Advanced Troubleshooting for Spray Drying of Pharmaceuticals

INTRODUCTION

Spray drying offers multiple opportunities for improving the formulation of both poorly soluble pharmaceutical compounds and inhaled drug products. However, while spray drying is a well-established manufacturing operation, it presents certain challenges throughout the drug development process. This article examines critical aspects of formulation development for spray-dried powders and the risk mitigation strategies that may be applied to address a range of common issues during production.

FUNDAMENTALS OF SPRAY DRYING

Spray drying is a process used to convert a solution containing dissolved solids into a fine powder. It is proven to be particularly valuable for the creation of amorphous solid dispersions (ASDs) of drug substances to enhance their solubility and oral bioavailability, as well as in the development of improved formulations for inhaled drug products.

Creating amorphous forms of active pharmaceutical ingredients (APIs) involves spray drying solutions of organic solvents containing the drug and polymers. As solution is pumped into the spray drying chamber through a nozzle, finely atomized droplets are created and rapidly dried in a stream of hot gas. The resulting fine powder, often referred to as a spray-dried dispersion (SDD), is collected in a cyclone.

An understanding of how the solution is atomized and how quickly it is dried is crucial to controlling the spray drying process and the properties of the resulting powder.

CONSIDERATIONS IN EARLY PHASE DEVELOPMENT

Key goals in early phase drug development (preclinical to first-in-human studies) include assessing drug safety with increasing doses, demonstrating initial signs of efficacy in animal models, and ultimately proceeding into the clinic, often while managing an often-limited supply of API.

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For APIs with poor solubility, SDDs are often used to improve drug solubility and oral bioavailability to reach sufficient and consistent systemic exposure in order to collect high quality *in vivo* data. At this stage, the goal of SDD development is to identify drug/polymer combinations that are capable of delivering enhanced dissolution and robust physical stability, ideally at high drug loads. An SDD development scheme can be carried out using API sparing techniques that minimize waste and ensure efficient use of limited API. When selecting the drug loading, polymer, and solvent system, developers must consider the effects of their choices on the ability to produce the SDD-based drug product at increased scales.

Solvent Selection

Selecting the solvent system for use in spray drying is an important early step in developing the SDD protocol. Initial screening involves examining multiple organic solvents with the goal of achieving at least 50 mg/g of API in solution (around 5% drug load) and maintaining stability for three days. The extended stability of the API in solution is important for late-stage development and manufacturing as spray drying a single batch at commercial scale could potentially take several days to complete. If this proves impossible with using only one solvent, the solubility and stability of the API can be tested in mixtures of two solvents at 20/80 and 80/20 ratios. After an appropriate system is identified, initial spray drying can proceed.

Commonly used solvent types include alcohols (e.g., ethanol, isopropanol), ketones (e.g., acetone), chlorinated solvents (e.g., dichloromethane), and esters (e.g., ethyl acetate). Key considerations influencing solvent choice include passing the residual solvent specifications that must be met in the finished product as well as solvent compatibility with the spray drying equipment. Finally, the solvent boiling point will be integral to developing the spray drying conditions to produce the SDD.

Polymer Selection

Another critical component of SDD development is polymer selection, for which there are two key aspects to consider: the need for a polymer that will both stabilize the amorphous state of the API; and one that maintains drug supersaturation following dissolution.

An initial step in the polymer screening process is to use film casting to examine combinations of the drug with a range of polymers at different drug loadings to see which produce amorphous films. Stress testing then determines which ones remain amorphous upon storage.

The next step involves identifying a polymer that can maintain drug supersaturation following dissolution by performing a liquid-liquid phase separation screen using fiber optic micro-dissolution equipment. Here, polymer is pre-dissolved in the dissolution medium at a known concentration. The drug, dissolved in a water-miscible organic solvent at high concentration, is then titrated into the dissolution medium. Monitoring response to ultraviolet light enables determination of the point at which the drug comes out of solution, either through crystallization or phase separation, permitting the calculation of how much polymer is required to keep the drug in solution.

The combination of these two experimental approaches helps to determine which polymers at which drug loads will be able to create physically stable SDDs capable of maintaining supersaturation of the drug in solution. Some of the polymers commonly used to generate SDDs include hydroxypropylmethyl cellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), polyvinylpyrrolidone (PVP), polyvinylpyrrolidone vinyl acetate (PVP-VA), and Eudragit® L100-55 (Evonik Industries AG).

The viscosity of the resultant solution for spray drying is also important. High polymer concentrations often result in high viscosity solutions, potentially creating issues around atomization. In addition, the solution should ideally have a total solids content of around 10% to ensure the manufacturing process is efficient.

Evaluation of data from the above studies provides the initial leads for laboratory-scale testing. Creation of SDDs using small scale spray dryers, followed by their characterization, allows for the identification and selection of solid dispersions that are appropriate for scale-up for phase 1 clinical supply.

SCALE-UP FOR PHASE 1 CLINICAL SUPPLY

Initial development work on lab scale spray dryers is important for optimizing the spray solution for solids content and confirming the composition of the solid dispersion. When moving to a larger spray dryer to manufacture SDD for phase 1 clinical studies, it is important to explore different process parameters, such as inlet and outlet temperatures, nozzle choice, atomization pressure, and feed rate, and to then correlate the results with the critical quality attributes (CQAs) of the SDD.

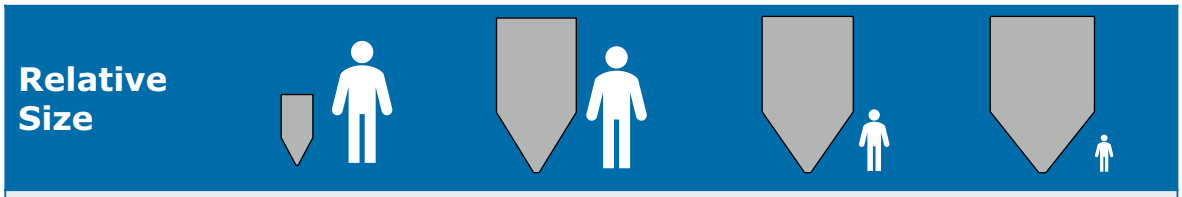
Making efficient use of the API, typically scarce at this stage, is critical, and demands a clinical manufacturing process which delivers high yield and minimal loss to fines. Additionally, when transferring from lab to clinical scale, the secondary drying technique becomes important since there may be a switch from a lab-scale vacuum oven to a rotary dryer to facilitate faster drying. Once early-phase clinical supply is established, the SDD can proceed forward for further product development.

LATE PHASE SCALE-UP AND TROUBLESHOOTING

When transitioning from early-phase to late-phase clinical manufacturing, key goals include increasing production capacity, optimizing CQAs and mitigating risk. Here, the use of science and experience-driven scale-up methodologies helps de-risk scale-up and makes troubleshooting easier should problems occur during manufacturing. It is imperative to start linking material attributes and process parameters to the desired product quality attributes and to understand the differences in throughput, key processing parameters and capital equipment size (**FIGURE 1**) as a program is scaled up. Conducting risk assessments throughout the entire process helps mitigate any challenges that may arise.

The scale-up process can be divided into easily solvable thermodynamic elements (e.g., calculating outlet saturation, selecting inlet/outlet processing temperatures, calculating droplet residence time, and determining recycled gas composition), and empirically determined elements (e.g.,

FIGURE 1: Spray dryer scale comparisons.



Dryer Scale	Feasibility	Pilot	Production	Large Capacity
Gas Flow	500 g/min 30 kg/hr	1600 g/min 100 kg/hr	6000 g/min 360 kg/hr	21000 g/min 1250 kg/hr
Gas Loop	Open	Open/Closed	Closed	Closed
Nominal Solution Flow	30 g/min	100 g/min	400 g/min	1400 g/min
Nozzle	2-Fluid	High Pressure	High Pressure	High Pressure
Particle Size Tunability	Limited	Moderate	Significant	Significant

atomized droplet size, cyclone efficiency, SDD sticking in the dryer, and powder flowability). It helps to think in terms of the impact of starting material attributes and the process parameters on the SDD product attributes.

For example, the API is most often required to be completely amorphous in the finished SDD to achieve the desired solubility enhancement. Polymer selection and API solubility in the solvent blend are key material attributes that affect the physical state of the API in the SDD. Critical process parameters that can have an impact on the presence of crystalline API in the SDD are outlet saturation and outlet temperature, which control the drying kinetics of droplets. Another example of a product attribute that needs to be controlled is particle size, as it can influence the dissolution and flowability of the spray dried powder. Particle size is impacted by polymer selection and excipient variability on the material attributes side, and by process parameters such as outlet saturation, outlet temperature, solids content and nozzle selection. Excipient variability, often overlooked, is an important consideration during late-stage development, especially when there is a need to evaluate secondary suppliers of excipients. With variations in grade from different vendors, understanding the impact of any changes in excipient properties on product attributes is crucial.

IMPORTANCE OF RISK ASSESSMENTS

Risk assessments are valuable tools that help when prioritizing resources and providing quick references for troubleshooting. The most basic form of risk assessment is *risk ranking*, which examines the severity of a risk and likelihood of occurrence. Determination of risk level then guides prioritization of time and the level of control required for risk mitigation.

For example, API degradation in solution exemplifies a high-risk event, potentially resulting in an out-of-specification product, and as a result demands tight control. Alternatively, poor cyclone efficiency would present a much lower risk if enough material can still be produced to meet program requirements.

Material processability challenges and equipment-driven issues can also be addressed using risk assessments and troubleshooting guides. For example, SDDs may have issues with powder flowability, a product attribute of the spray-dried intermediate that requires control and troubleshooting during scale-up. Poor flowability generally arises from the low bulk density and small particle size of materials. The issue can be identified through physical characterization of the SDD and clear communication between the spray drying and solid oral dosage development teams to understand its impact on the ability to produce the final product. Overcoming poor flowability of an SDD can be achieved by adjusting atomization to create larger droplets, altering the drying conditions to produce more dense powders, and optimizing the spray drying solution by increasing solids content, if feasible.

It is important to understand that if problems are identified and troubleshooting is required, there are always elements of the formulation or process that can be changed to achieve the desired product attributes and optimize process efficiency.

SPRAY DRYING LIPID-BASED FORMULATIONS

In drug delivery, lipids offer the benefits of low toxicity and good biocompatibility, and spray drying is increasingly being used for the provision of carrier-free delivery of dry powders for inhalation. Here, the use of readily inhalable lipid microparticles avoids many of the drug delivery inefficiencies associated with conventional carrier particles. Lipids are known to enrich the surface of the particle during spray drying, enhancing aerosolization and improving dry powder inhaler (DPI) performance. Spray drying also allows for tuning of different attributes for more effective respiratory targeting.

Rational process design is helping overcome the challenges of spray drying lipids, the most significant of which are their low melting temperatures (T_m), multi-phase complexity, and polymorphism. This approach combines critical material attributes (CMAs) with process parameters and process performance to produce simple lipid-based formulations at high yields. It begins

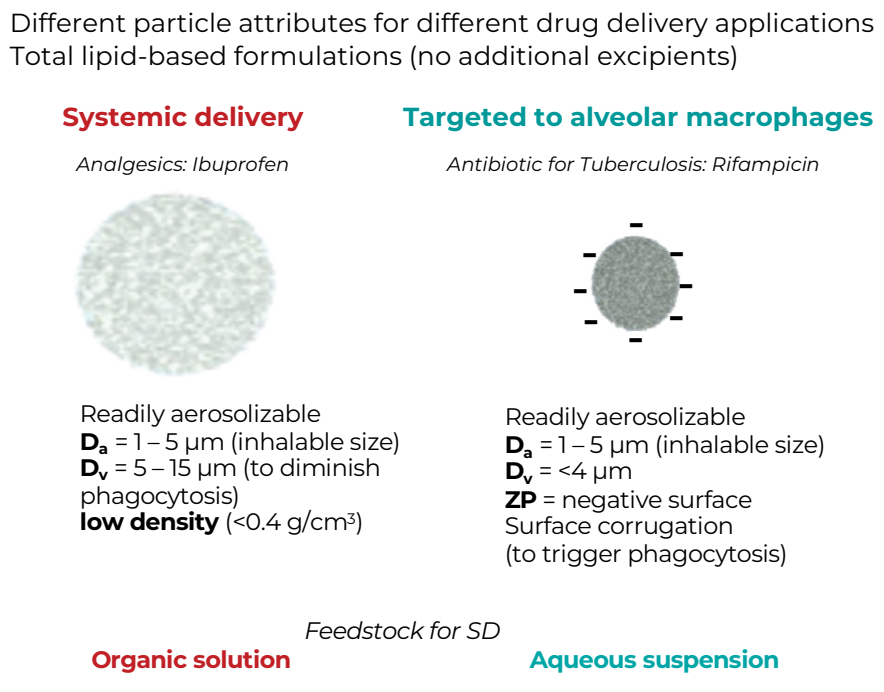
with selecting lipids with the highest possible melting point. A pre-formulation step then examines any interaction between the lipid and drug or lipid and solvent that might impact the melting point or polymorphism of the formulation. The resulting information is used to fix the boundary for the spray dryer outlet temperature. The following proof-of-concept case study demonstrates the general applicability of this approach.

Proof of Concept

The diagram in **FIGURE 2** provides details of two different drug delivery applications using lipid-based formulations and the specifications required. Taking the systemic delivery formulation as the exemplar, the first step is to select relatively high melting point lipids. In this case, polyglycerol esters of behenic acid showed the best performance. Pre-formulation solvent casting using lipids and varying amounts of ibuprofen helped predict the solid-state outcome from spray drying. When testing the lipid PG3C22p, the results showed that even though the selected lipid had a melting point of around 74°C, interactions between the lipid and ibuprofen caused the melting point of a mixture of 30% ibuprofen and 70% lipid to be closer to 60°C. An efficient spray drying process could be developed by selecting an outlet temperature sufficiently below 60°C. Once the outlet temperature is established, it is possible to define process parameters to achieve target particle attributes.

Experimentation using a variety of different lipids revealed that a difference of at least 20°C between the melting point of the mixture and outlet temperature provided the highest yields and the least agglomeration in the system. However, this alone was insufficient to achieve good yields for all lipid types, so it was necessary to look at the particle trajectory inside the drying chamber. Issues such as entrapment of particles, recrystallization, wall deposition, process loss and agglomeration at the outlet all affect yield. Screening with differential scanning calorimetry (DSC) at the pre-formulation stage helped determine T_m and crystallization behavior, enabling for selection of the correct inlet and outlet temperatures.

FIGURE 2: Systemic delivery and delivery targeted to alveolar macrophages.



CONCLUSION

In reviewing some of the challenges involved in spray drying for pharmaceutical applications, a science and experience-based approach to development and scale-up is needed to ensure efficient use of available resources, especially with the growing use of ASDs for solubility enhancement. Taking action to identify critical process steps and mitigate the risks at each stage is crucial for success.

In the quest for carrier-free inhaled drug products, the use of spray dried lipid formulations is being researched as a potential solution. As with SDDs, rational process design can help improve yields and increase the viability of these products.

For more information, watch the webinar Advanced Troubleshooting for Spray Drying of Pharmaceuticals.

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Matt Ling has over 20 years of experience in the pharmaceutical industry, mostly working in large pharmaceutical companies, with roles in analytical, formulation development, advanced drug delivery and project leadership spanning all phases of discovery and development. Ling has a keen interest in the application of drug delivery technologies and holds a doctorate in organic chemistry from the University of Nottingham, Nottingham, U.K.

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