Lonza
Pharma & Biotech

Particle Engineering For Inhalation Drug Delivery

INTRODUCTION

The development of therapies for pulmonary disease continues to be an expanding market in pharmaceutical research. Pulmonary illness rates are increasing and respiratory disease continues to be a leading cause of death and disability worldwide. The breadth of small-molecule and biological compounds requiring lung delivery is expanding, raising demand for inhalation therapies that are efficacious, robust, affordable, and compatible for use with dry-powder inhalers.

A key aspect to successful development of therapies to meet market demand is the manufacture of formulations with the product-quality attributes suitable for inhalation delivery. A wide range of particle engineering approaches is available but selection of which technology would be best for a given active pharmaceutical ingredient (API) can be challenging, requiring:

1. establishing the target product profile and intended delivery device (e.g., dry-powder inhalers);
2. evaluating API properties and conducting focused feasibility experiments; and
3. evaluating the risks associated with each candidate particle engineering approach.

By understanding the ways particle engineering approaches influence the attributes of the product, developers can be in the best position to accelerate clinical testing, commercial development, and patient treatment.

This summary presents an overview of particle engineering technologies and a case study in which two engineering approaches are compared: spray drying (a "bottom-up" technology) and jet milling (a "top-down" technology). These two proven, scalable approaches are relatively simple and are often a good starting point to determine if a more complex technology is required for success.

PARTICLE ENGINEERING: MANY CHOICES

Technological advancements in particle engineering make it possible to produce drug particles down to micron or nanoscale dimensions using many types of technologies. Generally, technologies can be divided into the following classifications: (1) bottom-up, which involves a form change from solution to solid; (2) top down, which involves milling a material to the desired size; and (3) combination approaches, which involve use of multiple technologies to address complex situations.

Bottom-Up Technologies

Bottom-up technologies involve dissolving the API in bulk solution, forming droplets, and then drying the droplets to form particles. These technologies include spray drying, spray freeze drying, thin film freezing, and supercritical fluid technologies. Many bottom-up technologies have precedence of use in the pharmaceutical industry and are backed by extensive understanding of process variables. Spray drying is one of the most commonly used bottom-up technologies because of its applicability to a wide range of APIs and excipients; the flexibility it offers in engineering the desired particle shape, size, and physical state (amorphous or crystalline); reliability; and scalability.

Top-Down Approaches

Top-down technologies involve milling to reduce the particle size of crystalline API in a single- or multi-step process. The starting material (i.e., API) can be a produced using many different manufacturing processes including crystallization, bulk drying, or lyophilization, typically at a particle size too big to be respirable. Most top-down approaches are continuous, scalable processes that can be used to micronize many types of APIs. Milling approaches are divided between dry and wet milling. The most common types of dry milling are jet milling, in which a gas stream is used to carry particles out of the milling chamber once the critical particle size is reached, and ball milling. In wet milling, stabilizers can be added to mitigate the higher surface energy of the particles and prevent problems with flow properties and content uniformity. Wet milling requires an additional process step to create a dry powder suitable for inhalation drug delivery.

Combination Approaches

Combinations of technologies can be used in complex situations, such as when an API tends to agglomerate or has low solubility in solvents typically used for spray drying. One example would be to use milling to reduce particle size, followed by spray drying to coat the API core with a thin layer of excipient to alter the surface chemistry of the formulation. Combination approaches create almost limitless engineering possibilities, but their advantages can be offset by the

complexity and cost they add to the manufacturing process train.

SORTING THROUGH THE CHOICES

While all the technologies described above can produce powder with ideal inhalation delivery characteristics, understanding the advantages and limitations of the various choices could save valuable development time and money. For instance, if milling and spray drying produce similar particle characteristics, milling could be the clear choice for a simpler, high-throughput development path.

In selecting a technology, developers must develop a thorough understanding of the physical and chemical characteristics of the API, including any limitations such as temperature sensitivity or agglomeration tendencies, since these may rule out certain approaches. For instance, jet milling works well when an API can be reproducibly crystallized with a relatively high melt temperature. However, if the starting crystallinity or crystallite size of the API varies, then the resulting particle size of the milled API may be more dependent on the attributes of the starting material than on milling process parameters, presenting scale-up and/or lot-to-lot variability challenges. Likewise, if the melt temperature of the API is too low, the likelihood increases of producing amorphous material during milling. While this alone would not preclude commercial development, it could raise questions about whether the recrystallization would occur during stability testing and storage, whether particle fusing could be a problem, and whether the API was more susceptible to degradation.

If, after comparing candidate technologies, no clear choice emerges, multiple technology choices can be considered concurrently early in development, aided by focused feasibility testing to further examine the choices. Concurrent evaluation is preferable to investigating technologies sequentially, since it speeds up the development process.

CASE STUDY COMPARISON

As a test case to compare bottom-up and top-down approaches for inhalation drug delivery, crystalline mannitol was engineered using spray drying and jet milling to produce particles of a respirable size. Mannitol has been used in an indirect osmotic bronchial challenge test and to increase mucociliary and cough clearance of secretions retained in the lung. For the bottom-up approach, mannitol was dissolved in water and spray dried using process parameters selected to produce the desired particle size distribution for inhalation drug delivery. For the top-down approach, the same starting material was jet milled—again, with parameters specifically chosen to yield the right particle size distribution for inhalation drug delivery.

Figure 1 shows the volume-weighted sized distribution of the particles and Table 1 shows the particle size distribution. As these results show, the jet-milled particle size was mostly smaller and had a wider size distribution than the spray-dried material. However, the particle morphologies were drastically different, as shown in the scanning electron micrography (SEM) images in Figure 2. The spray-dried particles were spherical, whereas the jet-milled particles had clearly defined edges and roughly rectangular cross sections. These differences may result in differences in aerodynamic size, even if the density of the particles is the same.

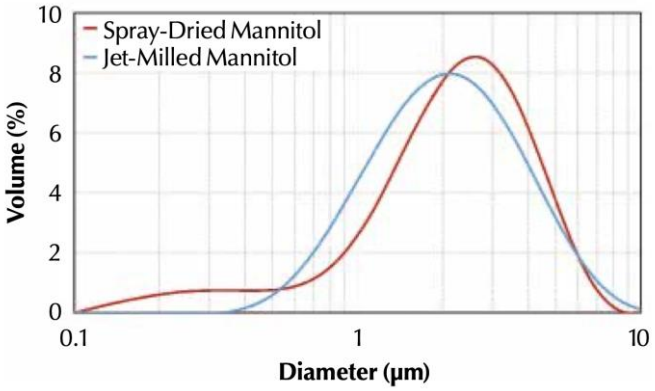

Figure 1
Geometric Particle Size Distribution of Spray-Dried and Jet-Milled Mannitol, Measured By Laser Diffraction

Table 1.
Particle Size Distribution of Spray-Dried and Jet-Milled Mannitol, Measured By Laser Diffraction [D(v 0.1) = 10th volume percentile size, D (v 0.5 = 50th volume percentile size, etc.]

Material	D (v 0.1) (µm)	D (v 0.5) (µm)	D (v 0.9) (µm)	Span
Spray-dried mannitol	0.8	2.4	4.8	1.6
Jet-milled mannitol	1.0	2.2	4.8	1.7

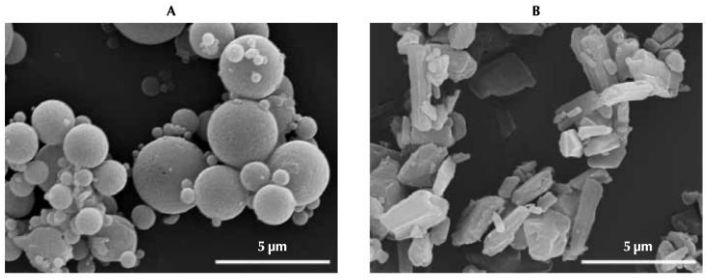

Figure 2
SEM Images of Spray-Dried (A) and Jet-Milled Mannitol

To gauge how these powders would perform in inhalation drug delivery, a TSI aerodynamic particle sizer (St. Paul, Minnesota,

USA) was used with time-of-flight analysis to determine the aerodynamic particle size distribution of the powders. Table 2 summarizes the data, showing that the mass median aerodynamic diameter (MMAD) of the two materials was similar. However, the broader distribution of the large particles in the jet-milled mannitol results in a smaller fraction being effective for inhalation delivery (defined as particles with an aerodynamic diameter of less than 5 µm).

Table 2
Aerodynamic Size Summary, as Measured by Time of Flight

Material	MMAD (µm)	Mean Diameter (µm)	Cumulative Mass <5 µm Diameter (%)	Geometric Standard Deviation (µm)
Spray-dried mannitol	3.2	3.8	84	1.7
Jet-milled mannitol	3.4	4.9	66	2.1

In this case, both spray drying and jet milling appear to be viable technology choices, despite the difference in particle morphology. Comparison of the crystallinity between the two types of particles may help elucidate whether either material contains significant amorphous material or whether the crystal structure may be susceptible to change with heat and humidity over time.

SUMMARY

Selecting the best technology for a inhalation drug delivery product requires careful consideration of API characteristics and target product profile. Generally, simple, scalable, well-characterized technologies are preferable, making spray drying and jet milling excellent first choices for many APIs. By evaluating these approaches initially, developers can determine if a more complicated technology is required and which path is best suited to the API and product in question. If multiple technologies are suitable, developers can optimize for speed to clinic and patient, taking into consideration process throughput, yield, and equipment availability.

ABOUT LONZA

Particle engineering—critical to achieving the particle size distribution required for effective inhalation 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 drug-delivery 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. Lonza has clinical- and commercial-scale jet-milling and spray-drying capabilities in place at sites worldwide. To learn more, please visit our website.