Aerosol performance details for both spray-dried and jet-milled material are summarized in Table 1. Overall, both manufacturing processes produced materials that had acceptable aerosol performance.

For this target product profile of a high dose, it is important to consider how fine particle dose changes with capsule fill weight. If fine particle dose increases with capsule fill weight, then the number of capsules required can be minimized.

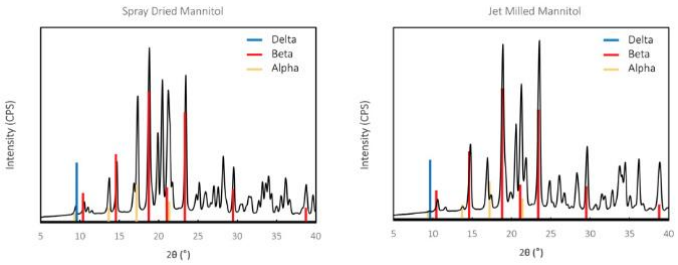

Figure 5
Crystallinity of Spray-Dried and Jet-Milled Mannitol

Table 1
Aerosol Performance Test Results

Material	Average Fill Weight (mg)	Fine Particle Dose (mg)	Fine Particle Dose/Fill Weight (mg)	Capsule Retention (mg)
Spray-dried mannitol	20.3 ± 0.7	11.0 ± 0.2	54.5 ± 1.6	0.3 ± 0.1
Jet-milled mannitol	20.0 ± 0.5	11.5 ± 0.1	57.6 ± 1.0	1.4 ± 0.2

An experiment looking at fill weights of 20, 30, 40, 60, and even 70 mg in a size 3 capsule indicated that fine particle dose increases linearly with capsule fill weight. Similar results were found with size 2 capsules and a size 2 inhaler with fill weights of almost 100 g.

It was also observed that with increasing capsule fill weight, multiple actuations were sometimes required to achieve the final result, as not all of the powder was emptied. This means that while higher fill weights are possible, higher fill weight may not reduce the number of inhalations needed to achieve a target dose. Reducing capsule handling by decreasing the number of capsules needed likely improves patient compliance, but requiring multiple inhalations from the same capsule may present an added compliance challenge.

RESULT SCORECARD: MANNITOL CASE STUDY

The overall results per the target product profile are summarized in Table 2. Both spray drying and jet milling produced desirable results in the keys areas of aerosol performance and physical stability. Jet milling exhibited a significant advantage in terms of powder process throughput, and any differences in encapsulation process efficiency remain unknown. Feasibility was demonstrated in both cases without excipients and it may be possible to improve the efficiency and/or stability of the product by introducing excipients.

At the feasibility scale, both methods successfully produce respirable powder. However, the relative difference in throughput between the processes suggests that spray drying may never be as efficient as jet milling, since spray drying requires dissolving the material in solution, whereas in jet milling, the powder can be milled directly. Encapsulation process throughput was not addressed and would require further study to assess process efficiency. Also, there was a visual difference between 60 mg of spray-dried material and 60 mg of jet-milled material filled in size three capsules. The spray-dried material took up less space, indicating there may be differences in how each material encapsulates.

Table 2
Scorecard for Spray-Dried and Jet-Milled Mannitol

Preliminary Assessment	Spray-Dried Mannitol	Jet-Milled Mannitol	Comments
Physical stability: temperature	Good	Good	Crystalline material in both cases
Physical stability: moisture	Good	Good	No change up to 90% RH
Aerosol performance (fine particle dose)	11.0 mg	11.5 mg	Similar at equal fill
Excipients	Unknown	Unknown	Feasibility demonstrated without excipients
Powder process throughput	0.3 to 0.5 g/min	1 to 4 g/min	Feasibility scale
Encapsulation process throughput	Unknown	Unknown	Process to be studied

PROPOSED STUDIES TO MITIGATE RISK

Additional studies for product development to mitigate potential risk are summarized in Table 3. There are questions remaining as to the impact of humidity on aerosol performance, the long-term stability of the formulation, whether or not the encapsulation process is equal for both materials, if there are fill weight limitations for the encapsulation process, and how significantly clinical data will

Table 3
Proposed Risk Mitigation Studies

Risk	Observation	Further Work To Manage Risk
Decreased aerosol performance at high humidity	Water uptake is higher for spray-dried mannitol, but total magnitude is lower	High-humidity aerosol performance test
Long-term stability	Both crystalline materials with low water uptake should have physiochemical stability	Stability study
Encapsulation may not be equal for both materials based on powder flow	Spray-dried and jet-milled materials pack differently in capsules	Powder rheometry studies
Machine encapsulation may provide different results or fill-weight limitations	Capsules were hand-filled for performance testing	Encapsulation feasibility screening
Clinical data may differ significantly from impactor results for aerosol testing	Standard impactor testing is different than patient inhalation of aerosol	Test using breath simulator with anatomically correct impactor equipment

differ from the impactor results for aerosol testing. A number of observations from this study provide preliminary indications, and further evaluations can be done to address these questions and progress the development of the product.

CONCLUSIONS

The intended target product performance was achieved and the aerodynamic size for both jet-milled and spray-dried material proved to be viable for the respiratory delivery of mannitol. A high dose of 100% active formulations was achievable with both powders. Fine particle dose linearly increased with capsule fill weight, suggesting that efficiency could be improved by filling the capsules to a higher weight.

Additionally, more than 50% of the capsule fill weight was delivered as fine particle dose, demonstrating the suitability of the powder for respiratory delivery. It should be noted that the study was conducted without excipients and it may be possible to increase efficiency and/or stability by exploring the addition of excipients to either the jet-milled or spray-dried formulation.

At this point, either engineering approach could be progressed to the next development stage. If speed to market is the primary motivating factor, then material from both engineering approaches could be subjected to a stability study to ensure selection of the best material. However, if cost is the primary motivating factor, jet milling offers a throughput advantage, which would minimize manufacturing costs. While the specific properties of an individual drug and its target product profile may influence whether spray drying or jet milling has a greater chance of success, it is not always obvious which process will yield the best drug product. In this case and in others, exploring both options allows product developers to understand the risks and trade-offs associated with each path to commercial success.

ABOUT LONZA

Particle engineering—critical to achieving the particle size distribution required for effective respiratory drug delivery—is a core strength at Lonza. The company's decades of experience, formulation and engineering expertise, and wide range of manufacturing capabilities make Lonza the preferred partner for inhalation applications. The company's development and clinical inhalation powder manufacturing capabilities—located at its Bend, Oregon, USA, site—support all phases of inhalation product development. Small-scale spray drying, wet milling and jet milling are all in place for early feasibility work. State-of-the-art clean rooms for spray drying and capsule filling are also in place, as is a high-containment suite for the safe handling of higher-potency small and biologic compounds. Clinical- and commercial-scale jet-milling capabilities are in place at Lonza's sites in Quakertown, Pennsylvania, USA, and Monteggio, Switzerland. To learn more, please visit our website.