An Executive Summary

An Integrated Approach to Spray Drying: From Scale-Up to Manufacturing

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The spray drying process parameters explained and improved by QbD.

Overview

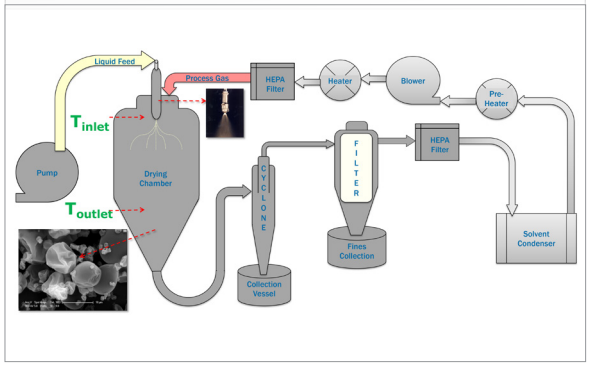
Amorphous solid dispersions (ASDs) improve the solubility of Developability Classification System (DCS) class IIb compounds. Spray-drying technology is one method of manufacturing high quality ASDs. The application of a phase-appropriate quality-by-design (QbD) framework to the spray-drying process can improve drug developer's understanding of the interplay between process parameters and product quality. When applied during scale-up, this increases the chances of a successful outcome of the commercial manufacturing process.

About 40% of new chemical entities screened by pharmaceutical companies fail to progress to later stages of development as a result of poor aqueous solubility (1). In the DCS, most of these low solubility drugs are categorized as class II. DCS class II includes both dissolution-rate limited (class IIa) and solubility-limited (class IIb) drugs.

Drug developers have found that the solubility of DCS class IIb compounds can be enhanced by mechanization and related techniques that expand the surface area of the drugs' molecules. To improve the solubility of DCS class IIb compounds, drug developers produce ASDs of the drugs.

Spray drying is one of two methods used to create ASDs. The spray-drying process begins with the dissolution of the API and one or more polymer excipients into an organic solvent. Polymers stabilize the API's amorphous state by physically separating the drug's molecules. Because of the random order of the API molecules inside the polymer matrix, ASDs completely release drugs without inducing re-crystallization.

Figure 1: Spray-dryer process flow diagram.



The solution is then pumped into a drying chamber as an atomized fine mist (see **Figure 1**). Hot processed gas enters through the top of the chamber (red arrow) and vaporizes the solvent to

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Figure 2: Early formulation development road map.

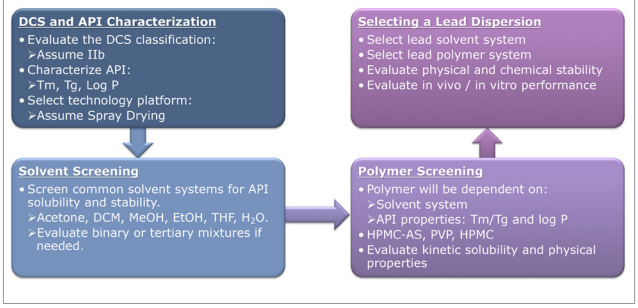
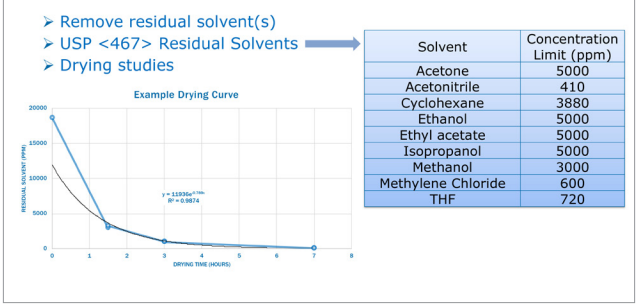


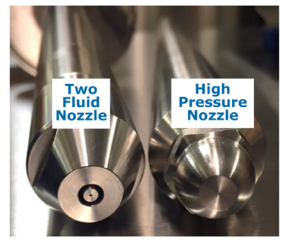
Figure 3: Secondary drying.



Solvent	Concentration Limit (ppm)
Acetone	5000
Acetonitrile	410
Cyclohexane	3880
Ethanol	5000
Ethyl acetate	5000
Isopropanol	5000
Methanol	3000
Methylene Chloride	600
THF	720

Figure 4: Nozzle selection.

Attribute	Two-Fluid Nozzle	High Pressure Nozzle
PSD Control	More	Less
Distribution / Span	Wider	Tighter
N_2 Consumption	High	None
Industry Prevalence	Lab Units	PSD1 and beyond



produce a spray-dried dispersion (SDD). The SDD particles, which are heavier than the air, spiral down the sides of the cyclone into the collection vessel. If the particles are large enough, very little material is deposited into the secondary collection vessel.

The processed gas stream then rises through the middle of the cyclone and through a cartridge filter where fines are collected. The condenser removes and collects most of the vaporized solvent from the processed gas. After recycling through a fan box and heat exchanger, the processed gas is then returned to the chamber, thereby closing the loop.

Early Development Roadmap

If the API is a class IIb compound and spray drying will be used improve its solubility, the following actions will occur.

In the first step, commonly used solvent systems will be screened to identify solvents that will improve the API's stability and solubility (see **Figure 2**). The result could be a single solvent, or binary or tertiary mixture of solvents such as acetone and a combination of DCM and methanol.

Based on the API's properties and the selected solvent, drug developers will select potential polymers for evaluation. A lead dispersion that will not affect the drug's stability while it is in a spray solution for several days also will be identified. In addition, drug developers will determine whether the solids loading in the solution will be high enough for the spray-drying process to be efficient.

Lab-scale spray dryers are usually used to manufacture small batches of SDDs for studies on the kinetic solubility, physical properties, and stability of the potential polymers. Based on the results, several polymer systems will be further evaluated. The final polymer and solvent selections will be locked in.

Drug developers also will use the spray dryer to manufacture several SDD formulations for physical and chemical stability analysis and *in-vivo* and ultimately *in-vitro* performance testing. Drug developers will want to be sure that the SDDs are physically and chemically stable and capable of improving ASD solubility and bioavailability.

The ideal SDDs have a relatively dense, raisin-like morphology, which is produced by low temperatures and slow drying. Raisin-like SDDs have better flow properties than do the bulky sphere-shaped SDDs produced by high temperatures and fast drying. Sphere-shaped SDDs are also difficult to work with during downstream processing. If the inlet temperature is set to the "scorched earth" setting and drying time is "ludicrous speed," the particles burst—creating even bulkier material and more downstream-processing problems.

Following the spray-drying process, SDD particles often contain residual solvents that must be eliminated by secondary drying. To predict the drying time for the SDDs, drug developers will pull samples for gas chromatography (GC) testing at several time points. Based on the GC results, a drying curve (see **Figure 3**) can be built to aid in estimating drying time.

Vacuum ovens with trays are typically used in lab-scale spray drying consisting of less than 10 kg of SDDs. Forced-air convection ovens are often used in larger-scale projects with 10–30 kg of material. The rotary vacuum dryer is the best option for late-stage and commercial projects involving 5+ kg of SDDs. Heat and/or nitrogen purge also can aid in the drying process.

Two-Fluid Vs. High Pressure Nozzles

Lab-scale spray dryers are typically equipped with two-fluid nozzles, while spray dryers for pilot studies and commercial production usually have high pressure nozzles (see **Figure 4**). In the two-fluid nozzle, a standard peristaltic pump sprays the feed solution, and nitrogen

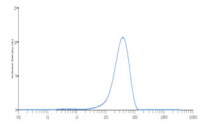
Figure 5: Lab to pilot scale-up.

	SD Micro	Mobile Minor
Target Particle Size - d(0.5)	20 µm	
Outlet Drying Air Solvent Saturation	0.021 kg vapor / kg dry air	
Residual Solvent	< 3000 ppm	
Total Solids In Feed	10%	
Outlet Drying Air Temperature	50 °C	
Drying Air Flow Rate	35 kg / hr.	80 kg / hr.
Inlet Drying Air Temperature	90 °C	115 °C
Feed Flow Rate	2.0 kg / hr.	6.0 kg / hr.
Atomization Air Flow Rate	1.0 kg / hr.	9.0 kg / hr.

- Mathematical scale-up can be done, but particle characteristics are more important!

Figure 6: Critical quality attributes.

- Physical State – **Amorphous** or **Crystalline**?
  - Single Tg, amorphous halo
- API:Polymer and residual Solvent(s)
  - Impacts physical stability
- Particle Size
  - May impact performance (and powder handling)
  - CPPs → Spray pattern
    - Spray solution viscosity
    - Spray rate
    - Atomization



gas disperses and atomizes the liquid stream. The ratio of atomization gas to liquid flow rate is key. If the liquid flow rate is increased, the droplets will be bigger and the particles will be larger. However, increasing the gas flow rate will break up the liquid stream and thereby reduce the sizes of droplets and SDDs.

Because atomization gas can be adjusted, two-fluid nozzles provide more control over the absolute particle size than do high pressure nozzles. Two-fluid nozzles, which are used to achieve particle-size distribution (PSD1) scale and above, have a tighter distribution than do high pressure nozzles.

High pressure nozzles do not use atomization gas and do not require nitrogen gas, which scales exponentially with increases in feed rate. A high-pressure diaphragm pump pushes feed solution through the nozzle's 0.1 to 0.4 mm-wide orifice. These nozzles have several hundred pounds per square inch (PSI) of pressure and create a very consistent conical spray pattern.

Framework for Development

By using the QbD framework, drug developers can decipher the interplay between product quality and the process parameters of spray drying. The knowledge gained from QbD's systematic approach can minimize the optimization work required to scale-up late-stage spray drying equipment. The three key elements of QbD are the quality target product profile (QTPP), critical quality attributes (CQA), and critical process parameters (CPP).

QTPP. The QTPP identifies the quality characteristics required for a specific drug to be safe, effective and commercially successful. Commercially-related characteristics include cost of goods sold, shelf-life, storage and distribution. Because of its broad scope, the QTPP should be compiled by a wide range of company stakeholders.

CQA. Once the QTPP is finalized, drug developers identify the CQAs, the physical and chemical properties or characteristics that should be within an appropriate limit, range or distribution to ensure desired product quality. These properties or characteristics are the individual attributes that make up the QTPP. Examples of CQAs for a typical spray-drying process are the API to polymer ratio and the amount of residual solvent in SDDs. Both can

Lab-Scale vs. Pilot-Study Spray Dryers

Examples of lab-scale spray dryers are Buchi B-290 and ProCepT 4M8-TriX, which can produce batches of several grams and is equipped with process controls for drying, gas, flow rate, set points and precise atomization. Because lab-scale spray dryers must be paused to collect products, they cannot run for long periods of time to produce large development batches. However, the GEA SDMICRO™ can run continuously and manufacture large batches and smaller GMP batches. Because of its butterfly valves, the GEA NiroMOBILEMINOR™, the most commonly used spray dryer for pilot studies, can collect product while the machine continues to run in a closed loop system. In addition, the MOBILEMINOR operates with about 6 to 11 kilos of solution each hour.

In the transition to a pilot-scale spray dryer, the starting points should be determined more by the characteristics of the SDDs than the mathematical and energy balance (see **Figure 5**). For example, the SDD particle size and residual solvent level should not change in the scale up. Both the solids loading and outlet temperature should not be changed.

The biggest challenge in the transition from a lab- spray dryer to a pilot-scale spray dryer is determining the co rrect preferred set point.

Figure 7: Final product QTPP.

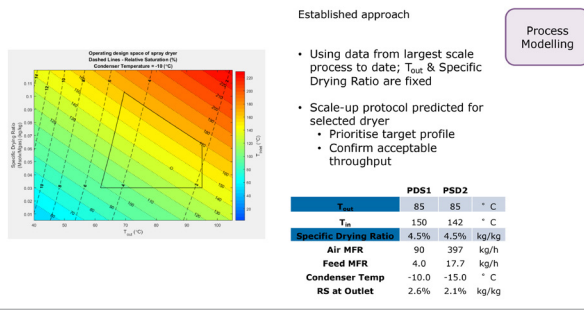
QTPP – Rx Finished Product (FP) *Characteristics*
Dosing route (oral, nasal, lung, topical, parenteral…)
Unit dose format (tablet, capsule, sachet, ODT…)
Unit dose image (color, shape, size, embossing…)
Unit dose strength (multiple strengths, placebo(s), fixed dose combo, dose uniformity…)
Dosing frequency (QD, BID, TID,…weekly, monthly?)
Pill burden (FDA IIG/GRAS limits, pediatric/special/compromised pt. populations?)
Performance (solubilization, release rate (MR/CR), tissue targeting, PK/TK, TI, ADME…)
Shelf life (long term stability, primary packaging, cold chain…)
Distribution (secondary packaging, kit format, mechanical robustness, global markets…)

Figure 8: Deriving a SDDD (DPI) QTPP.

FP Characteristic	SDD (DPI) Attributes
Dosing route	excipient choice, excipient levels (IIG limits), microbiological quality…
Unit dose format	flow, excipient compatibility, compressibility, wettability…
Unit dose image	**SDD drug loading,** colorant compatibility, compressibility, sticking…
Unit dose strength	**SDD drug loading,** multiple DPIs?, common granulation?…
Dosing frequency	**SDD drug loading**, release rate
Pill burden	**SDD drug loading,** %SDD in final formula
Performance	polymer choice, **SDD drug loading**, solubilization, physical form/stability, PSD/SSA…
Shelf life	long term chemical/physical stability, bulk SDI shelf life, functional packaging components
Distribution	Temperature cycling

SDD Drug Loading is single most limiting (enabling) factor. Determine early if early-phase product reformulation may be required to achieve commercially relevant Finished Product, **especially if unit dose must be > 100-200 mg.**

Figure 9: SDD process scale-up – thermodynamic parameters.



affect the ASD's physical stability. Another CQA example is SDD particle size, which can influence dissolution performance and downstream powder handling.

CPP. CPPs are the key variables that should be monitored to detect deviations in standardized production operations or changes in CQAs. For example, the CPPs for SDD particle size include spray solution viscosity, spray rate, atomization parameters and the drying process (see **Figure 6**).

Not all attributes or parameters in early drug development are CQAs or CPPs. For example, SDD flowability and compressibility are primarily controlled by drying temperatures and thus may not have a performance or quality impact on particles but could affect downstream processing.

SDDs are an intermediate product as well as a functional component of the finished ASD. SDDs are successful if they enable a high quality finished ASD. As a result, a separate QTPP is often compiled for SDDs and is derived from the QTPP for the finished ASD. The QTPP for the ASD includes such attributes as dosing route, frequency and strength, performance, and pill burden. (see **Figure 7**). Many of these attributes (see **Figure 8**) are influenced by SDD characteristics. Because it affects unit dose, dosing strength, pill burden and performance, drug loading is the SDD characteristic that has the greatest impact on the attributes of the finished ASD.

Before launching a phase 2 or 3 clinical trial or commercial manufacturing, drug developers should reconsider some of their previous decisions about, for example, their selection of spray drying equipment for producing clinical batches. Scale-up from a PSD-1 to a PSD-2 spray dryer can quadruple throughput. Depending on the clinical study design and dose trends, the next step could be a large increase in batch size with longer runtimes. Conversely, the scale-up to PSD-2 could result in lower yields if the batch sizes remain relatively small.

Prior to scale-up, drug developers also should consider simplifying or eliminating quirks in the development process such as a complicated solution preparation or filtration. These quirks could be difficult to replicate at a larger scale. Alternative polymers and solvents that could help improve performance and stability also should be evaluated. In addition, drug developers should reconsider increasing the throughput and efficiency of the manufacturing process by improving solids loading of the feed solution.

> “Drug loading is the SDD characteristic that has the greatest impact on the attributes of the finished ASD.”

Late-Stage Development

Drug developers must determine whether a drug in early clinical trials should be reformulated to achieve a commercially relevant finished product, especially if the unit dose must be greater than 100–200 milligrams. The typical 25% drug loading of SDDs in the product formulation for early clinical studies can cause problems in a reasonably sized tablet.

The main parameters of process scale-up for SDDs are thermodynamic and atomization. Both are critical for determining final product parameters

Figure 10: SDD scale-up process – atomization parameters.

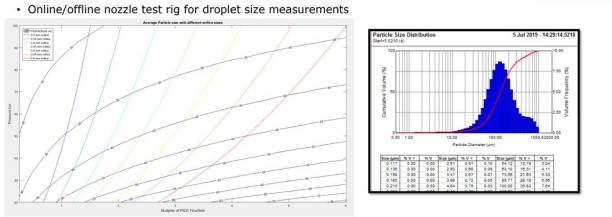


Figure 11: SDD scale-up technical approach.

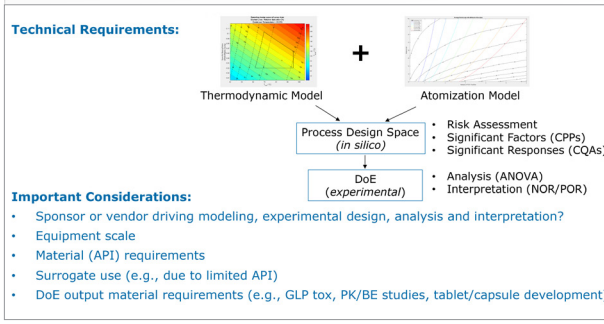
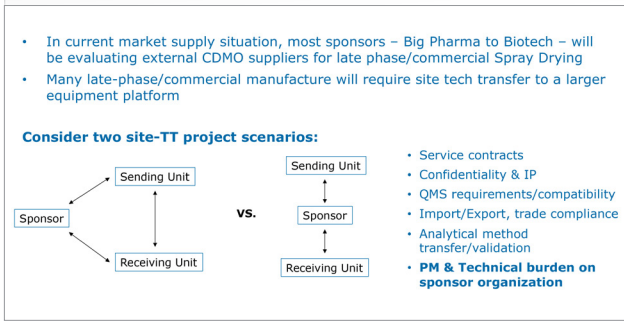


Figure 12: Vendor selection – late-phase SDD manufacture.



(see **Figure 9**). A graph on thermodynamic parameters of the SDD manufacturing process can be used to predict the scale-up protocol to target the required product properties. The outlet temperature is plotted as a function of a drying ratio that is defined as the mass feed rate of the feed solution over the mass feed rate of the drying gas. The contours represent inlet temperature and outlet relative saturation. The preferred operating parameters are represented as the small dot in the middle of the graph.

The table in **Figure 9** represents key process parameters for an ASD that maintains the relatively high outlet temperature of 85 °C. The inlet temperature floats to maintain a specific drying ratio and a reasonably similar relative saturation at the outlet. The objective is to obtain a similar product morphology during scale-up.

Also critical to determining final product parameters is the atomization component of the spray drying process (see **Figure 10**). The feed solution is atomized. Droplets become SDDs for initial scale-up trials. Thus, droplet size distribution is directly reflected in the distribution of the finished particle sizes.

When the development of an ASD moves from lab- or pilot-scale to clinical trials, researchers must scale-up the spray drying equipment. They must decide the type of nozzle that should be used in the spray dryer in the initial scale-up trials. Changing the nozzle type at scale-up can require additional work.

Both online and offline nozzle testing can be conducted to measure droplet sizes to determine the nozzle that will likely produce the same SDD particle size and distribution pattern that occurred in the lab and/or pilot study (see **Figure 11**) The thermodynamic and atomization models together constitute the in-silico process design space. Risk assessment typically is applied to the design space. The models enable the identification of the most significant factors (CPPs) and the most significant responses (CQAs).

> “The thermodynamic and atomization models together constitute the *in-silico* process design space. Risk Assessment typically is applied to the design space.”

Typically, the next step is the design and execution of experiments. As a result of appropriate statistical analysis (ANOVA) and interpretation, information such as normal and proven operating ranges can be understood.

CDMOs and Tech Transfer

In the current market supply environment, most biopharmaceutical companies will evaluate several contract development and manufacturing organization (CDMO) suppliers for late-phase/commercial manufacturing of SDDs. Many companies will require a site tech transfer to a larger equipment platform.

Two different tech transfer project options should be considered. (**Figure 12**) One is a two-site tech transfer scenario in which the sending and receiving units are in direct communication with the biopharmaceutical company. In the second option, the company is the intermediary between the sending and receiving units.

> There must be clear points of communication, clear responsibilities by organization, and clear timelines and deliverables by the organization, and clear timelines and deliverables by the organization across the entire program timeline.

The sending and receiving units can be two different CDMOs or members of the same CDMO. Each option has important implications for contracting and subcontracting, technical capabilities, and the talent and experience of the organization.

The selected option will affect service contracts; confidentiality and intellectual property; quality management; system requirements and compatibility; import, export, and trade compliance; and analytical method transfer and validation. The decision will be based on how much project management and tech transfer across multiple sites that the company is willing to absorb in the scale-up. Once the option is finalized, the company must consider how the program will be governed. There must be clear points of communication, clear responsibilities by organization, and clear timelines and deliverables by the organization across the entire program timeline.

The scale-up entails an entirely separate drug product intermediate manufacturing process. Thus, more API will be required. API availability is usually a limiting factor for scale-up and tech transfer. Therefore, API and drug-product chemistry, manufacturing, and controls (CMC) teams should collaborate early and often.

Summary

Spray drying is an effective and popular method to manufacture the ASDs that increase the bioavailability of low solubility APIs. Early development focuses on manufacturing the physically and chemically stable SDDs that form ASDs. The knowledge gained from QbD's systematic approach can minimize the optimization work required for scale-up to late-stage clinical trials and manufacturing a finished product.

Since producing a commercially viable pharmaceutical product is the goal, drug developers should develop a QTPP for SDDs to guide late development. CDMO selection should be guided by business complexities and site program management as well as technical burden on the biopharmaceutical company.

Reference

1. Roots Analysis Business Research & Consulting, Pharmaceutical Spray Drying Market, 2nd edition 2018-2028