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# Engineering Advances in Spray Drying for Pharmaceuticals

John M. Baumann, Molly S. Adam, and Joel D. Wood

Small Molecules, Lonza Pharma & Biotech, Bend, Oregon 97701, USA;
email: john.baumann@lonza.com, molly.adam@lonza.com, joel.wood@lonza.com

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## Keywords

spray drying, amorphous solid dispersions, biologics, particle engineering, inhalation, scale-up

## Abstract

Spray drying is a versatile technology that has been applied widely in the chemical, food, and, most recently, pharmaceutical industries. This review focuses on engineering advances and the most significant applications of spray drying for pharmaceuticals. An in-depth view of the process and its use is provided for amorphous solid dispersions, a major, growing drug-delivery approach. Enhanced understanding of the relationship of spray-drying process parameters to final product quality attributes has made robust product development possible to address a wide range of pharmaceutical problem statements. Formulation and process optimization have leveraged the knowledge gained as the technology has matured, enabling improved process development from early feasibility screening through commercial applications. Spray drying's use for approved small-molecule oral products is highlighted, as are emerging applications specific to delivery of biologics and non-oral delivery of dry powders. Based on the changing landscape of the industry, significant future opportunities exist for pharmaceutical spray drying.

## 1. INTRODUCTION

Spray drying is a well-established technology that was first patented in the 1870s, with initial development of equipment and techniques occurring over the subsequent three decades. However, it was not until the early 1900s that spray drying was used commercially for production of powdered milk products by the dairy industry (1, 2).

In general terms, spray drying converts liquids containing dissolved or suspended solids into dried powders. **Figure 1** provides an overview of the process and associated equipment for a pharmaceutical application. The liquid spray solution is delivered to the spray dryer, where it is atomized into fine droplets, enhancing heat and mass transfer and providing control of the final powder's particle size. Drying occurs immediately as the heated drying gas concurrently enters the drying chamber and contacts the droplets, causing rapid evaporation and solidification into a dried particle (2–4). Dried particles are then separated from the drying gas using a cyclone collector (2). The drying gas (typically nitrogen for organic solvents) is sent through a condenser to remove solvent, enabling reuse of the drying gas and reducing gas consumption at large scale. Depending on the process and the product profile, a secondary drying step can be used to further reduce the solvent content of the particles.

Spray drying has several advantages that make it attractive for pharmaceutical applications, including its rapid drying kinetics from liquid droplet to solid particle, the gentle temperature exposure of the drying droplet owing to evaporative cooling, and the short residence time of particles in the drying chamber. In-depth understanding of the atomization and drying processes allows precise control of product characteristics, straightforward process optimization, and increasingly predictable scale-up. Innovations across scales of equipment make the technology broadly applicable throughout the drug development process, from early research through commercial scale (5, 6).

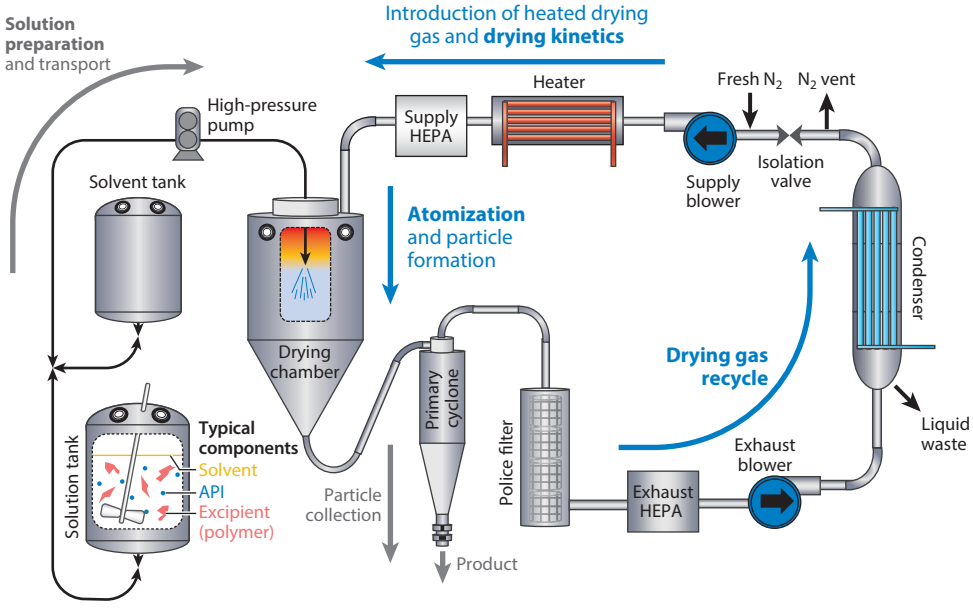


**Figure 1**

Spray-drying process and equipment overview. Abbreviation: API, active pharmaceutical ingredient.

Within the past two decades, spray drying has gained widespread adoption for small-molecule pharmaceutical drug delivery. This is due to the industry's drug property space evolving to include active pharmaceutical ingredients (APIs) that have high lipophilicity, crystallize rapidly, and/or have low aqueous solubility (7). Formulators and process engineers have increasingly turned to amorphous solid dispersions (ASDs) in their quest to develop efficacious drug products from these difficult APIs. ASDs prepared by spray drying—known as spray-dried dispersions (SDDs)—have been particularly successful in enhancing the solubility and thus bioavailability of these compounds. Spray drying has also been used successfully for isolation of excipients, particle engineering of drug substances, formulations with modified release profiles, solid-state formulation of proteins, particles for inhalation, and vaccines (8–13).

**Table 1** summarizes approved SDD products for oral delivery (14–17). As the table shows, the first commercial spray-dried product was Prograf®, a tacrolimus SDD that was approved in 1994. This paved the way for commercialization of a substantial number of new chemical entities (NCEs) using this technology (14, 17, 18). Over the past decade, SDDs have become a mature technology platform. Continuing research is focused on better understanding the effect of formulation and process parameters on the quality attributes of the spray-dried product (19).

In recent years, however, the emerging use of spray drying for delivery of biologics and application to new drug therapies has become an important area of research (20). Spray drying continues to be evaluated for solid-state stabilization of biologics and is particularly attractive given the continuous nature of the process (21). Another emerging technology area involves the use of spray drying to produce engineered particles of small molecules and biologics for inhalation (22, 23).

**API:** active pharmaceutical ingredient

**ASD:** amorphous solid dispersion

**SDD:** spray-dried dispersion

**NCE:** new chemical entity

## 2. SPRAY-DRYING PROCESS OVERVIEW

Previous literature has described the spray-drying process in detail. The quintessential resource remains Keith Masters's (2) *Spray Drying Handbook*. According to Masters (2), the four key areas for a spray-drying process are (*a*) atomization, (*b*) droplet–to–drying gas contact, (*c*) particle drying, and (*d*) particle collection. In this review, the second and third areas have been combined under particle formation, because they are intricately linked.

The relationship between process parameters and product attributes is the subject of intensive research that spans the drug development process from early stages to commercialization (24). The in-depth knowledge these studies provide makes precise control of product attributes possible and gives spray drying the adaptability to meet a wide range of problem statements.

The process parameters adjusted for spray drying include temperatures (inlet, outlet, and condenser), flow rates (drying gas and spray solution), and atomization conditions (nozzle type and pressure) (25, 26). These are discussed in more detail in Section 3.3.

### 2.1. Atomization

A variety of atomization techniques can be used in spray drying, and multiple prior references have provided overviews of nozzle attributes and mechanisms of atomization (4, 27, 28). The most applicable nozzles for pharmaceutical applications are two-fluid and pressure-swirl nozzles (4). Two-fluid nozzles are typically used if lower solution flow rates and smaller particles are desired (e.g., to produce powders suitable for inhalation) (29). Although two-fluid nozzles can be scaled up, practical limitations around atomization gas consumption and pressure limit their use at large scale. Pressure-swirl nozzles can achieve higher spray-solution throughputs, are more

**Table 1 Commercially approved spray-dried dispersion pharmaceutical products for oral delivery**

| Trade name | Active pharmaceutical ingredient | Biopharmaceutical Classification System | Polymer | Drug product | Use | Company | Filing year |
|---|---|---|---|---|---|---|---|
| Prograf | Tacrolimus | II | HPMC | Capsule/granules | Organ transplant failure prevention | Astellas | 1994 |
| Micardis | Telmisartan | II | PVP | Tablet | Hypertension treatment | Boehringer Ingelheim | 2000 |
| Crestor | Rosuvastatin | II | HPMC | Tablet | High cholesterol treatment | AstraZeneca | 2002 |
| Intelence | Etravirine | IV | HPMC | Tablet | HIV treatment | Tibotec/J&J | 2008 |
| Modigraf (EU) | Tacrolimus | II | HPMC | Sachet/granules for oral suspension | Organ transplant failure prevention | Astellas Pharma Europe B. V. | 2009 |
| Zortress/ Certican | Everolimus | III | HPMC | Tablet | Organ transplant failure prevention | Novartis | 2010 |
| Incivek (US), Incivo (EU) | Telaprevir | II | HPMCAS | Tablet | Hepatitis C treatment | Vertex | 2011 |
| Kalydeco | Ivacaftor | II/IV | HPMCAS | Tablet | Cystic fibrosis treatment | Vertex | 2012 |
| Noxafil | Posaconazole | II | HPMCAS | Tablet | Antifungal | Assumed Merck Sharp & Dohme | 2013 |
| Harvoni | Ledipasvir/ sofosbuvir | II/III | Copovidone | Tablet | Hepatitis C treatment | Gilead | 2014 |
| Orkambi | Ivacaftor/ lumacaftor | II-IV/II | HPMCAS | Tablet | Cystic fibrosis treatment | Vertex | 2015 |
| Epclusa | Sofosbuvir/ velpatasvir | III/IV | Copovidone | Tablet | Hepatitis C treatment | Gilead | 2016 |
| Zepatier | Grazoprevir/ elbasvir | II/IV | Copovidone/ HPMC | Tablet | Hepatitis C treatment | Merck | 2016 |
| Pifeltro | Doravirine | II | HPMCAS | Tablet | Antiviral/HIV treatment | Merck | 2018 |
| Symdeko | Tezacaftor/ ivacaftor | II/II-IV | HPMCAS | Tablet | Cystic fibrosis treatment | Vertex Pharmaceuticals | 2018 |
| Trikafta | Elexacaftor/ ivacaftor/ tezacaftor | II-IV/II-IV/II | HPMCAS | Tablet | Cystic fibrosis treatment | Vertex Pharmaceuticals | 2019 |
| XTANDI | Enzalutamide | II | HPMCAS | Tablet | Prostate cancer treatment | Astellas/Pfizer | 2019 |

Abbreviations: Copovidone, PVP/vinyl acetate copolymer; HPMC, hydroxypropyl methylcellulose; HPMCAS, hydroxypropyl methylcellulose acetate succinate; PVP, polyvinyl pyrrolidone.

easily scaled, and provide particles with more desirable attributes (e.g., particle size and bulk density) for manufacture of oral dosage forms (3).

For these types of nozzles, atomization begins with the liquid feed solution passing through the nozzle and breaking up into sheets or jets that reduce to ligaments (owing to surface instabilities) and further into droplets (28). Key characteristics of nozzles include droplet size distribution, spray density, spray angle, and velocity. These parameters define how the spray will interact with the drying gas and the final particle size, which is typically an important parameter for performance and manufacturability of the spray-dried product. In addition to previous references, a detailed collection of atomization theory, technique, and applications has been assembled (30), which also contains a specific chapter on the spray-drying process (31).

Much of the extensive research that has been conducted on these atomization techniques has been outside the pharmaceutical field, using pure liquid components such as fuels (28, 32). The behavior of these components contrasts with the complex rheological behavior that can occur with the polymeric excipients often used in pharmaceutical formulations (33, 34). Other authors have evaluated model systems that better simulate pharmaceutical spray solutions, but these model systems still lack the viscoelastic behavior and concentration of polymeric spray solutions used in pharmaceutical applications (35).

A review of two-fluid nozzles was conducted for pharmaceutical applications specific to fluid-bed coating and agglomeration, which serves as a pertinent resource for pharmaceutical spray solutions (36). Keshavarz et al. (37) proposed techniques to study shear and the extensional rheology of weakly viscoelastic solutions of polyethylene oxide solutions. Finally, Fansler & Parrish (38) discussed a variety of experimental measurement techniques that are commonly used to characterize sprays.

## 2.2. Particle Formation

The process of particle formation includes both droplet–to–drying gas contact and particle drying. These processes are linked because final drying behavior is affected not only by the initial spray solution properties but also by the evolving, transient properties during drying to the solid phase. Drying has two major phases: (*a*) free evaporation of solvent from the droplet surface and (*b*) hindered evaporation of solvent through a solid phase that forms during drying (39). Walton & Mumford's (40) single-droplet drying studies demonstrate the impact of drying conditions and material properties on the final morphology of the dried particle. They found that both the chemical and physical nature of the materials in the spray solution determine particle morphology; for example, the rheological properties allow the particles to inflate and deflate or rupture. The study also found that increasing solids concentration resulted in increased sphericity and skin thickness and decreased particle distortion and surface rupture. In another drying study, Vicente et al. (41) used a laboratory-scale spray dryer and combined models for predicting droplet size with mechanistic particle formation, using the results to provide general principles for predicting both particle morphology and size.

## 2.3. Particle Collection

Owing to the high value of pharmaceutical products, high product recoveries are required during spray drying. Reverse-flow cyclones are typically used to collect spray-dried particles from the laboratory to the commercial scale (42, 43). In this design, particle-laden gas from the spray-dryer exit enters the cyclone inlet at the side of the cylindrical segment. A vortex is created inside the cyclone, and centrifugal forces push the particles out to the cyclone's sides and down into the

bottom cone, because their density is greater than that of the gas. The particles are forced out the bottom of the cone, where they are collected in a continuous process, whereas the gas exits through an outlet gas pipe at the top of the cyclone (43).

**SCF:** supercritical fluid

Optimization of cyclone geometry is important to ensure high collection efficiency and address pressure drop constraints of the drying gas flow rate in the spray dryer. The simplest approach is classical cyclone design (44). However, advanced modeling approaches like computational fluid dynamics (CFD) are being increasingly applied to more accurately predict performance and better optimize cyclone design (42, 45, 46). Additional considerations specific to cyclone optimization for inhalation products are discussed in Section 4.3.

## 3. SPRAY-DRYING ASDS

In this section, we review the emergence of SDDs as a leading bioavailability-enhancement technology to address the large numbers of low-solubility compounds in industry pipelines. We describe bioavailability enhancement using ASDs and then focus on SDDs, covering formulation design, process design, application of SDDs to oral drug products, and emerging trends.

### 3.1. Bioavailability Enhancement using ASDs

Approximately 70% of NCEs in the pharmaceutical industry have poor water solubility and, consequently, poor bioavailability, falling into Class II or IV of the Biopharmaceutical Classification System (7, 47). Medicinal chemistry, focused on new therapeutic areas and modalities, now routinely produces NCEs whose high molecular weights and log P values are outside of the Rule of 5 criteria developed by Lipinski and colleagues (48, 49) to predict whether a drug molecule will have solubility and permeability issues. NCEs with these challenging properties have a narrow window of absorption in the small intestine, reducing the amount of drug absorbed into the body and significantly decreasing efficacy (50). Drug-delivery challenges may become so great that these otherwise promising compounds must be abandoned, resulting in lost economic and therapeutic opportunities (48, 49, 51).

Numerous established techniques exist to address drug-solubility issues, including salts, prodrugs, cocrystals, complexation, cosolvents, and ASDs, as well as newer technology areas, such as nanosuspensions, nano- and microemulsions, liposomes, and supercritical fluid (SCF) technologies (52–55).

Of these technologies, ASDs have proven to be the most widely successful and commercially viable option (55). This technology is based on increasing aqueous solubility through amorphization of the crystalline drug compound (56, 57). The amorphous drug form has more free energy than the crystalline drug form, enabling increased drug concentration in the gastrointestinal fluid (47, 51). However, this same free-energy increase makes amorphous forms metastable and is a thermodynamic driver for recrystallization in the solid state (47, 51). ASDs solve the problem of poor solid-state stability by adding a polymer with a high glass-transition temperature ($T_g$), decreasing molecular mobility and diluting pure drug into a homogeneous particle (58). **Figure 2** compares the key benefits obtained from conversion of crystalline drug to stabilized amorphous SDD with addition of a polymer. The functional, polymeric carriers are used to improve the drug release profile (e.g., drug concentration and sustainment) driven by the polymer's properties and have also dramatically improved the manufacturability and stability of ASD formulations (50).

ASDs can be made using various techniques, including the use of solvents, heat, mechanochemical action, or a combination thereof (59). Solvent- and heat-based techniques to form ASDs include emerging technologies such as SCF technology, electrostatic spinning, fluid bed coating,

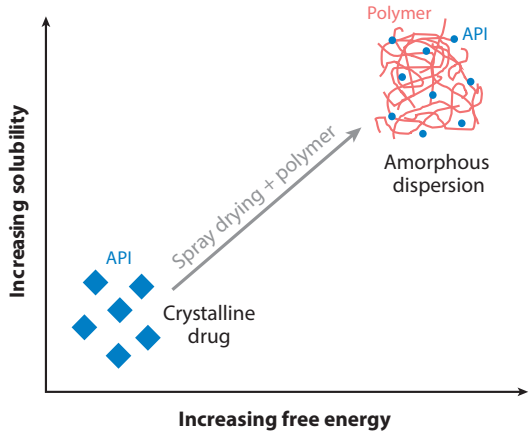


**Figure 2**

Conversion of crystalline drug to an amorphous dispersion. Abbreviation: API, active pharmaceutical ingredient.

freeze drying, thin film freezing, co-precipitation, and melt/quench cooling (59–61). Many of these methods hold promise but still present robustness, reproducibility, and scalability challenges when moving from a laboratory setting to routine commercial production (60).

The two most common processes used to form ASDs are spray drying (to form SDDs) and hot melt extrusion (HME) owing to their scalability, equipment availability, and commercial precedence (59, 62). These manufacturing methods and product performance for ASDs are compared extensively in the literature (63, 64).

The advantages of spray drying are the gentle temperature exposure, the ability to formulate ASDs with higher drug loadings owing to rapid kinetic trapping, and the range of particle properties that can be engineered. HME advantages are that the process is solventless and can generate high product throughputs with minimal space requirements for process equipment.

## 3.2. Formulation Design

Typical spray-drying solutions include an organic solvent, a polymer, and the API. Solutions for spray drying can be either fully dissolved solutions or suspensions. In dissolved solutions, the API concentration is defined by the drug or excipient solubility in the solvent or by reaching the maximum solution viscosity that can be atomized (6). When an amorphous form is not required, suspensions may be manufactured if API solubility is limited or to transfer structural properties of the excipients to the final product (8, 65).

Common polymers used in dispersions include cellulose derivatives, polyvinylpyrrolidone (PVP) and PVP/VA (vinyl acetate), and polymethacrylates. These function both to inhibit crystallization owing to the polymers' high $T_g$ stabilizing the amorphous drug form and to control dissolution by solubility, which may be pH dependent (66). Although $T_g$ is a good reference for stability, drug–polymer interactions, such as hydrogen bonding, can also be important to maintain the amorphous form (67). Multiple references contain comprehensive lists and material properties of dispersion polymers and other commonly used carriers (5, 13, 15, 68–70). Additional publications discuss cellulosic and polymethacrylate chemistries, respectively (16, 71).

**HME:** hot melt extrusion

**PVP:** polyvinylpyrrolidone

Typical organic solvents used for spray drying pharmaceuticals include methanol, acetone, and water, whereas more uncommon organics include tetrahydrofuran and dichloromethane. Binary

blends with water (1% to 30% by mass) are commonly used to maximize drug and excipient solubility (6, 13, 15, 26, 72).

**HPMCAS:** hydroxypropyl methylcellulose acetate succinate

**QbD:** quality-by-design

**PAT:** process analytical technology

Although spray drying solvent selection can be made relatively straightforward by finding a mutual solvent for the API and polymer, the changing composition of the solution as it dries to final SDD particles can cause unfavorable conditions. This can lead to physical instabilities such as phase separation that can initiate recrystallization. Crossing from the single-phase miscible region to the two-phase metastable region is common while manufacturing SDDs, and the drug loading often exceeds the solubility of the drug in the polymer because it is kinetically trapped in the amorphous state before crystallization can occur. Paudel & Van den Mooter (73) studied this phenomenon using SDDs of naproxen and the K25 grade of PVP that were prepared from solvent blends using methanol, acetone, or dichloromethane. Results indicated that solution-state drug and polymer interactions are not directly conveyed upon the solid state, and in the case of naproxen and PVP K25, the addition of a non-solvent (e.g., acetone) for the polymer improved drug and polymer miscibility in the solid state, thereby increasing the physical stability of the SDD.

To create a robust formulation, SDDs and the downstream dosage form must meet critical attributes, including performance, stability, and manufacturability (6). Small-scale screening tools have been developed to help ensure success during the early stages of formulation development. Such small-scale capability is important because of the limited availability and high cost of most NCEs (19, 74).

For effective screening, the formulator should have basic knowledge of the drug properties, such as $T_{g,}$ log P, melting temperature ($T_m$), and solubility profile, which can help predict successful formulations from historical data (51). Friesen et al. (51) tested 139 drug compounds with the dispersion polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS), and his team created a formulation design map using $T_g$ and log P that can be used as a guide for initial formulation selection of SDDs.

Multiple screening tests can determine the drug loading and polymer selection if an SDD is required to achieve the desired bioavailability enhancement of an NCE. Duarte et al. (75) described a methodology using solvent casting at small scale that leverages a thermodynamic and kinetic model to predict phase behavior. The results showed rank order between HPMCAS, PVP/VA, and Eudragit® EPO polymers using film casting, spray drying, and model predictions. Although maximum drug loading was not quantitatively predicted, this approach could be used to aid in selection of polymer or drug loading for SDDs. Equipment advances have made manufacture of SDDs using miniaturized spray dryers an attractive solution, often using less than 100 mg of NCEs (5, 76, 77). Although small-scale equipment exists for formulation screening, significant opportunity exists for scale-down of larger spray dryers by better matching the physical situation of droplet size and drying kinetics at large scale, thus producing similar particle properties and allowing earlier derisking of performance, stability, and dosage form considerations (78).

## 3.3. Process Design

This section describes spray-drying process design in a quality-by-design (QbD) framework, scalability considerations, and process development tools, including the use of process analytical technology (PAT) and modeling.

**3.3.1. Process design in a quality-by-design framework.** Although increasing numbers of spray-dried pharmaceutical products are being commercialized, the need still exists for more

robust, efficient approaches to spray-drying process design, scalability, and, ultimately, product quality assurance (15, 79). The importance of using a QbD approach throughout an SDD product's life cycle, from development to validation, is critical owing to spray drying's multidimensional nature. QbD, as defined by the International Conference on Harmonisation (ICH) (80, p. 18), is a "systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." QbD approaches to spray-drying process development are somewhat new in industry; however, the QbD framework complements the nature of the spray-drying process well. Substantial opportunity exists in continuing to adopt and document these approaches; therefore, further research and modeling around both formulation and process is exceedingly valuable in understanding key spray-drying relationships (81).

**ICH:** International Conference on Harmonisation

**CQA:** critical quality attribute

**CPP:** critical process parameter

**DoE:** design of experiments

A QbD approach to spray-drying process development starts with defining objectives. This means determining the target product profile to ensure the safety and efficacy of the drug product (80). The next step involves understanding the functional relationships between SDD critical-to-quality attributes (CQAs) and spray-drying critical process parameters (CPPs) so a robust control strategy can be developed, drawing upon past product and process experience. **Table 2** provides an overview of commonly identified spray-drying CPPs and general impacts on CQAs (3, 4, 15, 79, 81, 82). The examples shown in **Table 2** may vary for each spray-drying process and product changing the relative sensitivities; however, understanding these cause-and-effect relationships lays a groundwork for a successful control strategy.

Definition of CQAs and CPPs should be an iterative process, using risk assessments and quality risk-management methodology throughout the product life cycle (80). The development of a process control strategy around these factors should begin as early as possible in the product life cycle. The most robust technique when applying a QbD approach to any pharmaceutical process is the development of a design space used to define multidimensional interaction of variables and parameters that demonstrate assurance of quality (80). This approach offers a more thorough understanding of the product and process and includes risk assessments, multivariate experiments, and use of tools such as PAT.

The literature reports successful efforts to adopt a design-space approach in pharmaceutical spray drying, such as the work done by Sanghvi et al. (83) for scale-up of a telaprevir SDD (Incivek®). Telaprevir, a recent commercial product, leveraged a QbD approach with design of experiments (DoE) to define a design space across the entire process train and at varying scales. A total of 148 trials were performed to inform the DoE, and ultimately, a commercial process was identified to produce high-quality, low-variability spray-dried product. Gaspar et al. (24) presented another case study describing a statistical DoE approach broken up into three stages (screening, optimization, and robustness) to create a production-scale spray-drying design space. After executing the three-stage DoE process and performing more than 40 trials, they developed

**Table 2 Example spray-dried dispersion critical process parameters impact on critical quality attributes**

| Example critical process parameter (with increase) | Example critical quality attribute (typical response) | | | |
|---|---|---|---|---|
| | Particle size | Bulk density | Stability in amorphous state | Residual solvents |
| Inlet/outlet temperature | 0 | ↓ | ↓ | ↓ |
| Drying gas flow rate | 0 | ↓ | ↑ | ↓ |
| Nozzle pressure | ↓ | 0 | 0 | ↓ |
| Solution feed rate | ↑ | ↑ | ↓ | ↑ |
| Relative saturation | 0 | ↑ | ↓ | ↑ |

a design space. These types of rigorous empirical approaches, although successful, would benefit from further mechanistic understanding and fundamental modeling to save on experimental time and material needs.

Laboratory bench-scale approaches have also been evaluated to develop a design space for spray-drying processes using DoE. For instance, Lebrun et al. (84) used a Bayesian statistical approach in which CQAs for a pulmonary SDD product were tied to relevant process parameters. Finally, Kumar and colleagues (85) presented an approach for applying a full factorial design and surface methodology to understand a process for spray drying crystalline nanosuspensions. Overall, this study demonstrated the usefulness of a DoE approach and provided helpful insight into spray-dry processing of nanosuspension formulations. These examples proved useful in determining functional relationships during early development but highlight the need for further research to apply a design space approach across scales.

**3.3.2. Process scalability.** Development of an accurate design space for spray-drying process scale-up in the pharmaceutical arena has been a recent area of significant work and opportunity. Maintaining physical stability of the amorphous form while producing materials that are amenable to robust manufacturing and performance of the dosage form process is critical. Spray-dryer scales range from bench-scale feasibility units that produce milligrams of product to large-scale commercial units capable of kilogram to metric-ton throughputs. As described below, the use of scale-independent or dimensionless parameters and innovative modeling techniques, as recommended by the ICH, can improve scale-up efforts (80). Changes in manufacturing equipment at larger scale (e.g., nozzle size, chamber size, cyclone efficiency), shifts in thermodynamics (e.g., process temperatures), and differences in particle dynamics make fundamental understanding of these scale factors and functional product/process relationships key.

Spray-drying process and product functional relationships can be related through scale-independent factors and/or fundamental models in key areas such as drying and thermodynamics or atomization and particle formulation (4, 81). Examples of such factors found in the literature include (*a*) specific drying ratio (i.e., the ratio of spray solution feed rate to drying-gas flow rate), (*b*) bulk drying-gas temperatures (i.e., inlet and outlet temperature), (*c*) solvent saturations (i.e., condenser temperature), and (*d*) droplet size (3, 4, 83, 86). Generally, scaling by keeping these factors constant can be an effective starting point. However, equipment changes during scale-up require significant experimentation, rigorous modeling, or a combination of both. Spray-dryer equipment-scale impacts can include differences in (*a*) the solvent vapor content of the inlet gas stream in recycle operation, (*b*) nozzle spray plume densities, (*c*) mixing of droplets and drying gas, (*d*) droplet and particle residence times, and (*e*) particle collection efficiency and yield (3, 81, 86). Experimentation to reduce risk in these areas may be limited by time and material availability, so it is ideal to leverage data from the smallest applicable scale to inform scale-up risk (87). As discussed below, rigorous modeling (e.g., CFD modeling) can significantly aid in scale-up and initial process-space definition.

Thybo et al. (86) attempted to scale up a spray-dried acetaminophen formulation from pilot to production scale (~20× increase in spray solution flow rate) by matching droplet size distribution across scales, assuming a shrinking sphere model and matching two-fluid nozzle air-to-liquid ratio. They found that scaling up the process using this factor alone was not sufficient to produce particles of the same size across scales. The shifts in particle sizes were attributed to a change in droplet size, droplet drying thermodynamics, and particle residence time at larger scale. Particle size was matched after adjusting air-to-liquid ratio and solids composition (86).

Other approaches, such as that described by Gil et al. (4), use a thermodynamic scaling approach coupled with a shrinking-sphere model to predict resulting droplet/particle size. In this

case, droplet/particle size was not constrained to match between laboratory and commercial scale. Relative saturation was used as the scale factor to keep residual solvent levels constant across scales owing to product physical-stability constraints. Thermodynamic modeling was used to determine scale-up parameters to achieve the same relative saturations. Results of the study compared well with predictions based on lab-scale data to meet the intended goal of derisking thermodynamic product impact at the target scale. In this case, droplet size was intentionally allowed to increase across scales, but this is not always allowable if a target particle size has been identified before scale-up.

A combined scale-up methodology, such as the one Dobry et al. (3) proposed, uses thermodynamic modeling and direct droplet measurements from a phase doppler particle analyzer to determine an initial spray-drying process space. The methodology uses a fundamental modeling approach as well as offline bench-scale experiments to determine a thermodynamic space that is limited by formulation constraints (e.g., specific drying ratio, inlet/outlet temperature, and solvent saturation). This QbD-style approach attempts to limit the use of material by determining a scale-independent spray-drying process space that will yield acceptable product prior to at-scale screening experiments. The intent is to lay a groundwork for a robust design space while shortening timelines and limit potentially exhaustive statistical treatments (3). There are drawbacks to such an approach, as it may vary depending on problem statement, still requires experimental verification, and still does not directly address some of the previously described impacts of scale-up.

Overall, multiple approaches are taken in the literature to scale up spray-drying processes, with varying success depending on specific product needs. As understanding of the process continues to grow, scale-up should be a focus area, with a goal of making approaches and results more predictable and fundamental, leading to reduction in development time, cost, and API needs.

**3.3.3. Process development tools.** Various tools exist that can aid in developing a robust and scalable spray-drying process and ensuring that both process and product meet exacting quality standards. The most significant are PAT and modeling, which are discussed below.

***3.3.3.1. Process analytical technology.*** PAT is a leading component in a successful QbD approach, but its implementation in pharmaceutical spray drying has been limited. PAT is defined as a system for ensuring product quality by controlling a manufacturing process through measurements of critical quality and performance attributes (80).

Implementation of PAT for spray drying has focused on in-line particle sizing to determine how processing conditions impact particle size distribution. Particle size is frequently considered a CQA and has the potential to impact SDD performance and dosage form manufacturability. Generally, this method has provided rapid feedback regarding changes in process and product, but its utility has been constrained owing to equipment fouling and maintenance and reduced accuracy compared with at-line methods (88, 89).

PAT also has been explored in other areas of the spray-drying process, such as for solution preparation. For instance, near-infrared spectroscopy can be used to determine an endpoint for the dissolution of raw components (e.g., API, excipient), which directly impacts product potency. Near-infrared spectroscopy is a suitable quality-control method for pharmaceutical feedstocks but can be challenging to implement owing to sampling complexity (90). In summary, a significant opportunity exists to develop effective PAT methods for ensuring product quality and process control through direct measurements of typical SDD CQAs identified previously.

***3.3.3.2. Modeling.*** Modeling techniques have been useful in expanding knowledge about spray drying. Generally, these models are focused on either equipment or material models (91).

Equipment models are concentrated on spray-dryer performance and process conditions. These are straightforward mass and energy balances, with the primary unknown being the heat-loss coefficient of the specific equipment. Material models have evolved significantly and can be classified as (*a*) empirical or semiempirical models (e.g., correlations of product properties to process parameters, characteristic drying-curve models, or reaction engineering approach models) or (*b*) mechanistic or continuous species transport models, with or without population balance to provide radial distribution of components inside the dried particle (92, 93).

All these approaches have been demonstrated successfully and provide useful insight into the interaction of the process and formulation. The main trade-offs between model types are specific to complexity and precision. **Table 3** summarizes a range of purposes for these models and the approaches that have been evaluated recently in the literature (94–101).

The largest impact to predicting the influence of scale-up on final particle attributes has come from CFD simulations and continuous species transport approaches. Ploeger et al. (100) summarized the application of CFD to understanding the specific changes that occur during scale-up related to droplet break-up during atomization and drying gas droplet interaction. This allows for a quantitative approach to better understanding differences in the drying process across scale. Mechanistic approaches, as detailed by Abdullahi et al. (98), are also critical to better understanding the final distribution and state of components in the dried particle; for example, the authors included terms to account for mannitol recrystallization. Future work will likely enable coupling of these two approaches, allowing increased predictability during scale-up.

***3.3.3.3. Experimental validation.*** In parallel with spray-drying model development, experimental validation of models continues to be a large area of focus. Although spray-drying experiments can be designed at scale to determine key attributes, the complexity of the drying process and sample collection technique makes in-process interrogation challenging. Therefore, single droplet drying experiments have been a focus for model validation and mechanistic understanding. Both Boel et al. (102) and de Souza Lima et al. (92) summarize the typical techniques used to study single droplet drying, which include filament suspension, acoustic levitation, aerodynamic levitation by air flow, free-fall, and hydrophobic surface. However, to enable observation time and measurement in single droplet drying experiments, droplet sizes must be one to two orders of magnitude larger than during spray drying, resulting in a drying rate that is approximately two to four orders of magnitude slower.

Progress over the past decade has also benefited from advanced analytical tools such as focused ion beam–scanning electron microscopy and energy dispersive X-ray spectroscopy, which provide the enhanced resolution needed for particle-level understanding (103). This can be particularly useful when the bulk properties of materials may not be indicative of potential failure mechanisms (e.g., inhomogeneity of components in dried particles). Poozesh et al. (103) observed differences between particle size fractions for bulk morphology, but also homogeneity for felodipine and PVP, where the smallest particles ($<10$ μm) were homogeneous but the largest particles ($>20$ μm) showed evidence of phase-separated felodipine near the particles' surface.

Work is also under way to predict and measure key physical properties to enhance model accuracy. For models that predict particle drying after crust formation, drying-time predictions have been faster than what is observed experimentally. To better understand this phenomenon, Sturm used previous modeling work that applies the Vrentas–Duda free-volume theory to account for the change in diffusion coefficient as a function of concentration below the $T_g$ of the

**Table 3 Modeling approaches used for spray drying**

| Purpose | Approach | Results | Example |
|---|---|---|---|
| Define process space of spray dryer and scale-up | Mass and energy balance | Model technique applied from lab to commercial scales, minor scale dependence on heat loss. Initial process space that serves as a basis for design space definition based on formulation constraints or properties defined by spray-drying trials. Demonstrates and verifies the technique at commercial scale. | Lisboa et al. (94) |
| Predict particle size, density, and moisture content | Empirical droplet model, mass and energy balance | Empirical atomization model that was experimentally verified for droplet size input into a drying model. | Cotabarren et al. (95) |
| Compare CDC and REA modeling approaches to predict bacterial activity and moisture content | CDC, REA | Comparison of REA and CDC approaches for moisture content and inactivation of spray-dried bacteria. | Patel & Chen (96) |
| Assess impact of droplet size on drying kinetics | REA | Model generating a "material-specific master activation energy curve," which was applied to different droplet sizes and temperatures. An approach was proposed to extend the model to additional solids loadings. | Fu et al. (97) |
| Predict crust formation and particle size | CST with population balance | Provides insight into radial concentration gradient and locking point of particle. Progress toward predicting particle morphology, but recommend further optimization of drying after crust formation. Single-droplet drying experiments with an acoustic levitator using mannitol or mannitol/PVP in water. Includes nucleation and growth for mannitol crystallization during drying. | Abdullahi et al. (98) |
| Predict crust formation and particle size | CST | Single-droplet drying experiments with acetone or methanol and HPMCAS-L (using pendant and acoustic levitators). Evaluated onset time for $T_g$ (skin formation) to occur. Applied dependence of mutual diffusion coefficient as a function of solvent and temperature relative to $T_g$. | Sturm et al. (99) |
| Scale-up | CFD | Comparison of spray-dryer scales at nominal drying-gas flow rates of 110 and 750 kg/h. Injected predetermined droplet distribution, velocity, angle, and break-up length from LISA model. | Ploeger et al. (100) |
| Predict droplet temperature, moisture content, and size as a function of time | CFD | CFD simulations to compare results for residence time to drying model simulations for particles dryness. User-defined droplet size distribution discretized for drying model input. Defined concentration of crust formation followed by first-order falling rate drying. Likely underpredicts actual drying time. | Pinto et al. (101) |

Abbreviations: CDC, characteristic drying curve; CFD, computational fluid dynamics; CST, continuous species transport; LISA, linear instability sheet atomization; PVP, polyvinylpyrrolidone; REA, reaction engineering approach.

solvent-containing polymer (104–106). Advancement of experimental techniques in conjunction with increased resolution of analytical techniques will further drive research and provide fundamental material and transport properties, because there has been little published on this area for pharmaceutically relevant systems.

### 3.4. ASDs For Oral Solid Dosage Forms

Additional consideration of the composition and manufacture of SDDs and other ASDs relates to formulation of the final drug product for oral delivery. This area of research has lagged spray-drying process development but is a critical step in developing a final drug product. The most common oral dosage form for ASDs is a tablet. Démuth et al. (107) compiled a comprehensive review that focused on downstream processing aspects of ASDs, including manufacturability (flow and compression) and formulation (tableting excipients). Drug loading, excipient type, and moisture sorption all can significantly impact flow and mechanical properties, which have been evaluated for PVP/VA and HPMCAS polymers (63, 108, 109). Comparing the manufacturing of ASDs by HME or spray drying, Davis et al. (110) found SDDs had poor flow properties and good compressibility—both of which can be modified by adding tableting excipients. Ekdahl et al. (111) described a method to co-optimize the properties of spray-dried particles with the desired properties of the final dosage form.

A significant area of research centers on maximizing the dose that can be incorporated into a single dosage form unit (e.g., a tablet). Limitations in this area can be a common downside to ASD formulations. Mudie et al. (112) recently proposed a solution involving use of a polymethylmethacrylate copolymer (Eudragit® L100, Evonik) with an exceptionally high $T_g$ (~170°C dry) to manufacture a dosage form with double the drug loading that is possible using a conventional approach of formulating SDDs into tablets.

## 4. EMERGING TRENDS FOR PHARMACEUTICAL SPRAY DRYING

As described above, significant work has been performed to expand the fundamental knowledge and utility of spray drying for pharmaceutical applications. New research is addressing information gaps in formulation and process development, and numerous tools and models are under development to aid formulators and process engineers as they advance promising NCEs from discovery to commercial production.

### 4.1. New Capabilities for Processing Challenges

Several trends are driving innovation in this area: (*a*) industry changes that require more flexibility in processing capabilities, particularly regarding batch sizes; (*b*) increasing demands because of the challenging characteristics of NCEs; and (*c*) emerging applications.

This focus is driven by market demand for improved medicines and by growth in new drug-delivery technologies and therapeutic areas. A paradigm shift is resulting in attention to smaller patient populations, owing in part to a focus on orphan indications (conditions that affect fewer than 200,000 patients) and the trend toward personalized medicine (113).

In 2019, 44% of the US Food and Drug Administration's Center for Drug Evaluation and Research drug approvals were for rare or orphan diseases (114). This change has challenged traditional scale-up mentality, in which a commercial product would require a large spray dryer fully dedicated to a single product. Instead, this trend necessitates use of spray-drying process and equipment trains that are much more adaptable, as well as application of continuous processing techniques with much smaller equipment footprints. Although the spray-drying process is inherently continuous, most drugs are manufactured using a solution tank that defines the batch size of the product. A continuous method of preparing spray solutions must be implemented to make the process truly continuous. One solution, proposed by Vicente et al. (115), uses separate streams of product components (e.g., solvent, suspension) that are then combined using either a

single microreactor or multiple microreactors in series prior to atomization. Use of microreactors offers several advantages: (*a*) It reduces the API particle size, which increases the API dissolution rate, and (*b*) it increases the temperature of the spray solution without the need to apply external heating, allowing for higher drug loading in solution.

## 4.2. New Capabilities for Challenging APIs

Challenges in manufacturability, given the chemical properties of emerging NCEs, also require further innovation. One area of focus is on the class of compounds referred to as brick-dust compounds, which are generally identified as having a crystalline $T_m$ over 200°C, exceptionally poor aqueous solubility, and poor organic solubility. Frequently, manufacturing processes for these compounds require use of solvents that are less preferred owing to toxicity, environmental handling, equipment compatibility, and disposal considerations. Although use of these solvents may be suitable during formulation screening or early-phase clinical manufacture, further scale-up requires additional consideration of process design and formulation.

One solution is using a temperature-shift process in which the spray solution is heated by >100°C to increase the solubility of the drug significantly just before spray drying (116). In this process, a suspension of API and polymer is prepared at room temperature in the spray solvent. The suspension is transferred to the spray dryer under high pressure and passes through an in-line heat exchanger that rapidly heats the solution to a temperature that allows the API to dissolve before entering the atomizer. Residence time in the heat exchanger and crystalline API particle size are critical to balance the rate of dissolution versus the rate of potential degradation, as has been discussed in similar applications (117). Developing new technologies to enable the spray-drying process will be important to meet the evolving chemical properties of new APIs.

## 4.3. Emerging Applications and Technologies

Emerging applications and technologies represent a broad area of growth for spray drying. Significant work is being done in two new application areas: (*a*) engineered particles for inhalation and (*b*) spray-dried biologics. In the new technology area, advances are also being made in SCF-assisted spray drying for inhalation products and spray freeze drying for biologics.

**4.3.1. Engineered particles for inhalation.** A growing segment of the pharmaceutical industry is focusing on inhaled powders, because these therapies offer reduced variability and side effects, improved efficacy, and improved patient adherence (22). Lung delivery is an attractive way to effectively administer drugs that require local or systemic circulation owing to its ease of administration and increased patient compliance (118). However, local delivery of treatments specific to the lung has been the primary focus for developing inhaled products. Particle engineering approaches using spray drying have demonstrated both better dosing characteristics to the deep lung and dosing consistency when compared with conventional lactose carrier formulations (8, 119, 120). Although the first commercially approved spray-dried inhalation platform product was Exubera using the PulmoSol™ platform in 2006, tobramycin delivered with the TOBI® Podhaler® and PulmoSphere™ platform was the first commercially successful spray-dried inhalation product (121). **Table 4** describes current inhalation platform technologies developed for spray drying (121, 122). Bronchitol®, spray-dried mannitol for the treatment of cystic fibrosis, has been approved outside of the United States and is nearing approval there as well (123).

Reports of spray drying scale-up to manufacture particles for inhalation are not common in the literature because prototype formulations can be manufactured using laboratory-scale

**Table 4 Spray-dried platform technologies for inhalation**

| Platform | Commercial products | Description |
|---|---|---|
| PulmoSol™ | Exubera (insulin) | Sodium citrate dihydrate, mannitol, sodium hydroxide, and glycine used as matrix excipients |
| Technosphere® | Afrezza® (insulin) | Particle matrix of fumaryl diketopiperazine, prepared by crystallization at low pH, forming nanoparticle assemblies with electrostatically adsorbed insulin followed by pelletization and lyophilization into respirable microparticles |
| PulmoSphere™ | TOBI® Podhaler® (tobramycin) | Emulsion- (TOBI®), suspension-, or solution-based process with $CaCl_2$ and 1,2-distearoyl-sn-glycero-3-phosphocholine as excipients creating low-density porous particles |
| iSperse™ | Not applicable | Proprietary technology consisting of small, dense, and dispersible particles |

equipment. However, scale-up knowledge is essential to ensure formulation advancement. For instance, maintaining particle size distribution and particle density during scale-up is critical for the performance of these formulations. Close attention must also be paid to atomization and product collection as processes are scaled up. To optimize atomization, multiple lower-throughput nozzles that produce the desired droplet size distribution can be numbered up to provide the desired spray capacity (124). Processing of different solutions at the same time can also be employed with this technique, leading to improvement of blend uniformity (125). To improve product collection of fine particles, two approaches are commonly taken: (*a*) optimization of a single cyclone separator based on product and process constraints or (*b*) use of multiple smaller cyclones in a parallel array (126). The latter approach increases the efficiency of the individual cyclones by reducing their size while maintaining the desired pressure drop of the process equipment (127).

**4.3.2. Biologics.** Approvals for biologic therapies have increased significantly over the past decade. In 2018, based on sales, 9 of the top 10 therapies were injectable biologics (14, 20). These therapies have challenging delivery requirements owing to biologics' size, charge, hydrophilicity, and susceptibility to acid and enzyme hydrolysis (128). Biologic therapies also typically require cold-chain storage to ensure stability, potency, and efficacy (119). Proteins, peptides, viruses, bacteria, small interfering ribonucleic acids, and antibodies have been successfully spray dried in research settings.

Although significant research has been done on spray drying biologics, the only commercially approved spray-dried products to date are Raplixa™, a combination product of spray-dried fibrinogen and spray-dried thrombin, and Exubera® and Afrezza®, both spray-dried insulin products (23, 121, 129). While the particles are not exposed to high temperatures for long periods owing to evaporative cooling, proteins may denature, which leads to further instability and aggregation (130). In addition to drying stresses (e.g., dehydration and temperature), shear forces are exerted on the spray solution during atomization, and the large surface area of the droplets provides the protein access to the hydrophobic air–water interface, leading to additional chances for denaturation.

**hGH:** human growth hormone

Mumenthaler et al. (131) conducted a feasibility study on spray drying recombinant human growth hormone (hGH). The hGH, which is particularly sensitive to aggregation, showed that atomization alone substantially increases insoluble aggregates, but soluble aggregates formed from a combination of interfacial and thermal stress. The addition of 0.1% Tween® 20 (a polyoxyethylene sorbitol ester) reduced aggregation by approximately 90%. Furthermore, spray drying hGH without Tween 20 resulted in a similar amount of insoluble aggregates (~5%) as a solution that

was atomized and collected as a liquid, indicating that interfacial stresses may dominate thermal stresses.

Solid forms of biologics manufactured by spray drying have great potential to provide room-temperature stability to drug substance and drug product formulations (132). Controlled or sustained release represents an important growing need in this area. Biologics are often delivered parenterally to achieve desired bioavailability; however, their short half-life requires frequent dosing to maintain an efficacious concentration. Spray drying has been used to produce microparticles for sustained release (133).

The most-studied spray-dried biologics are proteins and peptides, which have successfully been spray dried at laboratory scale using trehalose, sucrose, mannitol, amino acids, hydroxypropyl methyl cellulose, chitosan, and Carbopol® (a crosslinked polyacrylic acid polymer) microspheres (128, 134–136). Sugars have been shown to stabilize proteins after the drying process because the interaction is like that of water–protein interactions (137–139). Other typical excipients that are added include buffers to maintain pH and isotonicity upon reconstitution and surfactants to reduce the adsorption of proteins to the air–water interface.

One current area of focus is creating high-concentration solutions to minimize the injection volume while maximizing the dose of monoclonal antibodies required for parenteral delivery. Challenges related to solution viscosity and stability with liquid-based formulations have arisen with this approach. Producing a spray-dried powder for immediate reconstitution and injection provides a potential way to further expand this delivery space.

Literature examples of process scale-up are almost nonexistent for spray drying biologics in the pharmaceutical area. One exception is a study by Gikanga et al. (140) that compared the effects of using a laboratory-scale spray dryer (Anhydro MS-35) scaled up to a pilot-scale dryer (Anhydro MS-150). This represented an approximate 4× increase in drying capacity and volumetric mean residence time in the drying chamber. No substantial change was observed between powders made at the two scales, but use of the larger dryer did lead to increases in turbidity and high-molecular-weight species indicative of insoluble aggregates.

Other focus is directed at aseptic spray-drying processes, which are required because biologics are delivered primarily through injection or infusion. Currently, only one company offers this service globally, including development and manufacture under Good Manufacturing Practice conditions (141).

**4.3.3. New technology areas.** To address emerging pharmaceutical industry needs, researchers are examining several new technologies: (*a*) spray freeze drying for biologics and (*b*) SCF-assisted spray drying for inhalation products. Spray freeze drying involves atomizing the feed solution, freezing the droplets into particles (typically, in liquid nitrogen), and sublimating the remaining solvent (142). Benefits of this process include the use of lower temperatures than in spray drying and faster solidification time than in traditional freeze drying, owing to the increased surface area of the droplets (143). The drawbacks to spray freeze drying are higher equipment and manufacturing costs and lack of commercial precedence (142). However, spray freeze drying has been used to produce the Nutropin Depot® product for controlled release of hGH from microparticles (144). Kennedy et al. (145) evaluated atomization in a chilled extraction solvent to eliminate the engineering challenges with liquified gases used in spray freeze drying and showed similar physical properties for poly(lactic-*co*-glycolic acid) microparticles and a significant reduction in residual solvent levels.

SCF processing applications have also generated significant interest recently. A potential advantage to this technology for biologics is local cooling effects owing to the expansion of SCFs. SCF-assisted spray drying was assessed using a DoE to produce engineered particles of trehalose

and leucine suitable for inhalation (146). This process involved immediate mixing of the spray solution and supercritical $CO_2$ with a static mixer immediately before it was sent to the two-fluid nozzle. This approach resulted in a design space to control fine particle fraction based on spray solution feed rate and spray-dryer inlet temperature. Shoyele & Cawthorne (147) provide additional discussion of SCF-assisted atomization for inhaled biopharmaceuticals. Although significant advances have been made in identifying new technologies based on spray drying, continued efforts toward reduction to practice and commercialization are a key focus for ongoing work.

## 5. SUMMARY AND CONCLUSIONS

Spray drying has evolved into a mature, versatile technology to address the changing landscape of drug delivery needs. It is an ideal technique to convert liquids into solid-state particles as well as a platform to address challenging molecules that require enhanced solubility to achieve efficacy. Owing to its wide range of formulation and process parameters, spray drying has been applied to small molecules and biologics for oral, inhalation, or injection delivery routes. Quantitative scale-up of spray-drying processes continues to be improved and is a focus of ongoing academic and industrial research. Significant work also continues to improve capabilities to quantitatively predict the impact of process parameters on formulation attributes. In addition, extension of spray drying to new drug-delivery applications and technologies will continue to evolve and shows significant promise.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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