Upperton
Pharma Solutions

PULMO*CRAFT*™: ENGINEERING SPRAY DRIED POWDERS FOR PULMONARY DELIVERY

Here, Richard Johnson, PhD, Founder and Chief Executive Officer, Upperton Pharma Solutions, discusses the techniques of jet milling and spray drying for the production of formulations for dry powder inhalers, and introduces Upperton Pharma's Pulmo*Craft*™ technology, which combines the advantages of both.

Pulmonary delivery is widely established as a viable dosage form for treating local airway diseases, with additional potential for systemic drug delivery. Within this space there are a number of possible delivery approaches that can be undertaken. These include formulations for dry powder inhalers (DPIs) and pressurised metered dose inhalers (pMDIs). Each of these delivery options has its own benefits and limitations and, as such, the applications they target differ. However, if the target patient profile allows, companies typically look towards using DPIs for their finished product.

When developing a DPI formulation, particle engineering is a major factor in a successful development programme. Indeed, the aerosolisation of the powder is key to delivery of the therapeutic.

Key factors in the successful delivery of drugs from a DPI are the formulation's particle size and aerodynamic performance. In short, the particles being inhaled need to have the correct aerodynamic properties to exit the device on inhalation and then deposit in the correct region of the lung. If the alveolar region (or "deep lung") is being targeted, an aerodynamic particle size in the 1–5 µm range is usually required.

Two approaches have been widely used to create suitable powders for lung delivery: jet milling and spray drying. Both techniques have been used to make particles in the 1–5 µm size range. In this article, we will compare and contrast the advantages and limitations of each of these traditional techniques, before focusing on a relatively new approach named Pulmo*Craft*™ (Figure 1), which has successfully combined the flexible formulation technology of spray drying with the precision engineering of jet milling to produce large quantities of powder suitable for delivery in commercially available DPIs.

MANUFACTURING POWDERS USING JET MILLING OR SPRAY DRYING

Particles suitable for lung delivery require an aerodynamic size between 1-5 µm in order to deposit in the alveolar regions; the portion of particles in a DPI formulation that meets this criterion is often referred to as the respirable fraction. The most widely used technology for creating these particles is jet milling.

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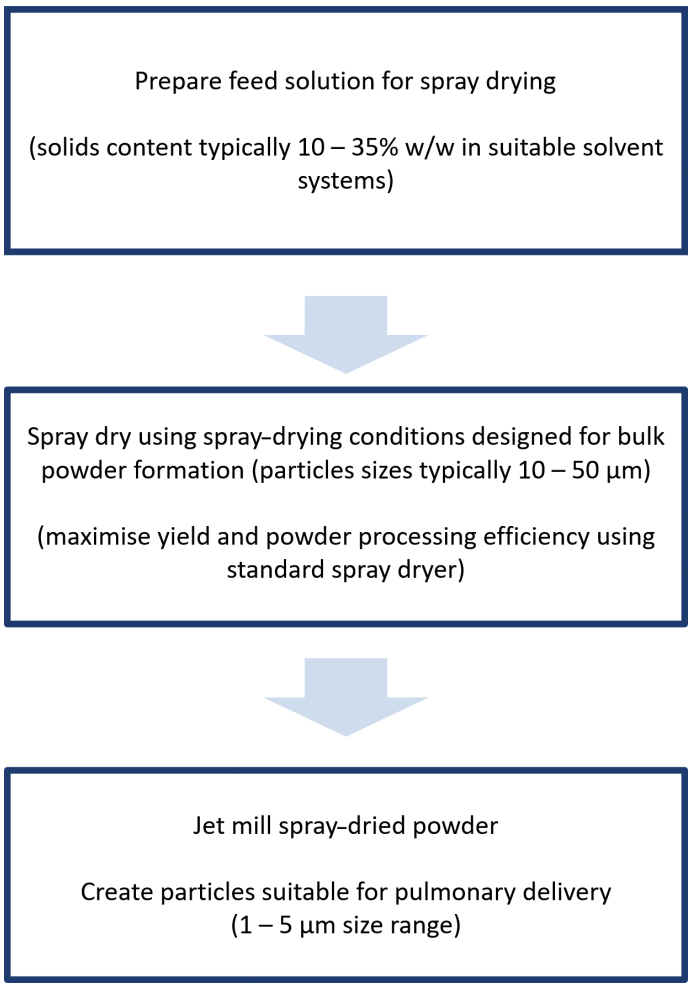

Figure 1: Overview of the Pulmo*Craft*™ manufacturing process.

Jet-milled particles are notoriously cohesive in nature, due to their high surface to volume ratio. The resultant electrostatic, Van der Waals and capillary forces result in powders that have poor flow characteristics and are difficult to disperse. To overcome this inherent problem, some formulations contain larger "carrier" excipients, such as lactose or mannitol, that loosely bind the smaller drug particles before releasing them on delivery.

In recent years, there has been growing interest in using spray drying to create microparticles that can deliver drugs into the lung without the need of a larger carrier particle. These spray-dried microparticles typically consist of an excipient (e.g. mannitol) and an API, in the form of a spray-dried dispersion, which can be amorphous or crystalline in nature.

Micronisation: Production of Respirable Particles by Jet Milling

The most common pharmaceutical jet mill used for micronisation (the manufacture of fine particles) is the spiral jet mill or "pancake mill". Using this technique, larger drug particles are fed into the grinding chamber and immediately accelerated by the high gas flow (typically in the range of 4–8 barg). The particles are reduced in size by collision with each other and the walls of the grinding chamber.

By adjusting the milling air pressure and the powder feed rate it is possible to create particles of the required size range required for lung delivery. For the small particles sizes required to be in the respirable range, it may require several passes through the jet mill before the target particle size can be achieved.

Production of Respirable Particles by Spray Drying

Whilst jet milling is a highly efficient and widely used technique for producing powders for DPIs, there are some classes of API that are not suitable for this process, for example:

- Waxy or "sticky" APIs that do not fracture on collision in the grinding chamber but instead aggregate together
- Sensitive APIs that cannot withstand the high shear forces created during the jet milling process
- Unstable APIs (e.g. peptides, biologics) that require other excipients to be mixed with them at a molecular level to impart the necessary stability on storage in the dry state.

For these more sensitive or difficult to formulate molecules, spray drying offers an alternative route for engineering particles of the correct aerodynamic size range needed for deep lung delivery.

Spray drying involves making a solution that contains both the API and the excipients required to formulate and stabilise the molecule. This solution is then pumped into the spray dryer and atomised into small droplets as the feed solution enters the drying chamber. Almost immediately on entry into the drying chamber, the fine droplets evaporate (usually in milliseconds) to create dry powder particles. These particles are carried on the drying gas flow and separated from the subsequent exhaust gas by a cyclone collection system.

By adjusting the spray-drying conditions it is possible to "engineer" the particle size produced by the spray-drying process. There are several processing conditions that have to be set and monitored during the process as they have a significant impact on particle size of the powders produced.

The Challenge of Producing Respirable Spray-Dried Particles at Commercial Scales

Producing particles in the respirable size range is relatively straightforward on small lab-scale spray dryers such as a Büchi B-290 (Büchi Labortechnik, Flawil, Switzerland) and ProCepT 4M8-TriX (ProCepT, Zelzate, Belgium). These dryers are used routinely on an experimental basis

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for producing small quantities of powder (in the gram scale) and are designed to produce and subsequently collect small particles (in the 1–5 µm size range).

A serious challenge soon becomes apparent when practitioners begin the process of scaling up their spray-drying processes following successful early stage trials. These larger spray dryers, such as those produced by GEA Niro (Søborg, Denmark), are routinely fitted with spray nozzles and cyclones designed to produce (and collect) particles of a much larger size. For example, a GEA Niro PSD-1 (Figure 2) will typically produce and collect particles with a mean size in the 10–15 µm range and recovery of particles below 5 µm will be much more problematic with associated low yields.

Scaling up to the larger PSD-3 or PSD-5 commercial scale spray dryers provides even greater challenges. These dryers are designed to create even larger particles, with mean sizes typically in the 10–100 µm size range. The spray nozzles and the associated cyclones provided as standard are not capable of producing and subsequently collecting the small particles required for pulmonary delivery.

The challenge of particle collection can be overcome to an extent by engineering higher efficiency cyclones that can more efficiently collect these small particles (or using several cyclones in series). However, even then, solutions with low solid contents have to be spray dried in order to yield the small particles needed, which pushes up production costs whilst process yields suffer as a result.

In conclusion, the ability to spray dry large quantities of particles in the respirable range remains a major challenge when looking to scale up a process that was initially successfully developed on a laboratory scale spray dryer.

PULMO*CRAFT*™: COMBINING THE BENEFITS OF SPRAY DRYING AND JET MILLING

The Pulmo*Craft*™ technology, developed by Upperton Pharma Solutions, has combined two established pharmaceutical manufacturing processes, spray drying and jet milling, to create a process capable of producing large quantities of spray-dried powder with particle sizes in the respirable size range at scale, with lower costs and better yields than can be produced by spray drying alone.

Figure 2: A GEA Niro PSD-1 spray dryer.

Processing conditions	VMD* (µm)	X_{10} (µm)	X_{50} (µm)	X_{90} (µm)
Spray dried on B-290 spray dryer	2.03	0.71	1.74	3.76
Spray dried on Niro Mobile Minor	22.97	4.16	17.86	51.43
Particles produced by Pulmo*Craft*™ technology**	2.43	0.77	2.00	4.55

*Volume Mean Diameter **Spray-dried powder produced on Mobile Minor and further processed by jet milling

Table 1: Particle size distribution of the spray-dried and Pulmo*Craft*™ powders by laser diffraction.

Case Study: Production of Respirable Powders Using the Pulmo*Craft*™ Technology

As an example of the flexibility and utility of the Pulmo*Craft*™ technology, batches of particles containing mannitol as an excipient and caffeine as an API were manufactured. The aim was to produce powders suitable for respiratory delivery using two approaches:

- **Conventional spray drying:** Spray drying on a Büchi B-290 laboratory spray dryer using the processing conditions required to produce small particles suitable for respiratory delivery: 2% w/w liquid feed concentration, 5 barg atomisation pressure, 2 g/min liquid feed rate.
- **Pulmo*Craft*™ technology:** Spray drying on a larger Mobile Minor spray dryer (GEA Niro) using processing conditions required to produce larger particles; 10% w/w liquid feed concentration, 1 barg atomisation pressure, 20 g/min liquid feed rate. Spray-dried powder recovered and further processed on jet mill to produce particles in respirable size range.

The spray-dried powders were collected and sized by laser diffraction. The size distribution of the spray dried particles produced on the two spray dryers is shown in Table 1.

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Based on the particle sizes of the spray-dried powders produced, the small batch of particles produced on the Büchi B-290 were of the desired size range for pulmonary delivery. However, the particles produced on the larger Mobile Minor spray dryer were significantly larger than those required for efficient delivery into the deep lung.

In a further processing step, the larger particle size of the spray-dried powder produced on the Mobile Minor was further modified using jet milling to achieve the target 1–5 µm particle size range (Pulmo*Craft*™ technology). The sizes achieved before and after jet milling are also shown in Table 1.

This demonstrates that the Pulmo*Craft*™ technology is capable of producing particles of the desired size range targeted for pulmonary delivery. Indeed, the particle sizes achieved were comparable with those from the B-290 research spray dryer, despite being produced on a much larger Mobile Minor spray dryer that routinely creates much larger particles, but has a significantly higher processing capacity when operated under fairly standard processing conditions.

Further analysis was undertaken to confirm that the Pulmo*Craft*™ particles had suitable aerodynamic properties, comparable with the smoother, more-spherical spray-dried powders of the same size range. The aerodynamic particle size diameters of both batches were measured by inertial impaction using an Andersen cascade impactor (ACI) at a flow rate of 60 L/min. Formulations were filled into size 3 hypromellose capsules and delivered from Plastiape HR RS01 devices (Plastiape, Osnago, Italy). Two doses (capsules) containing 35 mg fill weight were administered per ACI test.

Process	Fine Particle Fraction (%)	MMAD* (µm)
Spray Drying	63.0	3.3
Pulmo*Craft*™	63.0	3.3

*Mass Median Aerodynamic Diameter

Table 2: Aerodynamic particle Size Distribution by ACI.

The results obtained are summarised in Table 2 and show that the aerodynamic performance of the spray-dried and the Pulmo*Craft*™ particles, delivered from the Plastiape device, were effectively identical to the Büchi B-290 spray-dried particles in this particular study.

CONCLUSION

Whilst jet milling remains the most widely used technique for producing powders in the respirable size range, the use of spray drying to produce powders suitable for delivery by a DPI is of growing interest. This interest is driven by a requirement to formulate ever more difficult-to-handle APIs, including new biologics.

Whilst early-stage studies are delivering promising results, there remains a significant challenge when scaling up spray-drying processes from small lab-scale dryers to the larger spray dryers needed to produce commercial batches on a multi-kilogram scale. These challenges include both making particles small enough to be respirable as well as collecting them after they have been produced in the dryer.

An alternative approach is to combine traditional spray drying processes with the particle engineering capabilities of jet milling. This new approach, known as Pulmo*Craft*™, has been successfully used to produce batches of respirable powders that have excellent aerodynamic performance with the potential for commercial scale manufacture, without significant changes to conventional spray drying equipment.

ABOUT THE COMPANY

Upperton Pharma Solutions is a specialist CDMO, offering clients a complete development package: early feasibility studies, process optimisation, scale up and clinical trial (GMP) manufacturing. The company has experience working with a range of dosage forms and the expertise to develop challenging molecules. Upperton's formulation work is complemented by a comprehensive range of analytical services. The company's core expertise is in spray-drying technology, which has an ever-expanding list of applications.

Upperton has an extensive, multinational client-base, ranging from small start-ups to global pharma companies and the company prides itself on its client-focus, flexible approach and scientific excellence.

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ABOUT THE AUTHOR

Richard Johnson founded Upperton Pharma Solutions in August 1999, and continues to play a key role in the management and strategic development of the company. With over 30 years of experience in the pharmaceutical, biotechnology and drug delivery fields, Dr Johnson previously held senior management positions at Andaris Limited (Vectura) and Delta Biotechnology (now Albumedix, Nottingham, UK). Dr Johnson holds an honours degree in Biology from University of York (UK) and a PhD from the University of Warwick (UK) and has a proven track record in successfully developing innovative pharmaceutical products from early feasibility studies through to commercial products.