A Q&A

Explaining the Spray-Drying Process for Scale-Up and Commercialization

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Answers to key questions about developing a spray-dried dispersion for a drug substance with stability issues.

The use of spray drying to manufacture amorphous dispersions is continuing to grow due to the number of drug candidates exhibiting poor solubility. In a recent *Pharmaceutical Technology* webcast, Jon Scrafford, Associate Director of Process Engineering at Catalent, and Ryan Minikis, Principal at Arclight Pharmaceuticals, LLC, explored the use of spray drying to create amorphous solid dispersions (ADSs) and the optimization of process parameters for successful scale-up to commercial manufacture of the final dosage form. Here, Scrafford and Minikis answer several key questions posed by audience members during the *Pharmaceutical Technology* webcast.

How does particle size distribution change from small-scale spray driers to large-scale equipment?

Scrafford: Small-scale spray dryers run at a much lower throughput, have a shorter chamber length, and typically use a two-fluid nozzle with a smaller diameter orifice. Combined, these factors create small droplets and smaller particles. Some lab units, such as the ProCepT 4M8-TriX, have the flexibility to create larger particles via an extended drying chamber and multiple nozzle orifice sizes. With increasing scale, these features can be increased to produce larger droplets and particle sizes. In general, you may be able to double or triple your particle size going from lab-scale to a MOBILE MINOR™ or a PHARMA-SD™ PSD-1.

How do you determine the spray drying is complete on a given batch? What techniques are used to determine that the batch is complete?

Scrafford: Spray drying is a continuous process, so it's not "complete" until the entire batch has been processed. After the material has been sprayed, it goes through a secondary drying step under heat and/or vacuum to remove the residual solvent. After a certain period, samples will be pulled from this dried material and tested for residual solvent levels via gas chromatography. Once the specifications are met per USP guidance, the manufacturing run can be said to be complete.

Do you use process analytical technology (PAT) to monitor the spray-drying process?

Scrafford: PAT can be used for spray drying, however, it is impractical at small scales due to the material requirements needed to develop the necessary methods. At larger scales, some examples of PAT include determining the complete dissolution of a polymer and the API during solution preparation, real-time droplet and/or particle size monitoring via laser diffraction, and residual solvent content monitoring during secondary drying via near-infrared spectroscopy.

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What are some considerations when developing a spray-dried dispersion (SDD) for a drug substance with stability issues?

Scrafford: Drug substance instability can be attributed to various reasons such as solvent incompatibility with the feed solution, light or moisture sensitivity, or because of inherent API characteristics (i.e., a high ratio of melting temperature [T_m] and glass transition temperature [T_g] prone to crystallization). There are strategies to combat these scenarios, including selecting compatible solvents and polymers, adjusting the API-to-polymer ratio, protection from light, use of moisture barrier film coating, blister packaging, cold chain storage, and more.

Physical stability issues can be mitigated by changing to a polymer with a higher T_g or by increasing the ratio of polymer to API. If the physical stability issue is related to hygroscopicity, then it's possible to protect the product by maintaining low-humidity environments during downstream processing as well as using a moisture barrier film coat and/or utilizing special packaging such as blister packs.

When dealing with chemical stability issues, the first two variables to investigate are drug compatibility with the selected polymer and with the feed solution. Ideally, there will be negligible API degradation in the selected solvent (for a period of several days), which allows for the processing of a single batch of feed solution over multiple days and is much more efficient at larger scales.

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What key considerations should be taken when using spray-drying technology for an inhalable powder?

Scrafford: There are many differences when using a spray-drying process to generate a product for inhalation versus an ASD. One of the biggest considerations is particle collection. Due to the extremely small particle sizes required for inhalation (<10 µm), most of these particles will bypass a standard cyclone. Custom cyclones can be made, which will more effectively collect the small particles, but having multiple cyclones in parallel are often required. An alternative option would be bypassing the cyclone and instead, collecting the material from a bag house that can be back-pulsed to shake off material and into a collection vessel.

Which range of polymer loading shows similar results regarding particle morphology to that of the complete SDD (e.g., polymer percentage compared to API)?

Scrafford: The best option will always be to complete engineering runs with the complete SDD. Unfortunately, this is not always possible. In these situations, spraying with a polymer surrogate (no API) can help to determine the starting parameters for the spray dryer. In general, programs with higher polymer loading will correlate better with the polymer surrogate and the complete SDD (i.e., 75% polymer loading will correlate better than 50%). Before attempting this, it is important to characterize the feed solutions to determine if the API has a significant effect on the viscosity or surface tension of the feed solution. If not, then it may only be a matter of the resulting particle size being smaller than the polymer-only solution.

Can you scale-up from a ProCepT 4M8-TriX to a PHARMA-SD™ PSD-2 directly?

Scrafford: While this can be done, the significant jump in scale can lead to many challenges. For example, the solution feed rate could increase from ~10g/min to ~900g/min. The droplet and particle size will be undoubtedly larger at the PSD-2 scale and could have an impact on performance. In addition, the lack of information obtained on extended run times could result in powder build-up or product sticking to the chamber. In addition, due to the jump in scale, the temperature, pressure, and flow rates used on the ProCepT will likely not provide the relevant information you need to choose the starting parameters on the PSD-2.

What if you want to reduce the particle size distribution rather than increase it in scale-up?

Scrafford: There are a few options to decrease particle size with the most straightforward being to increase the nozzle pressure (both two-fluid and pressure nozzles). Alternatively, the droplet and particle size can also be decreased by reducing the viscosity and/or surface tension of the spray solution, which could be accomplished through the addition of a surfactant or by lowering the solids content.

What are the main considerations if you increase the solids content of the spray solution during scale-up?

Scrafford: The first consideration is the solubility of the API, as having an undissolved drug in the feed solution can create a nucleation point in the SDD and negatively impact physical stability. Additionally, the feed solution will generally become more viscous, which will result in larger

droplets and larger particles if no adjustment is made to the operating parameters and could therefore impact performance. If the objective is to maintain the original particle size but increase the solids content for throughput benefits only, then the atomization parameters would need to be increased to generate smaller droplets.

> For most typical spray drying applications, the goal will be to achieve a homogeneous and amorphous dispersion of the drug and excipient; usually a high T_g polymer.

My API is currently being lyophilized. How difficult would it be to switch over to spray drying?

Minikis: Spray drying is a precedented alternative to lyophilization for powder preparation, but the product performance and quality considerations are typically quite different than those for ASDs for oral delivery. As an example, consider a sterile powder for reconstitution and meant for parenteral delivery, which is often lyophilized from an aqueous solution of drug and excipients. In that case, you will need to engineer a powder (particle) that is amendable to spray drying (e.g., can withstand exposures to elevated drying temperatures) and that meets requirements for reconstitution time and absence of particulates. In addition, the product will either need to be processed aseptically, or with appropriate "low-burden" controls followed by terminal sterilization. Finally, as lyophilization typically occurs directly in the unit dose vial while spray drying produces a bulk powder intermediate, you will most likely also need to develop an aseptic powder vial filling process. Another challenge may be finding the requisite capabilities on a single manufacturing site, so you may need to engage multiple sites or vendors to accommodate the overall manufacturing process.

Are spray drying solutions that contain suspended particles (e.g., mesoporous silicas) less scalable because using a pressure nozzle is not a viable option?

Minikis: Pressure nozzles have technical and cost advantages for typical ADSs (e.g., no additional nitrogen consumption, larger and narrower particle size distributions). However, there is ample precedent for alternative atomization mechanisms being used at multi-ton scale. In the case where a spray suspension creates concern around orifice clogging with a pressure nozzle, you might consider either rotary or twin-fluid atomization techniques. Rotary atomization will be the most energy and cost efficient alternative but may have limitations for high-viscosity solutions due to relatively low shear forces. Twin-fluid atomization is more commonly available and is a very robust and well-understood technology but has the disadvantage of higher energy and cost of goods sold (COGS). To summarize, there are certainly commercializable solutions for the spray drying of suspensions. Significant scale-up challenges may include feed agitation and product homogeneity.

Although the outlet temperature impacts the final form of the particle, the crystalline habit also plays an important role in particle engineering. Which of these factors is most important?

Minikis: For most typical spray drying applications, the goal will be to achieve a homogeneous and amorphous dispersion of the drug and excipient; usually a high T_g polymer. In this case, it is true that one of the most important process parameters for particle morphology—and therefore bulk powder properties like density and flow—will be outlet temperature. In most cases, the crystal habit will be irrelevant if we achieve the goal of no crystalline material in the spray dried product. This may not be true in specialty applications where a crystalline material is desired. For example, with extremely fast crystallizers, this may be possible during the spray-drying process itself, or in some cases, it may be forced through annealing post-spray drying. It may also be possible to couple traditional API solvent/anti-solvent crystallization processes directly to spray drying for the isolation of crystalline API, though it's hard to imagine how that would be the most cost-efficient API purification approach.

During the scale-up process, what are the main challenges for a hydrophilic API loaded formulation and a hydrophobic formulation when manufacturing an ASD?

Minikis: The product will retain certain properties of both the API and the chosen polymer. The best-known example of this is T_g, which for the ASD, will typically lie between those of the drug and the polymer. For hydrophilic APIs, the concern may be hygroscopic product, which should be confirmed through vapor sorption experiments. This may lead to failure modes in processing for instance, a "wet" product may cause hang-up on equipment and significant yield loss, in which case, you will want to avoid water in the manufacturing process. The same hygroscopic product properties may cause issues with downstream tablet or

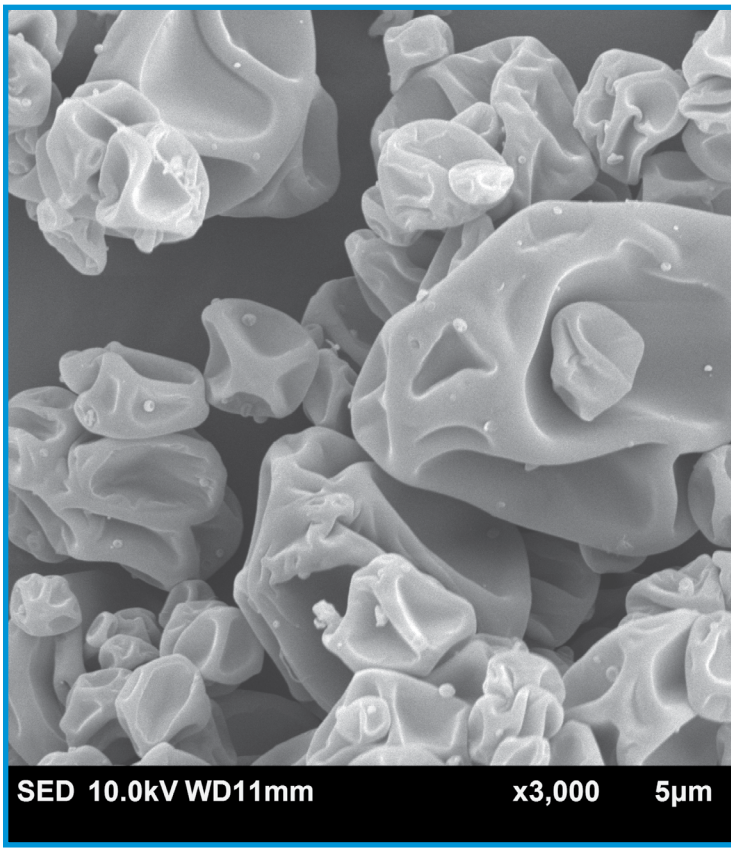
capsule formulation and processing, where mitigation such as low relative humidity processing rooms may be required. The other challenge for hygroscopic material is stability; both chemical and physical. Water sorption could induce T_g depression and subsequent recrystallization of the ASD or affect the potency and appearance of associated final products.

> Hydrophobic materials will more likely have performance challenges, especially if the goal is solubilization and improved oral bioavailability.

Hydrophobic materials will more likely have performance challenges, especially if the goal is solubilization and improved oral bioavailability. As explained previously, ASDs tend to have properties reflective of their composite materials. Hydrophobic APIs may yield dispersions with poor wettability, slow dissolution rates, or low supersaturation capacities. This can be compensated for by engineering product with smaller particle size and/or higher specific surface area, but these will in turn, tend to create problems with flow and downstream processing. For extremely hydrophobic APIs, where partition coefficient (LogP) is more than 8, excipient choice(s), in some cases requiring ternary or even quaternary mixtures, will be more important in striking a balance between manufacturability and performance.

What secondary drying technologies are available for continuous operations?

Minikis: While spray drying is theoretically a "continuous process," most installations have not achieved end-to-end continuous processing at scales relevant to commercial production. Batch operations are typically employed for both solution preparation and secondary drying. Established process technologies that may be amendable to continuous secondary drying of ASDs are continuous fluid bed and ribbon dryers.



A SEM image showing raisin morphology of spray dried particles.