Particle engineering approaches for dry powder inhalers

Considerations of API properties and target product profile to determine an appropriate particle engineering technology for inhaled drug products

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Pulmonary illness rates are increasing and respiratory diseases continue to be a leading cause of death and disability worldwide.[1] Although often treatable, diseases such as chronic obstructive pulmonary disease (COPD), asthma and pulmonary infections continue to increase in number. Medications to treat respiratory disease are increasingly accessible but the clinical need for options that are affordable, robust and efficacious remains.

Inhalation drug products are a unique field of pharmaceutics in that they combine the physical attributes of the active pharmaceutical product ingredient (API), carrier and device into a single drug product. As the pharmaceutical industry continues to expand the breadth of small molecule and biologics compounds requiring lung delivery, it is expected there will continue to be an outstanding need to develop technologies capable of delivering these compounds through inhalation. At the same time, there is a growing patient need for innovative inhaled drug products and therapies.

Whether solid, liquid, crystalline or amorphous, there are many possible particle engineering technologies available to manufacture formulations with the appropriate product quality attributes for pulmonary delivery, and each has advantages and limitations. Particle engineering approaches can be divided among "bottom-up" (e.g., form change from solution to solid), "top-down" (e.g., milling), or a combination of both (e.g., milled then coated with a second component from solution) and each has its own characteristics and benefits for drug product delivery. Some particle engineering approaches may change the crystallinity of the active compound and potentially change the solubility.

It is not always obvious which particle engineering approach is best suited to a particular API. Choosing the right particle engineering technology requires first: establishing the requirements of the formulation and delivery device of the end product, second: evaluating material properties and conducting feasibility experiments, and third: evaluating risks associated with the most suitable engineering approaches. By understanding the ways different particle engineering approaches influence the end product, developers can be in the best position to accelerate clinical testing, commercialization and patient treatment. Ultimately, selecting a particle engineering technology may depend on the target product profile (TPP) such as API stability, delivered dose and device type.

Furthermore, there have been discussions about the TPP for inhaled drug products, which includes views of a consortium sponsored by the Product Quality Research Institute (PQRI) on the relevance of a Pulmonary Biopharmaceutical Classification System (BCS)[2] in defining a TPP. In addition to presenting a BCS classification for inhaled drug products, the fate of inhaled particles and regional deposition in central vs. peripheral airways was reviewed by the group.[3]

Bottom-up approaches: Bulk solution to droplet formation to dried particles

Bottom-up particle engineering techniques share a high-level process path that goes from bulk solution to droplet formation to dried particles. Bottom-up approaches include spray drying, spray freeze drying, thin film freezing and supercritical fluid technologies.

Spray drying is one of the more common techniques used throughout the pharmaceutical industry in terms of bottom-up approaches. Part of the popularity of spray drying is due to flexibility in solvent selection, which can be tailored to varying API and excipient solubilities. Processing parameters (nozzle selection, feed rate, temperature, etc.) also have a large operating range, which can make it seem daunting to identify optimal operating conditions. The advantages to this broad processing space include flexibility in engineering the particle shape, size and the physical state (amorphous or crystalline) depending on material properties, all of which can be extremely beneficial for pulmonary delivery. Excipients can be added to aid in stability, aerosol dispersibility or bioavailability. Spray drying can produce reliable powder from batch to batch, and scalability is relatively easy compared to other approaches, making it a front runner for commercial consideration. While there have been concerns about potential denaturing of proteins with respect to elevated temperatures and shear from a spray dryer,[4] drug developers can evaluate this concern on a case-by-case basis.

Spray freeze drying (SFD) combines spray drying and freeze drying techniques into one process. Typically, the process breaks down into atomization of liquid into droplets, solidification of droplets as they contact cold fluid (typically, liquid nitrogen) and sublimation of droplets using low temperature and pressure. The extremely fast cooling rates can reduce phase separation between the drug and excipients, yielding improved molecular distribution. This approach can be very beneficial for compounds sensitive to temperature, pH and salt concentration, and may eliminate organic solvent use as well. This technique demands low pressure and low temperature, which can involve high capital and operational costs. Compared to spray drying, spray freeze drying costs may run 30-50 times higher and most developed SFD units are not appropriate for commercial use, often making scale-up extremely challenging.[4,5]

Thin film freezing[4,6] is related to SFD, but involves droplets of solution applied to a steel drum filled with a cryogen such as liquid nitrogen. The droplets freeze on the drum as it rotates and are then scraped off by a blade. The frozen material falls into a collection container cooled by liquid nitrogen or dry ice. The collection container then gets lyophilized to remove solvent through sublimation. While this technique can be used to improve bioavailability of poorly water-soluble compounds, solvent selection can greatly affect this process. Not only does the solvent need to be spread to a thin layer, it also needs high thermal diffusivities for this process to be effective. The overall cost of operations must be considered, given the use of cryogen and optimally low humidity environmental controls to minimize water vapor condensation on the steel drum.

Supercritical fluid technologies[7] use high pressure to change physical properties of a gas (as defined at standard room temperature and pressure). Carbon dioxide is typically used since, under supercritical conditions, it mimics solvent properties of a liquid and diffusivity of a gas. This carrier is typically selected based on inertness, cost and nontoxicity. Oftentimes, the process is limited by drug solubility in carbon dioxide, which is typically low. Carbon dioxide's low critical temperature can also help protect sensitive compounds from thermal decomposition. The process can be beneficial in terms of eliminating organic solvents and harsher processing conditions, but its effectiveness tends to be limited for more hydrophilic compounds. Addition of water or ethanol can aid in dissolution of polar compounds.

Controlled solidification to achieve appropriate particle sizes is a technique based on generating an environment where the API (with or without excipients) is forced from solution into a solid by adjusting the solubility into a highly mixed zone, either by changing the solution[8] or reacting an intermediate to the final product, which is insoluble in the liquid phase.[9] Depending on the kinetics and the API properties, the particles may be amorphous. Additionally, as the API or formulation is precipitated into a suspension, another step is required to remove the liquid and yield the dry powder.

Top-down approaches: Milling to reduce particle size

Top-down engineering approaches to manufacture aerosolizable powders entail milling a crystalline material to the desired size. Prior to milling, the starting material may be produced from the API manufacturing process, including crystallization, bulk drying or lyophilization. The starting material sizes are typically larger than what is respirable. Depending on the material, an initial milling step may be required before it is further processed into respirable particles.

Milling approaches can be divided between wet milling and dry milling. In the case of wet milling, stabilizers can be added to mitigate the higher surface energy associated with smaller particles. However, wet milling requires a subsequent process step to create a dry powder suitable for inhalation, so dry milling tends to be a more direct approach for creating respirable powders.

The most common type of dry milling for the creation of respirable particles is the jet mill, which relies on a gas stream to add energy to the milling chamber and carry the particles out of the chamber once a critical size is reached. The gas flow within the jet mill causes particles to collide with each other and fracture. Large particles remain in the jet mill for further size reduction, while smaller particles are able to change direction and are carried out of the mill via a classification port.

Other milling approaches, like ball milling, rely on collisions between a hard grinding media and the product. In this case, some care must be taken to ensure no contamination of the product with the milling media as well as to separate the product from the media. Due to the jet mill's reliance on particle/particle collisions in air, the risk of contamination is lower and product losses in the machinery or on the grinding media are minimized.[10]

Jet milling is amenable to size reduction for respirable powder manufacturing but under certain circumstances it may not be the ideal approach. While the technique is most appropriate when a material can be reproducibly crystallized with a relatively high melt temperature, if the starting crystallinity or crystallite size of the API is variable, then the resulting milled particle size may be more dependent on ingoing attributes than on milling process parameters. This outcome can then present scale-up and/or lot-to-lot variability challenges. If the melt temperature is too low, the likelihood of producing amorphous material while milling increases. The formation of amorphous material may not prohibit commercial product development, but the risk of future form change can be considered by assessing whether the amorphous material will re-crystallize on stability, whether recrystallization results in particle fusing, if amorphous material is more susceptible to degradation and whether bioavailability is significantly affected due to changes in dissolution. By considering risks like these based on prior knowledge of the API or specifically designed studies, researchers can determine whether jet milling is the right engineering approach. Overall, jet milling offers the advantages of a continuous, scaleable process for micronizing many different types of material with no solubility requirements.

In top-down approaches, API aerosol formation and powder flowability can be further modified after milling by blending the micronized API with excipients such as carriers (e.g., lactose) or surface modifying agents (e.g., magnesium stearate). There are a variety of lactose carrier grades, from coarse particles to fine particles, that can be used to adjust the balance of adhesion between carrier and API particles. Blending also provides a benefit for indications with low-dose requirements (i.e., < 5 mg API). In these cases, it may be possible to improve powder handling in dose-filling operations, which, in turn, improves the consistency of dose delivery to the lungs. In cases of low interaction forces between particles, it may be possible to dose the micronized API without excipients, thereby enabling higher active content per dose while also circumventing concerns about powder blend content uniformity. Initial feasibility studies would evaluate the neat API without the use of excipients before additional formulation approaches were taken.

Combination approaches for complex situations

In certain complex situations, like an API with a tendency to agglomerate in a micronized state and low solubility in suitable solvents for spray drying, combination approaches offer almost limitless engineering possibilities. In particular, milling followed by suspension spray drying enables the creation of core-shell structures in which a crystalline API core may be coated with a thin layer of an excipient to alter the surface chemistry.[11, 12] This alteration could be performed to improve the aerosolization process or to stabilize the powder to prevent fusing. Additionally, this approach also provides a means of re-isolating the milled API from a wet media milling process.

While there are many advantages to jet milling, achieving sub-micron particle size may not be possible in a jet milling process. If sub-micron particles are required to achieve sufficient bioavailability of a low aqueous solubility API, then wet media milling may be most appropriate. During process design for wet media milling, an appropriate anti-solvent and stabilizing excipients to limit Ostwald ripening must be evaluated.[13] If a stable sub-micron suspension can be formed (such as by a flow-through wet media mill or by a batch-style resonant acoustic mixer), then spray drying offers a means to reproducibly isolate and collect the milled material from the suspension.

While a combination approach may allow additional degrees of freedom in particle engineering, it adds complexity and costs to the manufacture of these particles. Before using them, drug manufacturers will likely benefit from evaluating whether these approaches are required or provide significant benefits that a simpler approach would not be able to achieve.

Choosing the correct particle engineering approach for speed to clinic and patient

Many factors influence the development speed for a new drug product. Understanding the options and limitations of the API is a crucial first step. While all the approaches previously mentioned can produce powder with ideal pulmonary delivery characteristics, understanding the advantages and limitations of multiple approaches early on could save time and money. For instance, if milling and spray drying result in similar powder attributes, milling could be a clear choice for a simpler, high-throughput path forward. It may be beneficial to consider a concurrent approach while evaluating particle engineering techniques at the feasibility stage, as compared to a step-wise approach.

Engineering approach comparison: Bottom-up vs. top-down

As a test case to compare bottom-up and top-down approaches for respiratory drug delivery, crystalline mannitol, which has been used in an indirect osmotic bronchial challenge test and to increase mucociliary and cough clearance of the retained secretions in the lung,[14] was engineered to a particle size suitable for inhalation using one of each technique. For the bottom-up approach, mannitol was dissolved in water and spray dried with parameters specifically chosen to yield a desirable particle size distribution for respiratory drug delivery. For the top-down approach, the same starting material was jet milled, also with parameters specifically chosen to yield a desirable particle size distribution for respiratory drug delivery.

The volume-weighted size distribution of these engineered particles is plotted in Figure 1, which shows that both engineering approaches resulted in powders consisting almost entirely of particles less than 10 µm in diameter. As shown in Table 1, the median volume-weighted diameter of the spray-dried material was 2.4 µm with a span of 1.6, and the median volume-weighted diameter of the jet-milled material was 2.2 µm with a span of 1.7. These results mean that while the jet-milled material is mostly smaller, it has a wider size distribution than the spray-dried material.

While the powder size distributions are fairly similar, these engineering approaches result in drastically different particle morphologies, as shown in Figure 2. The spray-dried mannitol particles have a spherical morphology, while the jet-milled mannitol particles have clearly defined edges and a roughly rectangular cross-section. These differences in particle morphology may result in differences in aerodynamic size, even if the density of the mannitol is the same between the two engineering approaches.[15]

Figure 1

Geometric particle size distribution as measured by laser diffraction, comparing mannitol that has been engineered to a desirable size for respiratory delivery via spray drying (red) and jet milling (blue).

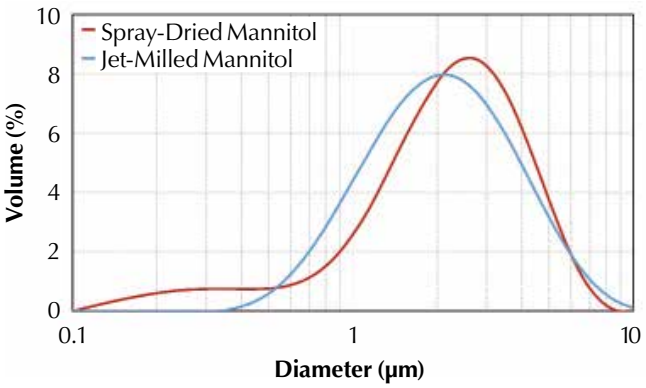


Table 1

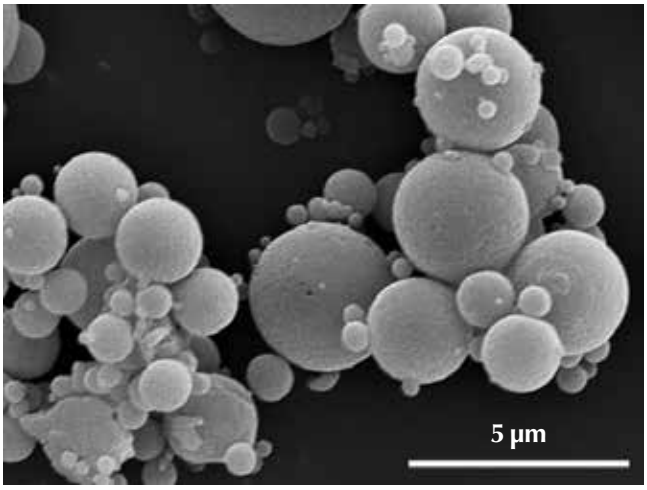
Summary particle size distribution values as measured by laser diffraction including the 10th volume percentile size (D (v 0.1)), the 50th volume percentile size (D (v 0.5)), the 90th volume percentile size (D (v 0.9)), and the span, a measure of distribution breadth defined as the difference between the 90th and 10th percentile divided by the midpoint.

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

Scanning electron microscope images for (A) spray-dried mannitol and (B) jet-milled mannitol.

A



B

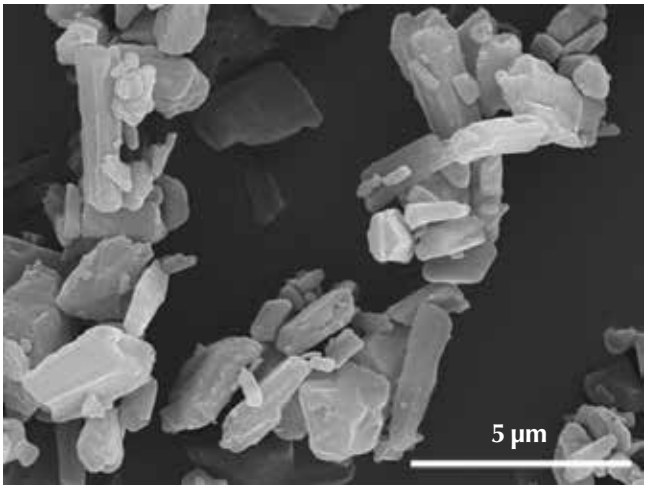
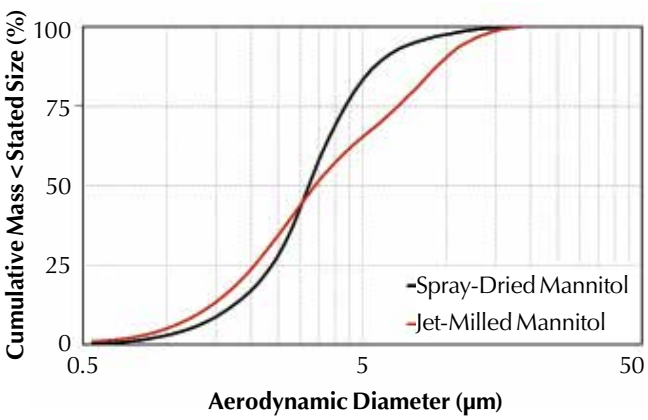


Figure 3

Cumulative mass under the specified aerodynamic particle size as measured by time-of-flight, based on an assumed density of 1.6 g/cc for crystalline mannitol.



In order to understand how effectively these engineered powders would perform in respiratory delivery, the TSI Aerodynamic Particle Sizer (St. Paul, MN, US), using a time-of-flight principle, was used to determine the aerodynamic particle size distribution of these powders. The mass-weighted cumulative distribution (assuming a density of 1.6 g/cc) is plotted in Figure 3, which shows that the aerodynamic size distribution is narrower for the spray-dried material than for the jet-milled material. Table 2 provides several aerodynamic diameter summary values for the two distributions, showing that the mass median aerodynamic diameter (MMAD) is similar between the two materials. However, the broader distribution of large particles in the jet-milled material results in a smaller fraction of the jet-milled powder that is effective for inhalation (most commonly defined as particles with an aerodynamic diameter less than 5 µm).

In this case, both jet milling and spray drying appear to be viable approaches for engineering respirable mannitol particles, although they produce differently shaped particles, which combined with any differences in density directly impact the aerodynamic size. Comparison of the crystallinity between the two particles may help to elucidate whether either material contains significant amorphous material or whether the crystal structure may be susceptible to change with heat and humidity over time.

Table 2

Aerodynamic size summary as measured by time-of-flight, including the mass median aerodynamic diameter (MMAD), mean diameter and geometric standard deviation (GSD), a measure of log-normal distribution breadth.

Material	MMAD (µm)	Mean Diameter (µm)	Cumulative Mass < 5 µm Diameter (%)	GSD (um)
Spray-Dried Mannitol	3.2	3.8	84	1.7
Jet-Milled Mannitol	3.4	4.9	66	2.1

Summary

There are many different technologies that drug developers can use to advance innovative inhaled drug products. These include bottom-up techniques that form droplets and dried particles from bulk solution, top-down approaches that reduce API particle size to manufacture aerosolizable powders and a combination of the two. Selecting the best approach for a given problem statement depends on the API characteristics and the target product profile, including the inhaled BCS, of the drug in development.

While multiple particle engineering approaches are available for pulmonary formulation development, spray drying and jet milling are proven, scalable approaches and drug developers may benefit from considering them as a first pass. By evaluating these approaches initially, developers can determine whether a more complicated approach is required and which path is best suited for the API and treatment. In the event that multiple particle engineering technologies are suitable, developers can optimize for speed to patient and take into consideration the process throughput, yield and equipment availability.

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