Spray drying to enable new inhaled drug products

Concepts and considerations for engineering inhaled powders and their application in next generation therapies

Lliralyn M. McEachern, BSc; Thomas S. Lund, BSc and Alan B. Watts, PhD
Catalent Pharma Solutions

Introduction

Spray drying is a well-established technology used to produce engineered, inhalable dry powders and is a critical tool for new drug developers. Typically, powders delivered by dry powder inhalers (DPIs) are composed of either cohesive blends of active pharmaceutical ingredients (APIs) on carrier particles or engineered composite particles [1]. The spray-drying process enables the production of powders with a tightly controlled range of particle sizes and solid-state properties. Formulators have control over the crystalline and amorphous character as well as the radial distribution of components and particle morphology [2]. This control comes from understanding the impact of each material's physicochemical properties and the kinetics of droplet drying [3].

There are many key process inputs and variables that must be considered when designing an inhaled formulation and the associated spray-drying process. Atomization, solution composition, solvent and excipient selection, and particle collection are some of the factors that have the largest influence on material properties. Since the particle size of the drug product is critical for inhaled therapies, optimizing these variables to manufacture particles of the targeted size, with appropriate aerodynamic properties, is a primary objective of respiratory programs. This article discusses ways in which scientists and engineers should consider the variables under their control and expands these considerations into current applications.

Process considerations for the spray drying for inhaled powders

Atomization

Spray drying powders for inhalation requires producing powders with small particle sizes, typically targeting aerodynamic particle size distribution (APSD) in the range of 1-5 µm in diameter. APSD is one of the most crucial measurements for inhalation products because it predicts deposition region, therapeutic performance and bioavailability of the product [4]. A particle's geometric particle size distribution (GPSD), measured by laser light diffraction, may also be useful as a rapid test for an initial indication of flowability and aerosolization properties [1]. While other particle properties such as morphology, density and surface composition also affect APSD, GPSD is often a simple and rapid indicator of APSD.

To achieve a particle size suitable for inhalation, two-fluid atomizers are typically used, as they are able to produce smaller particles compared to rotary or pressure nozzles. Two-fluid nozzles, or air atomizing nozzles, have two streams: a gas stream and a liquid stream. The gas stream surrounds the liquid stream, and when they contact each other, the high velocity of the gas stream imparts a shear force on the liquid stream and causes atomization. Two-fluid nozzles also allow for tunability of the particle size by adjusting the flow rates for either the gas stream or the liquid stream. Generally, as the ratio of the atomization gas flow rate to liquid flow rate increases, the particle size decreases [5].

There are two principal types of two-fluid nozzles: external mixing and internal mixing. Both types have a channel in the center of the nozzle that contains the liquid stream and a surrounding channel that contains the gas stream. For external mixing nozzles, the liquid stream encounters the atomization gas outside of the nozzle and is disrupted and atomized into droplets. In contrast, internal mixing nozzles combine the liquid and gas streams inside the nozzle chamber. Both nozzle types can produce particles in the low micron range. They also share similar limitations, such as low solution flow rates, high atomization gas requirements and the potential for wide particle size distributions [6].

As the liquid feed is atomized, droplets form and the solvent or suspension medium begins to evaporate. During the initial stage of droplet drying, solvent molecules rapidly evaporate from the droplet surface, due to the heat in the spray-drying chamber, and the droplet shrinks in size. During the process, solvent molecules diffuse towards the surface of the droplet. As solvent leaves the droplet, the solids components nucleate and precipitate out of solution, typically at the droplet surface, often forming a shell. Precipitation kinetics are driven by supersaturation of the solids components as the solvent evaporates, resulting in increased dissolved solids concentrations. The solvent continues to diffuse through the solidified crust to the surface of the particle as the remaining solute components continue to precipitate and solidify [7]. The droplet drying stage of atomization impacts the morphology of the final dried particles and is dependent on the selected formulation as well as the thermodynamic conditions in the dryer. Different material properties and evaporation rates will lead to different morphologies and surface compositions [8]. Figure 1 and Table 1 depict and explain key stages in the spray-drying process and their associated temperatures.

Figure 1

Depictions of particle engineering by spray drying

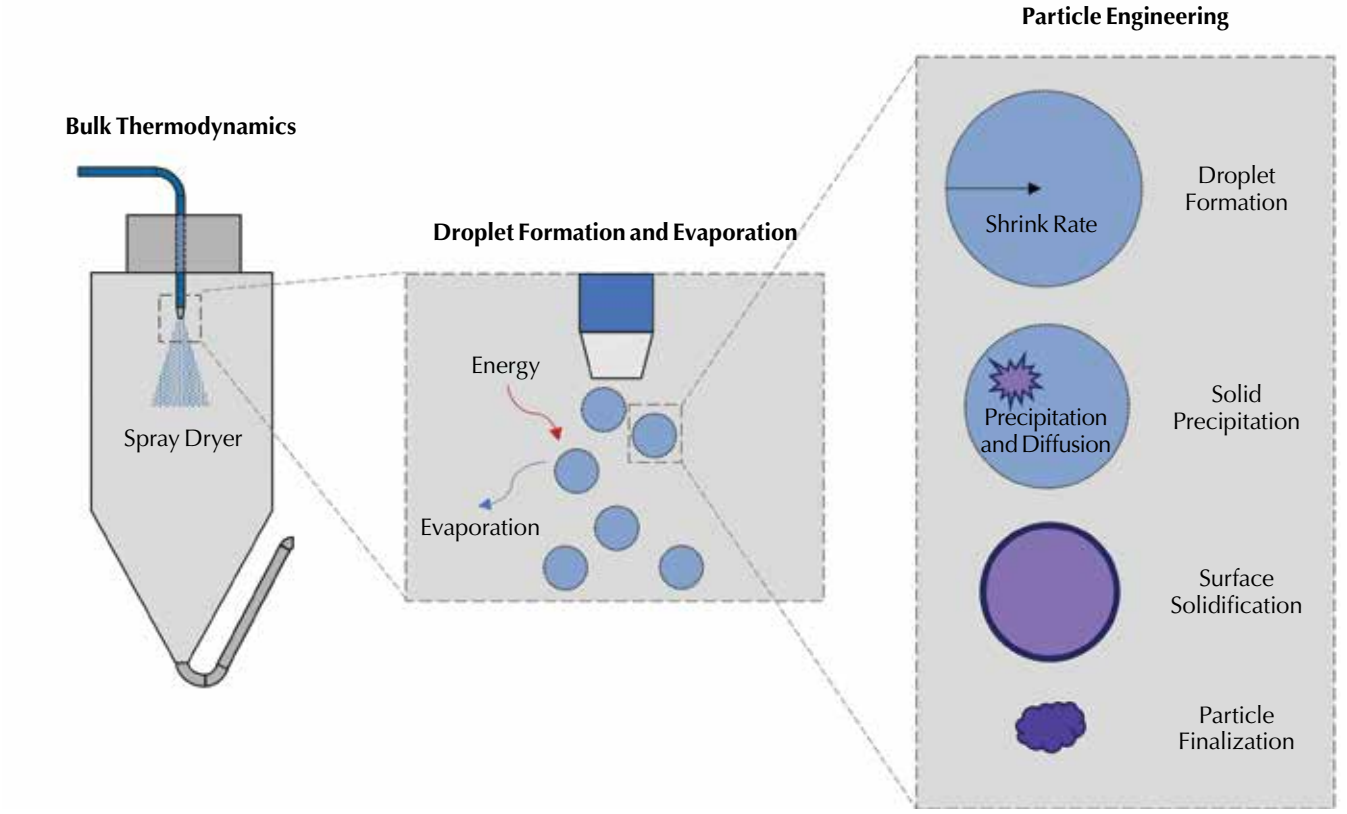


Table 1

Spray-dried particle-engineering stages depicted in Figure 1

Stage	Temperature at Stage Beginning	Temperature at Stage End	Key Considerations
Droplet formation	Liquid feed temperature	Wet bulb temperature	Droplet size
Solid precipitation	Wet bulb temperature	Wet bulb temperature	Kinetics of precipitation Kinetics of crystallization
Surface solidification	Wet bulb temperature	Spray-dryer outlet temperature	Surface enrichment Particle surface area
Particle finalization	Spray-dryer outlet temperature	Collection container temperature	Particle size Particle density

The temperature of the droplet, and the particle that forms from it, transitions during the drying process, starting at the feedstock temperature. As the droplet comes into contact with the heated drying gas, it reaches the wet bulb temperature and enters the constant drying rate phase as the droplet shrinks and is cooled by evaporation. The solute begins to concentrate on the surface of the droplet and as it forms a solid, the temperature progresses to the outlet temperature of the spray dryer. This stage is referred to as the falling drying rate phase [7]. The change in droplet temperature and drying rate during these phases is illustrated in Figure 2. Importantly, while drying of the droplets into particles takes place primarily in the spray-drying chamber at these temperatures, particles held in the collection container are exposed to the temperature and relative saturation conditions within that container. Collection containers can often approach room temperature. For a high throughput aqueous process, room temperature could be below the water dew point, resulting in a high risk of condensation and water being taken up by the powder.

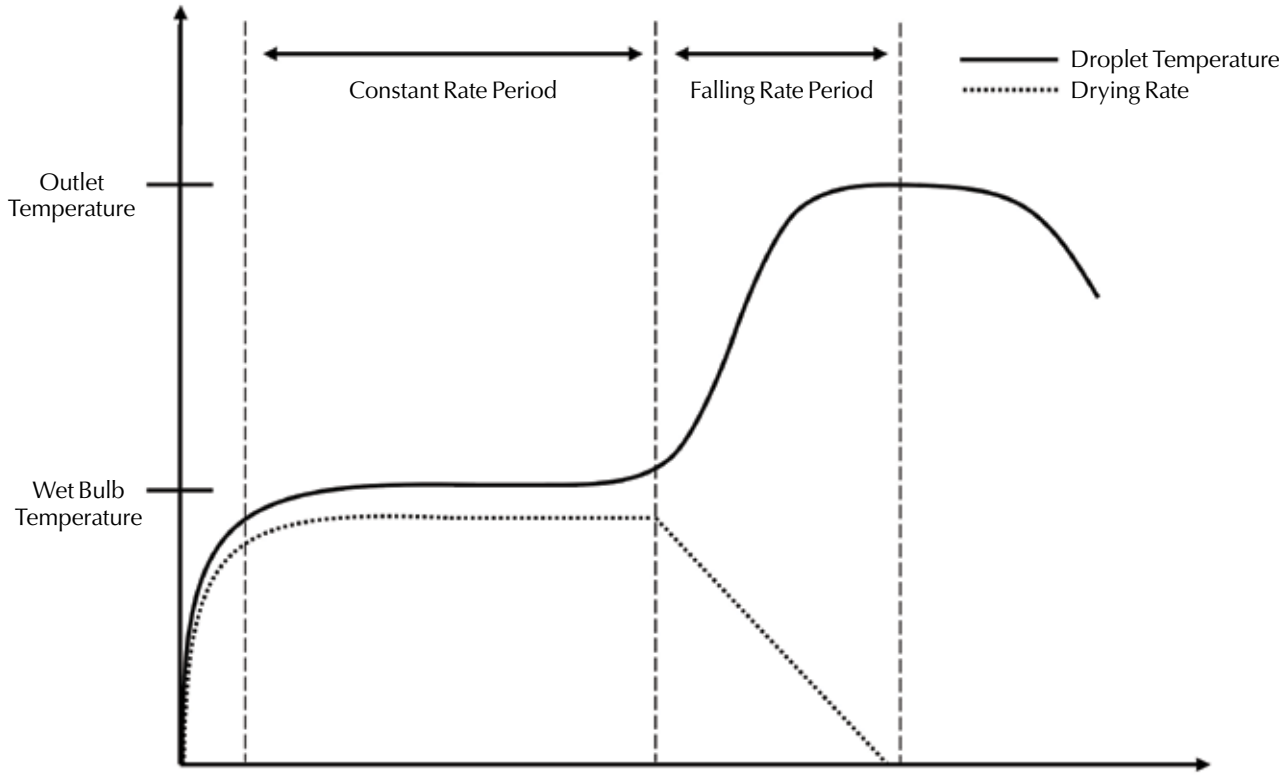
Formulations and solutions

Solids loading in the feedstock is impactful for inhalation formulations as it contributes to the particle size of the spray-dried powder. For solution feedstocks, weight percentages are often less than 5% solids in solution but may be higher depending on the processing conditions and excipients in the formulation. Solids content in the feedstock is typically kept low to aid in enabling the formation of small particles and is also limited by API and excipient solubility in the selected solvent or solvent blend [5]. Many small molecules have poor water solubility while the standard inhalation excipients have poor organic solubility. This results in many feedstocks being a blend of water and an organic solvent. An additional consideration is the direct relationship between feedstock solids content and manufacturing output rate. This means that optimizing the solids content is critical to balancing manufacturability with product performance.

Poorly water-soluble compounds can be sprayed as a suspension or an emulsion instead of a solution [9]. Since two-fluid nozzles are often used for spray drying of inhalation products, clogging or blockage of the nozzle liquid orifice is unlikely. These nozzles typically have liquid feed diameters ranging from 300 µm to greater than 2 mm, which is much larger than the suspension particle size. Prior to spray drying, API particle size is typically reduced by jet-milling or wet-milling techniques to less than 5 µm. Ensuring that the feed tank is well mixed and that settling risk in the feed lines is controlled are critical to ensuring that the product assay is on target and that the collected product is homogenous from start to finish. Emulsions have also been used to engineer specific particle morphologies and achieve high drug loads [10].

Figure 2

Theoretical plot of the change in droplet/particle temperature and drying rate over time



Formulation options available for pulmonary delivery are more limited than for oral delivery. The number of precedented excipients is relatively small and the total amount of each excipient acceptable for lung exposure is often low. As of July 2022, the United States Food and Drug Administration (FDA) Inactive Ingredient Database listed 62 materials precedented for delivery to the lungs, compared to more than 1,300 materials listed for oral delivery [11]. Of these 62, only a few have been used in a spray-dried products for inhalation. With occasional exceptions for materials that are Generally Recognized as Safe (GRAS), most development programs aim to only use materials already precedented for use in inhaled formulations, due to the additional safety and tolerability data required to justify using novel materials [12]. Table 2 illustrates the limited number of precedented materials. Alternative materials can be evaluated, but development teams should weigh regulatory requirements for demonstrating the respiratory safety of novel excipients prior to formulating [13].

Excipient selection is a key aspect of respiratory product development because while the options for excipients are limited, they can provide essential product improvements. These may be increased solid-state stability, enhanced aerosolization properties or dissolution performance, or other product-specific changes [14]. Lactose has been used in carrier-based DPI formulations and as a bulking agent in engineered particle formulations, as can other sugars such as trehalose and mannitol [13]. Selection of bulking sugar depends on API properties and target product attributes and is a complex topic beyond the scope of this article. Leucine is a common excipient for pulmonary particles and is used to achieve product attributes such as modified surface morphology, enhanced aerosolization and flowability, and improved physical stability through reduction in hygroscopicty [14].

Product collection

Separating the spray-dried powder from the exhaust gas stream is a critical step in recovery of the newly engineered drug particles. Two primary technologies are used for this: cyclones and filter baghouses.

Cyclones operate on inertia to remove solids from gas streams, using a basic operating principle similar to that of a centrifuge. Gas enters the cyclone and is forced into a spiraling motion. Inertia carries the particles to the outer edge of the cyclone, where they impact with the chamber wall then drop to the bottom of the cyclone and into the collection container. Cyclones are simple to operate and low cost to maintain, as they contain no moving parts. However, the collection of respirable-sized particles using a cyclone is difficult, due to their small geometric size and corresponding aerodynamic properties. Typical cyclone collection efficiency decreases rapidly as particle size falls below 5 µm. Specialized high efficiency cyclones can be used to increase batch yields, but often result in considerably higher pressure drops compared to

Table 2

Excipients used in the manufacture of inhalable dry powders by spray drying

Level of Precedence	Spray-Drying Excipient	Purpose
Approved	DPPC	Microcarrier, dispersibility, bulking
	DSPC	Microcarrier, dispersibility, bulking
	Mannitol	Osmolality
	Glycine	Buffer, stabilizer
	Buffer salts (e.g., citrate, sulfate)	Buffer, glass stabilizer
Clinical Development	Leucine	Dispersibility
	Trileucine	Dispersibility
	Trehalose	Glass stabilizer, bulking agent
	Fumaryl diketopiperazine (FDKP)	Carrier
Literature	PLA, PLGA	Controlled-release
	Polysaccharides	Dispersibility, bulking
	Cyclodextrins	Dispersibility, bulking
	Lactose	Bulking
	Sucrose	Bulking

Adapted from reference 30.

cyclone designs used to collect larger spray-dried materials [15]. This pressure differential can become significant if the spray-drying system must be operated at reduced system flows to account for the increase in pressure drop.

Filter baghouses can be used in place of a cyclone or in secondary filtration of the exhaust gas after cyclonic collection. Material is collected from the exhaust gas stream on the filter surface and a reverse air pulse is used to remove the material from the filter so that it can fall into the collection container below. Extremely high yields can be achieved with these systems, as the filter pore size can be much smaller than the typical spray-dried inhalation powder. This leads to the collection of almost all the material produced, including particles < 1 µm that would preferentially bypass a cyclone. The materials used to construct a filter system are critical to its design, as they need to be chemically compatible with any solvents used and minimize the risk of filter shedding [16].

Optimizing collection of the primary product is critical to efficient production and can help prolong the life of any secondary recirculation or exhaust filters. Research into the cleaning of industrial exhaust air shows that using multiple cyclones in parallel can improve overall collection efficiency at a given pressure drop. However, care must be taken to ensure that the product quality and attributes of the powder collected by each cyclone are equivalent [17].

Defining the target product profile and critical attributes are key to advancing a new compound. The formulation, process parameters and equipment specifications should be selected to achieve the program goals. Considering important variables such as atomization, particle collection and formulation strategies will increase knowledge of the process and contribute to successful product development.

Applications of spray drying for inhaled powders

Delivery of high doses to the lungs

The most common DPI products utilize a carrier-based approach, where an ordered mixture of coarse lactose is homogenously blended with a smaller amount of micronized, potent API. These formulations represent the majority of DPI products for asthma and COPD therapeutics, where the amount of API to be delivered to the lung in a single actuation is between 1 and 100 µg [3]. More recently, niche products requiring high doses of API (e.g., > 1 mg) have been developed, the majority of which are inhaled anti-infectives intended for localized treatment of lung infections [3]. Because of the limitation of powder mass, the amount a patient can comfortably inhale is generally less than 50 mg. Delivering between 1 and 100 mg of drug becomes difficult to achieve with poor-performing coarse blends and fine particle fractions (FPF) of < 25%, where drug loading is limited to approximately 10% API [18]. A more effective formulation solution to maximize drug loading and aerosol performance can be achieved by spray drying.

Two high dose products produced by spray drying are currently approved for use in cystic fibrosis patients, TOBI® Podhaler® (Tobramycin Inhalation Powder, Viatris, Canonsburg, PA, US) for the treatment of chronic *P. aeruginosa* infection and Bronchitol® (Mannitol Inhalation Powder, Chiesi, Parma, Italy) for improved sputum clearance. The dosing regimens of these products require inhalation of four 28 mg capsules b.i.d and ten 40 mg capsules b.i.d., respectively, and in the case of TOBI Podhaler, have shown to reduce administration time by approximately 30 minutes compared to tobramycin nebulization [10]. Further reduction in dosing time and capsule count could be achieved in these and future formulations by increasing the mass of respirable API delivered from a single device reservoir.

From the patient perspective, an ideal product could achieve a complete dose in a single actuation and breath with minimal device manipulation. Given constraints around packaging volume and device, the formulated powder should be designed to maximize packing density, limit excipient mass and maximize aerosol performance. The multiplication of these three attributes has been described as product density [3, 9]. As an example, the incorporation of a small amount of excipient in an inhaled mannitol product, while slightly decreasing the API load, could improve product density by increasing packing density and aerosol performance [7], thereby reducing the number of capsules and inhalations required. Another example of the utilization of spray drying to enable a high-dose inhaled product was recently investigated in a formulation of a drug suspended in Pulmophere™ (Novartis AG, Basel, Switzerland) particles [9]. Using a suspension feedstock where a poorly soluble crystalline drug was dispersed in a lipid and calcium chloride matrix, researchers demonstrated the ability to deliver 25 mg of API to the lung in a single dose. The formulation demonstrated increased tap density and decreased particle size with increasing suspended drug loading while maintaining an FPF and delivered dose (DD) above 75% and 90%, respectively [9].

Formulating biologics as respirable powders

Inhalation of biopharmaceuticals to treat pulmonary disease is an attractive alternative to delivery via the subcutaneous and intravenous routes, enabling higher localized therapy to the lungs while limiting systemic exposure. In addition, formulation of a dry powder for inhalation, rather than a nebulized solution, allows for room-temperature-stable products that can be rapidly administered. The manufacture of biologics for dry powder inhalation involves careful consideration of processing steps and stabilizing

excipients to avoid aggregation and/or degradation of the API, all while ensuring the resulting powders are fillable, respirable and stable.

Processing steps during spray drying, if not properly controlled, can lead to loss of activity of a biologic. Of these, feedstock atomization (shear and high pressure) and droplet drying (heat, desiccation and osmotic stress) merit close consideration. Therefore, measures to minimize the degrading impact of atomization and exposure of dried particles to high temperature during the falling rate period (Figure 2) should be evaluated. Generally, it is thought that the degradation due to shear and pressure of atomization is less impactful than biologic accumulation at the droplet surface during droplet drying [19].

The impact of thermal stress caused by the spray-drying process and elevated storage temperatures can be reduced by incorporation of saccharides. Among the proposed mechanisms of stabilization by saccharides, the most commonly referenced are the water replacement theory, where hydrogen bonds formed with water in aqueous solution are replaced with those formed with a carbohydrate in a solid state, and the vitrification hypothesis, where drug substance molecular movement is reduced through immobilization in a glassy matrix. While saccharides with high glass transition temperatures (Tg) such as trehalose and sucrose are most desirable for stability reasons, mannitol is also commonly used and can be stabilized in the amorphous state by other excipients. Higher molecular weight saccharides, such as dextran, can also be used for stabilization. Interestingly, it was found that higher molecular weight dextran (with a higher corresponding Tg) was not as effective in protein stabilization as lower molecular weight dextran (with a lower Tg) [19]. While this is counter to the vitrification explanation of stabilization, it was hypothesized that higher molecular weight dextran was sterically hindered from forming as many hydrogen bonds as the lower molecular weight variety.

When considering saccharide selection and ratio to drug substance, it is important to consider hydrogen bonding sites of a biologic. Those biologics with relatively higher numbers of hydrogen bonding sites could benefit from a matrix with increased molecular mobility (lower Tg) [20]. Lactose, although commonly used in inhaled products, should be avoided for formulation in biologic products due to potential deamidation during a Maillard reaction. Initial concentrations of saccharide and shell former are important to consider. Generally, feedstock with lower saturation of saccharide will enable solubility for longer durations during droplet drying. Conversely, shell formers closer to their solubility limit will begin to precipitate earlier in the drying process, allowing for increased crystallization time and reduced diffusion to the center of the drying particle. As the drying process continues, ions and buffering excipients will increase in concentration, which has the potential to impact the pH or osmolality of the remaining water in the droplet [19]. Therefore, it is important to have a well-buffered feedstock to avoid large pH shifts that can impact biologic activity.

Denaturing effects of biologic accumulation at the air/liquid interface of droplets can be reduced by the incorporation of surface active excipients that out-compete a drug substance for the position at the denaturing interface. In some cases, hydrophobic shell-forming excipients like leucine provide a moisture-protective layer on the dried particles, shielding the matrix from plasticizing water and the contained biologic from hydrolytic degradation. Other amino acids used in spray drying like histidine, glycine and arginine offer matrix-stabilizing effects. However, these excipients are hydrophilic and do not provide as effective a moisture barrier as leucine. Trileucine has been incorporated in some formulations to reduce the weight percent of shell former need, enabling higher loading of the drug substance and other excipients [21].

Control of moisture levels in spray-dried biologics is critical to their long-term stability. While low residual moisture reduces molecular mobility and biologic hydrolysis, powder that is overly dry may induce protein aggregation and powders may suffer from poor filling and aerosol performance, due to heightened electrostatic charge. Further, consideration of moisture contribution from the capsule (if using a capsule-based device) and ingress through blistering, bottling and packaging is critical. Ultimately, controlled storage using equilibrated desiccant in multiple layers of sealed packaging may be necessary to ensure long term stability [19, 21].

The first spray-dried biologic approved for the market was also the first spray-dried product approved for delivery by inhalation. In 2006, Exubera® (Pfizer, New York, NY US) was approved by the FDA as a needle-free alternative for the treatment of diabetes mellitus. The formulated powder was produced by spray drying an aqueous feedstock adjusted to pH 7.3. It resulted in an amorphous powder containing 60% insulin, 27.1% sodium citrate dihydrate (buffer), 10.0% mannitol (stabilizer), 2.6% glycine (buffer) and 0.3% sodium hydroxide (for pH adjustment). While mannitol alone has a low Tg, it has been noted that the presence of sodium will increase the Tg, stabilizing the amorphous form [22]. To ensure long-term stability, it is necessary to maintain a product Tg much greater than the desired storage temperature. Typically, a Tg at least 50 °C higher than the desired storage temperature is necessary. Additionally, since residual water in a dry product will plasticize (reducing the Tg), it was desirable to maintain a moisture content of less than 5% in the Exubera spray-dried powder during storage [23]. The powder produced by spray drying had a low bulk

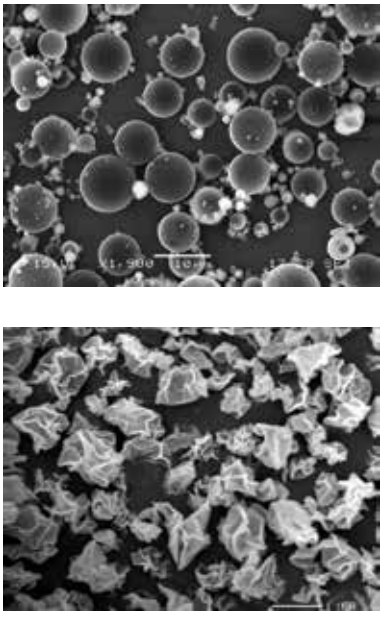
density (0.2 g/cm^3), comprising rugose particles with a narrow particle size distribution (where the X_{10} = 0.7 µm and X_{90} = 2.7 µm), enabling efficient delivery to the deep lung [23]. From a pharmacokinetic perspective, the stabilized amorphous insulin and the deposition in the lung's alveolar region (where less than 1 µm of surfactant and a single cell layer separate the airway from blood vessels) likely contributed to a more rapid systemic absorption. In the clinical study, peak serum concentration was reached more rapidly with inhaled insulin (average 49 minutes) compared to subcutaneous human insulin injection (average 105 minutes). While Exubera ultimately did not meet commercial expectations, the innovations made in particle engineering via spray drying, both for small molecules and biologics, continue to be seen in development pipelines today.

Inhalation for non-respiratory indications

Utilization of the respiratory tract as a route to reach therapeutically significant levels of systemic drug has long been the ambition of many in the field. In the example above, Exubera became the first approved therapy to do so, utilizing spray drying to generate fine particles capable of reaching the alveolar space where > 100 m^2 of surface area is available for deposition and subsequent diffusion into the blood [24]. Another spray-dried product targeting a non-respiratory indication approved by the FDA in 2018 is Inbrija® (Levodopa Inhalation Powder, Acorda Therapeutics, Pearl River, NY, US) for the treatment of OFF episodes in Parkinson's disease. Spray-dried powders are formulated and delivered by ARCUS® technology (Acorda Therapeutics) to achieve large porous powders containing 90% levodopa [3] and, when inhaled, achieve a pharmacodynamic response within 10 minutes [25]. Two types of ARCUS particles with distinct surface morphologies—spherical shells and crumpled paper—can be achieved through the selection of excipient matrix and spray-drying process parameters (Figure 3).

Figure 3

Spray-dried, large, porous powder with hollow sphere (top) and rugose (bottom) surface morphologies (ARCUS® technology, Acorda Therapeutics)



Delivery to the upper respiratory tract is also a viable route to obtain therapeutic levels of API systemically or in cerebrospinal fluid (CSF). Products currently in clinical development include nasal vaccines, therapies for central nervous system (CNS) disorders, and rescue therapies for anaphylaxis and overdose [26]. The nasal cavity has approximately 150 cm^2 available for deposition and will accommodate between 10 and 25 mg of powder in a single inhalation [26]. Spray drying is particularly well suited for engineering particles for nasal powders, where a D50 of 25-50 µm is desired and an amorphous API or biologic can be stabilized. Two-fluid nozzles can be used at lower air-to-liquid ratios (ALRs) to produce larger particles. However, it should be noted this can affect the dryness of the resulting powder and may require secondary drying after collection. Compared to pulmonary delivery, a broader range of excipients is available (approximately 60 in approved products) to facilitate mucoadhesion, glass stabilization and permeation enhancement. Chitosan, a biocompatible polysaccharide, is used in clinical investigations as both a nasal mucoadhesive and a permeability enhancer, due to its ability to open tight junctions [27]. Utilization of chitosan during spray drying has been shown to increase feedstock viscosity (allowing for large particles) and alter particle morphology [28]. While neither of the two marketed nasal powder products utilize spray drying, the advantages of spray drying to produce stable, aerosolizable powders capable of increasing bioavailability have been demonstrated in development pipelines.

Conclusion

Formulating an inhalable dry powder product and designing the associated spray-drying process requires understanding the properties of the ingoing API, the utility of the available excipients and the process parameters connected to product quality attributes. Products for respiratory indications require small particle sizes, necessitating that atomization and particle collection be carefully evaluated. The products must be formulated and manufactured thoughtfully to achieve the required aerosol properties. Spray drying has proven useful for producing high-dose aerosols as well as enabling inhaled dry powder biologics. Spray drying can also be effectively used to produce inhaled powders intended for non-respiratory indications. While there are currently only six commer-

cial inhalation products manufactured using spray drying [3, 29], products in development that require high drug load, delivery of a biologic or rapid onset are increasingly using spray drying to manufacture a stable, highly respirable powder.

References

1. Telko MJ, Hickey AJ. Dry powder inhaler formulation. Respiratory Care. 2005;50(9):1209-1227.

2. Vehring R. Pharmaceutical particle engineering via spray drying. Pharmaceutical Research. 2007;25(5):999-1022. doi:10.1007/s11095-007-9475-1.

3. Son YJ, Miller DP, Weers JG. Optimizing spray-dried porous particles for high dose delivery with a portable dry powder inhaler. Pharmaceutics. 2021;13(9):1528. doi:10.3390/pharmaceutics13091528.

4. Chow AHL, Tong HHY, Chattopadhyay P, et al. Particle engineering for pulmonary drug delivery. Pharmaceutical Research. 2007;24(3):411-437. doi:10.1007/s11095-006-9174-3.

5. Mosén K, Bäckström K, Thalberg K, et al. Particle formation and capture during spray drying of inhalable particles. Pharmaceutical Development and Technology. 2004;9(4):409-417. doi:10.1081/pdt-200035795.

6. Hede PD, Bach P, Jensen AD. Two-fluid spray atomisation and pneumatic nozzles for fluid bed coating/agglomeration purposes: A review. Chemical Engineering Science. 2008;63(14):3821-3842. doi:10.1016/j.ces.2008.04.014.

7. Alhajj N, O'Reilly NJ, Cathcart H. Designing enhanced spray dried particles for inhalation: A review of the impact of excipients and processing parameters on particle properties. Powder Technology. 2021;384:313-331. doi:10.1016/j.powtec.2021.02.031.

8. Vehring R, Foss WR, Lechuga-Ballesteros D. Particle formation in spray drying. Journal of Aerosol Science. 2007;38(7):728-746. doi:10.1016/j.jaerosci.2007.04.005.

9. Tarara TE, Miller DP, Weers AE, et al. Formulation of dry powders for inhalation comprising high doses of a poorly soluble hydrophobic drug. Frontiers in Drug Delivery. 2022 Mar 15;2:862336.

10. Geller DE, Weers J, Heuerding S. Development of an inhaled dry-powder formulation of tobramycin using PulmoSphere™ technology. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2011;24(4):175-182. doi:10.1089/jamp.2010.0855.

11. United States Food and Drug Administration. Inactive ingredients in approved drug products. Database. https://www.fda.gov/media/164856/download.

12. Wang H, Connaughton P, Lachacz K, et al. Inhalable microparticle platform based on a novel shell-forming lipid excipient and its feasibility for respirable delivery of biologics. European Journal of Pharmaceutics and Biopharmaceutics. 2022;177:308-322. doi:10.1016/j.ejpb.2022.07.013.

13. Pilcer G, Amighi K. Formulation strategy and use of excipients in pulmonary drug delivery. International Journal of Pharmaceutics. 2010;392(1-2):1-19. doi:10.1016/j.ijpharm.2010.03.017.

14. Alhajj N, O'Reilly NJ, Cathcart H. Leucine as an excipient in spray dried powder for inhalation. Drug Discovery Today. 2021;(10):2384-2396. doi:10.1016/j.drudis.2021.04.009.

15. Masnadi MS, Grace JR, Elyasi S, Bi X. Distribution of multi-phase gas–solid flow across identical parallel cyclones: Modeling and experimental study. Separation and Purification Technology. 2010;72(1):48-55. doi:10.1016/j.seppur.2009.12.027.

16. Miller DA, Ellenberger D, Gil, M. (2016). Spray-drying technology. In: Williams III R, Watts A, Miller D. (Eds). Formulating poorly water soluble drugs. AAPS Advances in the Pharmaceutical Sciences Series, Vol 22. Springer, Cham. doi.org/10.1007/978-3-319-42609-9_10.

17. Muschelknautz U. Design criteria for multicyclones in a limited space. Powder Technology. 2019;357:2-20. doi:10.1016/j.powtec.2019.08.057.

18. Sibum I, Hagedoorn P, de Boer AH, et al. Challenges for pulmonary delivery of high powder doses. International Journal of Pharmaceutics. 2018;548(1):325-336. doi:10.1016/j.ijpharm.2018.07.008.

19. Carrigy N, Vehring R. (2019). Engineering stable spray-dried biologic powder for inhalation. In: Pharmaceutical Inhalation Aerosol Technology. pp. 291-326. doi: 10.1201/9780429055201-12.

20. Abdul-Fattah AM, Kalonia DS, Pikal MJ. The challenge of drying method selection for protein pharmaceuticals: Product quality implications. Journal of Pharmaceutical Sciences. 2007;96(8):1886-1916. doi:10.1002/jps.20842.

21. Lechuga-Ballesteros D, Charan C, Stults CLM, et al. Trileucine improves aerosol performance and stability of spray-dried powders for inhalation. Journal of Pharmaceutical Sciences. 2008;97(1):287-302. doi:10.1002/jps.21078.

22. Costantino HR, Andya JD, Nguyen PA, et al. Effect of mannitol crystallization on the stability and aerosol performance of a spray-dried pharmaceutical protein, recombinant humanized anti-IgE monoclonal antibody. Journal of Pharmaceutical Sciences. 1998;87(11):1406-1411. doi:10.1021/js9800679.

23. Stevenson CL, Bennett DB. (2014). Development of the Exubera® insulin pulmonary delivery system. In: das Neves J, Sarmento B. (Eds). Muco-

sal Delivery of Biopharmaceuticals. pp.461-481. Springer. doi:10.1007/978-1-4614-9524-6_21.

24. Hastedt JE, Bäckman P, Clark AR, et al. Scope and relevance of a pulmonary biopharmaceutical classification system AAPS/FDA/USP Workshop March 16-17, 2015, Baltimore, MD, US. AAPS Open. 2016;2(1). doi:10.1186/s41120-015-0002-x.

25. Inbrija. Patient brochure. Acorda Therapeutics. 2021; www.inbrija.com/patient-brochure.pdf.

26. Henriques P, Fortuna A, Doktorovová S. Spray dried powders for nasal delivery: Process and formulation considerations. European Journal of Pharmaceutics and Biopharmaceutics. 2022;176:1-20. doi:10.1016/j.ejpb.2022.05.002.

27. Davis SS, Illum L. Absorption enhancers for nasal drug delivery. Clinical Pharmacokinetics. 2003;42(13):1107-1128.doi:10.2165/00003088-200342130-00003.

28. Giuliani A, Balducci AG, Zironi E, et al. *In vivo* nose-to-brain delivery of the hydrophilic antiviral ribavirin by microparticle agglomerates. Drug Delivery. 2018;25(1):376-387. doi:10.1080/10717544.2018.1428242.

29. Moon C, Smyth HDC, Watts AB, Williams RO 3rd. Delivery technologies for orally inhaled products: An update. AAPS PharmSciTech. 2019;20(3):117. doi:10.1208/s12249-019-1314-2.

30. Lechuga-Ballesteros, D. (2019). Particle engineering technology for inhalation. In: Hickey AJ. (Ed.) Pharmaceutical Inhalation Aerosol Technology, Third edition. pp. 349-361. CRC Press.

Lliralyn M. McEachern, BSc, is an Engineer and Thomas S. Lund, BSc, is a Senior Engineer in the Catalent Spray Drying Center of Excellence and Alan B. Watts, PhD, is Director of Innovation and Partnerships for Orally Inhaled Products at Catalent Pharma Solutions, 14 School House Road, Somerset, NJ 08873, US. Corresponding author: Alan B. Watts, PhD, alan.watts@catalent.com, www.catalent.com.