Particle Engineering for Respiratory Drug Delivery
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INTRODUCTION

Pulmonary illness rates are increasing and respiratory diseases—including chronic obstructive pulmonary disease (COPD), asthma, and pulmonary infections—continue to be a leading cause of death and disability worldwide. The increasing prevalence of these diseases, as well as the onset of COVID-19, have increased the need for respiratory drug products that are affordable, safe, and efficacious.

Development of these drug products can be challenging, since they require combined development of the formulation, carrier, and device into a single drug product. Dry-powder inhalers are increasingly used for pulmonary delivery, and come in a variety of types including devices based on reservoirs, blister packs, and capsules. Regardless of inhaler type and drug form (solid crystalline, solid amorphous), the characteristics of the active pharmaceutical ingredient (API) are a key factor in success. In developing a respiratory drug product, a key question becomes which particle engineering technique offers the best chance of producing an API with the quality attributes needed to achieve the target product profile.

Based on its extensive experience with particle engineering, Lonza has developed an efficient methodology to compare competing technologies so the technology with the greatest likelihood of success can be selected, knowing that speed to clinic and patient are crucial. Here, we provide an overview of particle engineering technologies, describe Lonza's methodology for technology selection, and summarize a case study in which two particle engineering technologies are compared for suitability for respiratory drug products.

PARTICLE ENGINEERING

Technological advancements in particle engineering make it possible to produce drug particles down to micron or nanoscale dimensions using many types of technologies.

In ***bottom-up technologies***, API is dissolved in bulk solution, formed into droplets, and then dried to form particles. These technologies—which include spray drying, spray freeze drying, thin film freezing, and supercritical fluid technologies—have numerous advantages: precedence of use in the pharmaceutical industry, suitability for a wide range of APIs, extensive engineering understanding of process variables, and ease of scale-up. Most of all, they offer a high degree of control over the characteristics of the finished product, including particle shape, particle size, and the physical state of the API (crystalline or amorphous).

Top-down approaches involve milling to reduce the particle size of material in a single- or multi-step process. 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 a critical size is reached, and ball milling. In wet milling, stabilizers can be added to mitigate the higher surface energy of the particles and prevent poor flow properties and content uniformity problems. Wet milling does require an additional process step to create a dry powder suitable for respiratory drug delivery.

Combination approaches 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. Combination approaches—such as milling followed by spray drying—create almost limitless engineering possibilities. These approaches overcome the limitations of a single technology, but the additional advantages can be offset by the complexity and cost they add to the manufacturing process train.

MAKING THE RIGHT CALL

While all of the approaches described here can produce powders with the right characteristics for respiratory drug delivery, choosing the ideal technology or technologies

Figure 1
Selection methodology for inhalation formulations

can be difficult. Lonza has developed a proven methodology to make this important decision, saving time and money. This methodology, outlined in Figure 1, is grounded in decades of processing experience and an in-depth understanding the advantages and limitations of the different approaches.

Lonza's approach begins with developing an in-depth understanding of the target product profile, including the product design and delivery profile (such as critical parameters, desired dose, location of drug deposition, and mechanism of action). Technology feasibility is then assessed using a variety of tools, allowing rapid, material-sparing analysis of critical properties. For instance, flash differential scanning calorimetry can be used to determine API thermal characteristics that may preclude use of certain technologies. Formulations are prepared and tested to determine their characteristics such as particle morphology, size distribution, crystallinity, and water content. Finally their performance is assessed in the desired delivery device. In this phase, we look at metrics such as the impact of capsule fill weight on fine particle dose. Using a standardized scorecard, we determine the overall feasibility and determine whether further development is needed to meet the target product profile or to mitigate risk.

At times, concurrent approaches are investigated at the feasibility stage to accelerate product timelines. If more than one approach is being evaluated, preference is given to the simpler of the two technologies if they will produce powders with similar characteristics.

CASE STUDY: MANNITOL

A case study using a model compound, mannitol, illustrates use of this methodology to compare the bottom-up and top-down particle-engineering approaches for respiratory drug delivery. Crystalline mannitol, which has been used to increase clearance of retained secretions in the lung, was engineered to produce inhalable particles using two techniques: spray drying and jet milling. The particles were characterized using numerous tests and analytical techniques: morphology (scanning electron micrography), particle size (time-of-flight aerodynamic particle sizing), thermal characteristics (differential scanning calorimetry), water uptake (dynamic vapor sorption and Karl Fischer titration), particle size distribution (powder x-ray diffraction), and capsule fill weight (fast screening impactor).

Both approaches produced powders with particles largely in the desired 1- to 5-µm range, with the jet-milled particles being slightly smaller but having a wider size distribution than the spray-dried material. While particle size distributions were similar, the particle shape was drastically different: spray drying produced spherical particles, whereas jet milling produced angular particles with less symmetry, as shown in Figure 2. These differences can result in differences in aerodynamic size, even if the particle density is the same.

To understand how these engineered particles would perform, time-of-flight aerodynamic particle size distribution was measured using a TSI aerodynamic particle sizer. The results, shown in Figure 3, reveal two things: (1) the aerodynamic size distribution of the powders proved narrower for spray-dried material, and (2) the broader distribution of large particles in the jet-milled materials resulted in less of the powder being suitable for inhalation. Taken with the other characterization results (summarized in the scorecard results in Table 1) and considering the target product profile, spray drying and jet milling are both feasible particle engineering approaches and deserve to advance for further investigation. In this case study, evaluating two approaches—spray drying and jet milling—from the outset makes it possible for developers to determine whether a more complicated approach is needed or whether

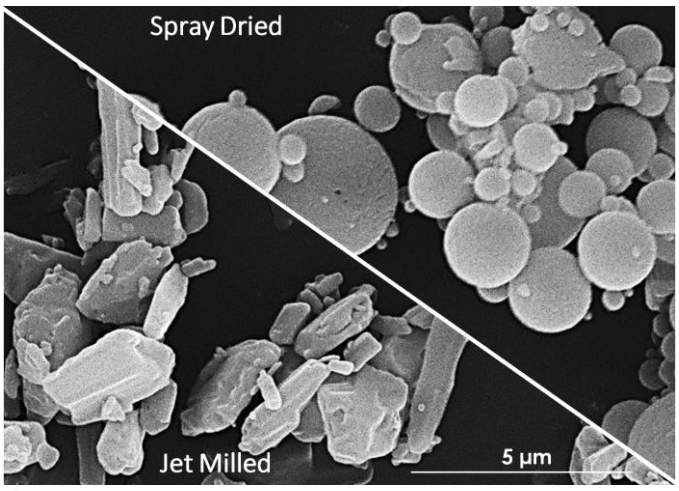

Figure 2
Particle morphology comparison for spray dried and jet milled mannitol

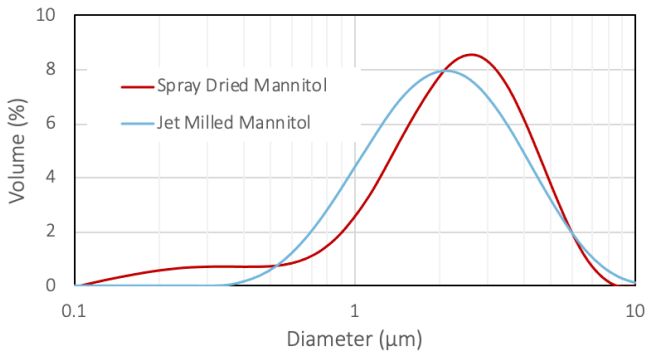

Figure 3
Comparison of time-of-flight aerodynamic particle size distribution for spray dried and jet milled mannitol

Table 1

Scorecard results for spray-dried and jet milled mannitol

Preliminary Assessment	Spray Dried	Jet Milled	Comments
Physical stability: temperature	Good	Good	Crystalline material in both cases
Physical stability: moisture	Good	Good	No change up to 90% RH
Aerosol performance	11.0 mg	11.5 mg	Similar fine particle dose 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	Filling process to be studied

one technology is better suited for the API and product requirements. If the technologies both continue to appear viable after further investigation, developers can make a selection based on development timing (speed to clinic and patient), process throughput and yield, and equipment availability.

Summary

To develop an effective dry-powder inhaler product, it is critical to have access to particle engineering technologies and expertise so morphology and particle size distribution can be optimized. Lonza has more than 25 years of experience in jet milling, spray drying and developing inhaled formulations across an array of drug substance and particle engineering challenges. We also provide integrated product development, analytical method development, and manufacturing services inclusive of phase-appropriate encapsulation. To learn more, please visit our website.