Chapter 8
Spray Drying: Scale-Up and Manufacturing

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List of Abbreviations

A	Area of the spray dryer chamber
API	Active pharmaceutical ingredient
BD	Bulk density of the product
CCF	Central composite face-centered design
C_{feed}	Solids content in the feed
Cp	Heat capacity coefficient
d_{D}	Droplet size
D_{noz}	Diameter of the nozzle orifice
DoE	Design of experiments
D_{v}	Diffusion coefficient in the gas phase
Dv50	Volumetric median particle size
F_{feed}	Flow rate of feed fed to the spray dryer
F_{drying}	Flow rate of drying nitrogen
m	Mass flow rate
MFP	Maximum free passage
MW	Molecular weight
P_{feed}	Atomization pressure of the feed
P_{out}	Vapor pressure at outlet temperature
P^{sat}	Saturation pressure of the solvent
PSD	Pharmaceutical spray dryer
P_{wb}	Vapor pressure at wet bulb temperature
QbD	Quality by design

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Q_{loss}	Heat lost from the drying chamber walls
RS_{out}	Relative saturation at the outlet of the drying chamber
T_b	Boiling temperature
T_{cond}	Drying gas temperature at the exit of the condenser
T_{dew}	Dew point temperature at the outlet of the drying chamber
T_{feed}	Temperature of the feed solution
T_g	Glass transition temperature
T_{in}	Drying gas temperature at the inlet of the drying chamber
T_{out}	Drying gas temperature at the outlet of the drying chamber
T_{room}	Room temperature
T_{wb}	Web bulb temperature
U	Overall heat transmission coefficient
V_m	Molecular volume
x	Molar fraction in the liquid phase
y	Molar fraction in the gas phase
σ	Surface tension
μ	Viscosity
ρ_l	Liquid density
ρ_g	Gas density
ρ_P	Particle density
ΔH_{vap}	Vaporization heat
γ	Activity coefficient

8.1 Technology Transfer and Scale-Up to Commercial Units

In the pharmaceutical industry, the production of spray-dried powders is still widely based on the batch concept. The quantities required in the early stages of the development are typically small but may increase by many orders of magnitude as the drug candidate advances through the clinical phases and reaches the market. This requires the scale-up to different units along the process. Pharmaceutical spray dryers are available in a wide range of scales: from lab units where milligrams of material can be produced to large commercial units capable of handling multiple tons of powder per day. If necessary, a spray drying process can be scaled up directly from the laboratory to a final production scale. However, the quantities required for clinical trials are more efficiently produced in pilot or small production scales, where product losses and scale-up risk are considerably lower. Therefore, these intermediate production scales are commonly used during the development of the process. Nevertheless, it is important to mention that during scale-up, some quality attributes of the product can change, and there is need to understand whether these changes are acceptable, and if so, desirable. For example, powder properties such as flowability and compressibility can be improved significantly when moving from lab units to larger ones. Changes in the particle size distribution, level of residual solvents, friability, density, and compressibility of the powder may strongly influence the properties of

the final tablet, viz. hardness, friability, disintegration time, and dissolution rate. A careless scale-up strategy may lead to considerable losses of expensive materials and ultimately jeopardize the timelines of a clinical program.

Despite its criticality, the scale-up of the spray drying process is still vastly empirical and based on costly experiments, and their statistical interpretation. To minimize the experimental burden of such an approach, recent efforts have focused on applying mechanistic models and simulation tools to describe the process of spray drying. In fact, mechanistic modeling and process simulation tools have been successfully used in chemical and oil industries for more than half a century. This rational approach has gained wide recognition, and pharmaceutical scientists are now making use of it during development, scale-up, and manufacturing (Koulouris and Lagonikos 2002). Nevertheless, pharmaceutical process development will require some sort of simulation and experimental testing at small scale, and at least some level of verification in a production environment.

The following sections highlight some important considerations regarding the most critical decisions related to the spray drying process, viz. selection of scale, atomizer, and key process parameters. Common challenges associated with the operation of the process will also be addressed. At the end of the section, a scale-up methodology based on scientific first principles, simulation models, and process characterization techniques are presented.

8.1.1 Manufacturing Scales

The way droplets are dried within the drying chamber dictates the characteristics of the final product. Several aspects like evaporation rate, particles trajectories, residence time, and wall deposition are governed by the factors like atomization device and conditions, design and positioning of the gas disperser, the dimensions of the chamber, and the location of the atomizer and exhaust gas duct. Spray dryers are available in multiple configurations, including cocurrent, countercurrent, mixed flow, fountain, or fluidized spray drying mode. The pharmaceutical industry predominantly uses the cocurrent mode since it minimizes the exposure of the product to high temperatures which may be crucial when processing thermally labile products or materials with a low glass transition temperature. The cocurrent mode is therefore considered the most suitable for the majority of the pharmaceutical applications.

Spray drying is a continuous process capable of full automation, and can be designed to meet any capacity required in the pharmaceutical industry. A process can be run in a large size unit for as short as 30 min or 1 h, or can be run continuously for many days. The selection of the right scale involves several considerations, but ultimately, it is primarily driven by the targeted process throughput and batch size requirements.

Fig. 8.1 Lab-, pilot-, and commercial-scale spray dryers at Hovione

8.1.1.1 Lab to Production Equipment

Laboratory scale spray dryers are particularly useful for producing small quantities of prototype formulations in early stages of development. They can process small quantities of solution (as low as 2 ml) with relatively high yield. On the other extreme, the process can run continuously for hours or days providing the flexibility of producing hundreds of grams or even a few kilograms of material. It is not surprising that lab-scale units have been used to produce commercial quantities of very-low-volume products. A typical feature of these small-scale systems is that the drying chamber and cyclone are constructed in glass (Miller and Gil 2012), enabling the privileged visualization of the drying and separation processes (see Fig. 8.1a). The main limitation of the lab units is the powder properties of the resulting materials, namely particle size. The small dimensions of the drying chambers limit the residence time, and therefore, the droplets need to be small in order to be dried completely before leaving the drying chamber, or they will collide with the walls. Therefore, most small units produce powders with mean particle sizes below 10–20 μm, more often between 3 and 10 μm. There are, however, lab-scale units (e.g., ProCepT R&D Spray Dryer) that operate under laminar flow, allowing the drying of much larger droplets (100 μm and larger). These units represent an excellent platform to mimic the size and morphology of the industrial-scale spray-dried particles and can be used at early stages of development to assess the criticality of particle size and other powder attributes in the quality of the product.

Pilot- and commercial-scale spray dryers (see Fig. 8.1b, 8.1c) are suitable for a wide range of batch sizes, ranging from less than 1 kg to several metric tons. They share many similarities regarding the configuration, materials of construction (typically stainless steel), ability to handle most organic solvents, and level of automation. Additional features such as cleaning-in-place or recirculation of the drying gas (close-loop units) may be included. Some units can operate under vacuum (to minimize risk of powder exposure of highly potent drugs) but commonly operate under slight

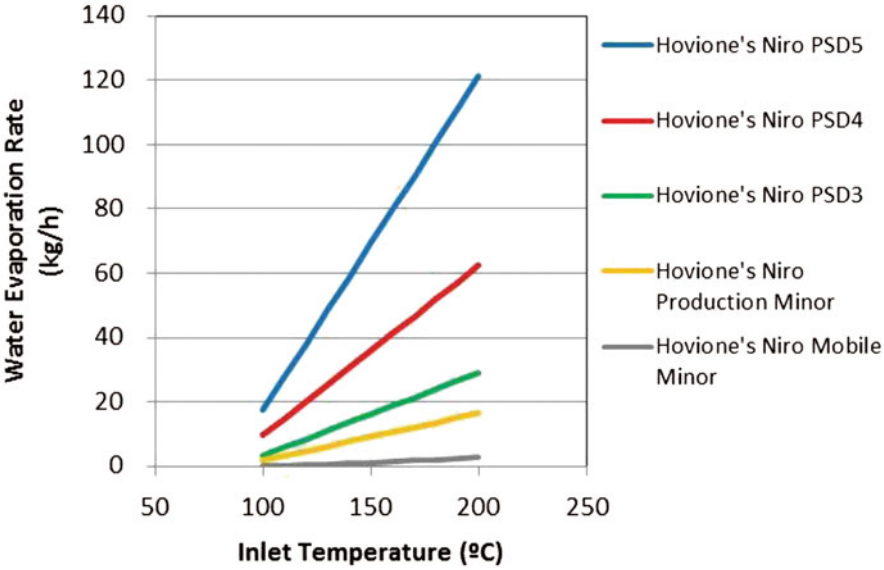


Fig. 8.2 Water evaporation capacity for different spray dryer units

positive pressure. Despite these many options, the main difference between scales is the evaporation capacity and the throughput.

The evaporation capacity depends mainly on the drying gas flow rate, solvent, temperature profile (inlet and outlet temperature), and heat loss of the spray drying unit. Fig. 8.2 shows the water evaporation rate at different production scales and nominal drying gas flow rates.

8.1.1.2 Considerations for the Selection of Scale

Scaling up a spray drying process offers in most cases a more energy-efficient process, lower manpower input per kilogram produced, and greater flexibility in adjusting and optimizing product attributes. The latter is particularly advantageous if the purpose is to obtain large and denser particles for solid oral dosage forms. For inhalation, however, the challenge is to maintain particle properties unchanged throughout the scale-up processes. The selection of ideal scale for a given product is dictated by the commercial demand projections and the real throughput of the process. To calculate real throughput, one needs to know not only the throughput in the spray drying step (and how it changes at different scales—see example in Fig. 8.2) but also which step (e.g., solution preparation, spray drying, or secondary drying) is the bottleneck of the process. Other variables with significant impact on the real throughput of the process are batch size, cleaning regime, and the duration of the cleaning process.

8.1.2 Nozzle Selection

Once the scale of spray dryer is established, it is important to select an atomization nozzle appropriate to the scale. The purpose of the atomization stage is to produce a fine mist (spray) from a liquid feed to substantially increase the liquid surface area and improve the efficiency of heat and mass transfer. For example, 50 ml of a solvent atomized in 800 million droplets of 50 μm creates a surface area about 6 m^2. By the generation of such high surface area, droplets dry fast, in the order of seconds or fraction of a second depending on the drying conditions. Moreover, the control of the atomization process dictates droplet size and consequently the particle size.

Sprays may be produced in various ways, but essentially, all that is needed is a high relative velocity between the liquid to be atomized and the surrounding gas. Some atomizers accomplish this by discharging the liquid at high velocity into a nearly stagnant gas. Notable examples include pressure nozzles and rotary atomizers. An alternative approach is to expose the relatively slow-moving liquid to a high-velocity gas stream. The latter method is generally known as two-fluid atomization. Independent of the device, atomization is a complex phenomenon of inertial, shearing, and surface tension forces, the balance of which determines the angle and penetration of the spray as well as the density number, droplet velocity, and size distribution. All these characteristics are markedly affected by the internal geometry of the atomizer, the properties of the gaseous medium, and the physical properties of the liquid itself, particularly its surface tension and viscosity.

Atomizers are generally classified according to the type of energy used. Rotary atomizers (centrifugal energy) use high velocity discharge of liquid from the edge of a wheel or disk. Two-fluid nozzles (kinetic energy) rely on the breakup of liquid on impact with high-speed gas at the orifice. Pressure nozzles (pressure energy) feature the discharge of liquid under pressure through an orifice, and ultrasonic nozzles (acoustic energy) breakup of liquid is promoted through sonic excitation. For each class of atomizer, there are several configurations and designs available to handle the diversity of feed materials and to meet the specific spray-dried product characteristics (Masters 2002). The liquid feed properties (viscosity, surface tension, solids concentration) impact the atomization performance in all types of atomizers. However, their sensitivity to each property depends on the particular type of nozzle.

8.1.2.1 Rotary Nozzles

For rotary nozzles, atomization is achieved by centrifugal energy transmitted to the liquid stream by a disk or wheel rotating at high speed (from 10,000 to 50,000 rpm). The liquid is fed into the center of a rotating wheel, moves to the edge of the wheel under the centrifugal force, and is disintegrated at the wheel edge into droplets. A spray angle of about 180° is best accommodated in large-diameter chambers (Mujumdar 2006). Rotary nozzles can be used to atomize slurries, suspensions, or solutions of high viscosity. Besides the feed properties, the operating variables that influence

droplet size are feed flow, rotational velocity, wheel diameter, and design. Rotary nozzles typically produce droplets of a wide range of sizes: from 20 to 200 μm (Masters 2002).

8.1.2.2 Two-Fluid Nozzles

Two-fluid nozzles, also known as pneumatic nozzles, use a compressed gas to atomize the liquid feed. There are different designs of nozzles on the market. The two major groups of two-fluid nozzles are known as an external mixing nozzle and an internal mixing nozzle.

External mixing nozzle is operated with low liquid pressure. The liquid feed is provided through an inner duct while an atomization gas is fed by an external annular opening around the liquid orifice. On the other hand, internal mixing nozzles take advantage of gas expansion at the nozzle outlet. Part of the pressure energy applied is used to scatter the liquid fragments within and beyond the nozzle orifice by the sudden gas expansion (Walzel 2011).

Although an external mixing two-fluid nozzle is the most common in the lab- and the pilot-scale spray dryers, an internal mixing nozzle is far more efficient in regards to the gas to liquid ratio and, therefore, preferred for larger-scale spray dryers, especially when small particle sizes (less than 10 μm) are required (Miller and Gil 2012). The main disadvantage is the air/nitrogen pressure required to overcome the high pressure drop of this type of nozzle. Nevertheless, both internal and external mixing nozzles produce droplet sizes within the range of 5–75 μm (Masters 2002) and offer, probably, the best control over droplet size since feed and gas flow rates can be controlled independently. However, the gas consumption and pressure required may limit their use at industrial scales mainly when drying organic solvents. Therefore, pneumatic nozzles are most suitable for small scales or when very small particle sizes are required.

8.1.2.3 Pressure Nozzles

In pressure nozzles, atomization is achieved by converting pressure energy into kinetic energy. Often the design of pressure nozzles includes the inlet slots to impart a swirling motion to the liquid at the swirl chamber entry and a convergent section to accelerate the flow as it enters the orifice. The swirl motion of the liquid pushes it to the wall and, consequently, the liquid is ejected from the orifice as a conical sheet that spreads outwards due to centrifugal forces. These nozzles require the use of high-pressure pumps as pressures can go up to 450 bar. Droplet size can be manipulated with the operating pressure, but feed flow is dependent on that pressure. With increasing atomization pressure, the droplet size decreases and the feed flow increases. This dependent manipulation of the droplet size is one of the major drawbacks of this type of nozzles, i.e., in order to change droplet size at constant feed flow,

it is necessary to change the nozzle dimensions or design. Further, as they involve the acceleration of the liquid feed, they are not suitable for high viscous feeds.

In large-scale spray dryers, these nozzles are used for production of medium to large particles (30–200 μm). They also produce more uniform powders with a narrower particle size distribution than pneumatic or rotary nozzles and, therefore, are preferred for the production of powders for oral dosage forms.

8.1.2.4 Ultrasonic Nozzles

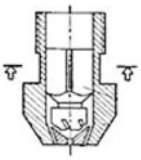
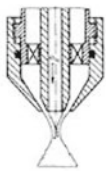
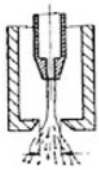
The principle of the ultrasonic nozzles is based on the usage of high-frequency sound waves to atomize the feed and produce very narrow droplet size distributions with low velocities. For ultrasonic nozzles, the feed delivery pump controls the liquid flow. The ultrasonic nozzle generates a uniform droplet size distribution ranging approximately from 20 to 100 μm. However, the frequency of vibration is specific for a given nozzle, and so does the droplet size produced. In practice, in order to change the droplet size, it is required to use a different nozzle. Higher-frequency nozzles produce smaller droplets. The major drawback of these devices is that the throughput is limited (typically up to 50 ml/min) which limits their applicability to laboratorial- and pilot-scale units.

8.1.2.5 Considerations for the Selection of Nozzle

In the selection of the atomizer and atomization parameters, two general requirements should be considered: one is to provide the throughput that meets the required powder production and the second is to generate a droplet size that provides for the target particle size distribution. In the pharmaceutical industry, the most commonly used nozzles are two-fluid and pressure nozzles, owing to their simplicity of use, easy of cleaning, ability to handle wide variety of feeds and the reduced tendency (when compared to rotary nozzles) to generate wall deposits. In most applications, a pressure nozzle is preferred than a two-fluid nozzle, primarily because pressure nozzle provides powders with a narrower particle size distribution. Exceptions include very fine powders or when feeds have very high viscosities or large suspended particles which may block or damage the pressure nozzle. In the former case, the greater flexibility to manipulate and control particle size in the fine range favors two-fluid nozzles. Powders with higher densities are generally obtained from pressure nozzles compared to two-fluid nozzles. This is associated with the degree of aeration of feed during the atomization process. Low particle densities, if required, can be obtained by optimizing the aeration effect (gas ejection or pressurization of the feed).

Table 8.1 below summarizes the main characteristics of pressure and two-fluid nozzles.

Table 8.1 Guidelines for nozzle performance

Pressure Nozzles	Two-fluid nozzles	
Pressure swirl 	External Mixing 	Internal Mixing 
Feed flow > 5 kg/h (not suitable for lab units)	High atomization gas consumption restricts the production of small particles at larger scales	Efficient atomization at low gas-to-liquid ratios
Flexible angles: 40-70º	Narrow angles: ~20º	Flexible angles: 20-60º
Eroded by suspensions	Suited for suspensions	Eroded by suspensions
Not suitable for viscous feeds	Insensitive to viscosity	Sensitive to viscosity
Weak manipulation of droplet size (for the same throughput)	High degree of control over droplet size	
Favors flowability Particle size – 20 to 500 μm	Fine powder with low densities Particle size – 3 to 200 □m	
Narrow distribution span ~ 1.4-1.8	Wide distribution; span ~2.0-2.4	

8.1.3 Typical Challenges

Most of the causes of unplanned shutdowns and/or limited run times are related either to (1) excessive buildup of material or the equipment walls, (2) improper atomization of the feed, and/or (3) chemical stability constraints (feed solution and/or powder). These issues and the ways to overcome (or account for) them are addressed in this section.

8.1.3.1 Product Accumulation

Product accumulation on the walls of the equipment is one of the most common occurrences when developing or during scale-up of a spray drying process. Product may accumulate on the walls of the drying chamber, cyclones, conveying ducts, or at the nozzle tip. Wall deposits are more commonly observed in the small scales since radial distances from the atomizer and residence time are shorter. Product buildup can be caused by several factors:

- Product stickiness; materials with a low glass transition temperature exhibit sticky properties and tend to build up on the walls of the equipment. The level of buildup is related to the content of solvent in the powder, the glass transition temperature of wet product, and the drying temperature at which the product is exposed. In the production of amorphous forms, this is particularly important since the deposits

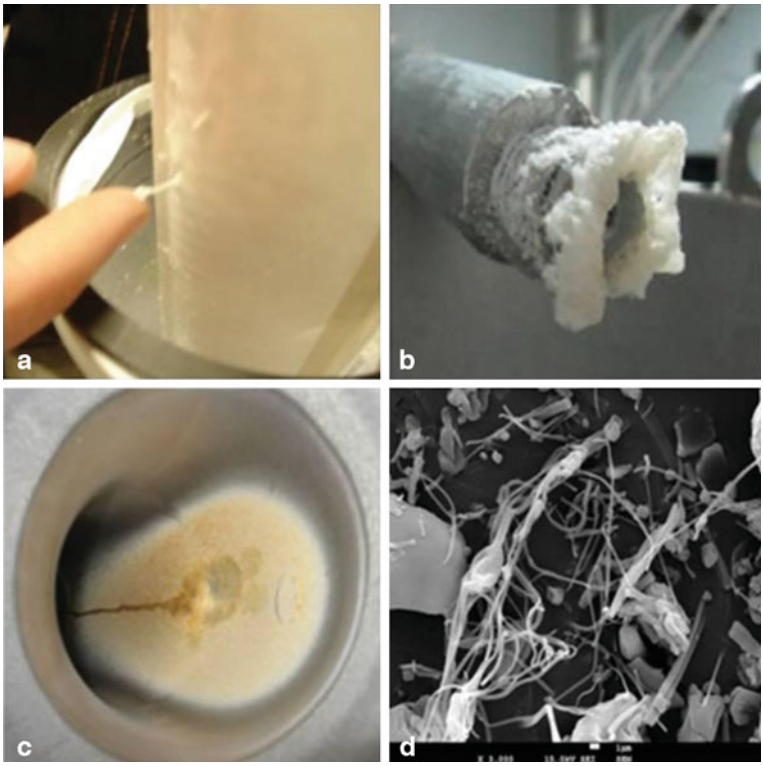


Fig. 8.3 Typical problems associated with spray drying operations: **a** condensation in the bag filter, **b** nozzle bearding, **c** dripping, and **d** stringing

on the equipment surfaces will occur when drying at temperatures close or above the glass transition temperature. The problem can be mitigated by reducing the outlet temperature (T_{out}) or by operating at lower relative saturation (RS_{out}) at the same outlet temperature. The latter is achieved by reducing the condenser temperature (T_{cond}) and/or the feed flow rate (F_{feed}). The stickiness tendency can be predicted offline, for example, using a hot stage and exposing the product to different temperatures.

- Solvent condensation; the gas inside a spray drying process equipment is partially saturated with solvent and, therefore, is prone to condense if exposed to cooler surfaces. If the surface is allowed to cool down below the dew point of the gas stream, then condensation will occur and the powder will accumulate on those wet surfaces (Fig. 8.3a illustrates an example where condensation occurred in the filter bag). To prevent this, the spray dryer is typically insulated or heat jacketed and the heating of the chamber prior to start of the atomization process is done in a gradual manner and over an extended period of time (typically between 20 and 60 min).

- Bearding; during spray drying, some droplets entrapped in the eddies around the nozzle may collide with the tip of the nozzle, dry on its surface and start building up around it. (see Fig. 8.3b). This process is commonly referred as bearding. If left unattended, the buildup can interfere with the spray formation and/or fall down into the drying chamber, promoting further powder deposition and ultimately clogging of the equipment. There are several approaches to overcome bearding. The simplest way is the repositioning of the nozzle (by changing the depth of the nozzle tip inside the chamber) to reduce or eliminate the droplet entrapment into the eddies. A change of atomization conditions as well as the drying gas flow may also be beneficial, though often there are narrow margins to manipulate these parameters. An engineering alternative is to include an additional gas stream concentric to the nozzle tip to prevent the collision of the droplets at the nozzle level. Another option is to use a nozzle with an anti-bearding cap which provides less deposition area for buildup to occur. More commonly, a combination of the above approaches is needed to successfully overcome bearding.
- Too large droplets; if droplets are too large for the drying chamber, they will touch the chamber wall before drying is complete. The solution is to decrease the droplet size or increase the drying temperature. Production scale may need to be changed if the target particle size cannot be achieved. This should be well thought out early in the development since all units have their own requirements regarding the maximum droplet size allowed.

8.1.3.2 Improper Atomization

Atomization is probably the most critical step involved in the spray drying process. The problems that can be associated with poor atomization include:

1. Inadequate atomization settings; this is the most common cause of poor atomization. Often in an attempt to increase particle size, atomization is set to maximize droplet size either by using low operating pressures (for pressure nozzles) or by using low atomization ratios (for two-fluid nozzles). However, there is a fine line between the conditions that allow maximum droplet size and those that lead to not fully developed spray.
2. Dripping; in pressure nozzles, the spray is fully developed only above a critical pressure. Below the critical pressure, often between 10 and 30 bar, large droplets may form which will fall into the drying chamber, which in turn may cause the formation of a wet layer of product in the discharging pipe of the drying chamber (see Fig. 8.3c). Dripping may also occur when restarting the operation after an unexpected shutdown. To prevent dripping, pressure nozzle with check valves that only allow the passage of liquid above a preset pressure can be employed. Some suppliers offer integrated check valves that can be adjusted for different pressures. Other option is the use of a compressed gas to purge the feed line once the high-pressure pump is switched off.
3. Stringing; stringing is the term used to refer to a bad atomization that happens in high evaporative systems. If a fine spray with high specific area is exposed to high

temperatures, string like particle formation may occur before the spray pattern is completely developed. String-like particles are obtained and agglomeration occurs, see Fig. 8.3d. In order to avoid stringing, it is required to delay the onset of particle formation by operating at lower temperatures or by reducing the concentration of the feed. Both approaches will reduce the throughput. If not resolved, solvent system or even the type of atomization system may have to be replaced.

4. Poor assembly of the nozzle; most nozzles require careful assembly of the internal and external components. Incorrect installation will result in poor atomization and often results in the shutdown of the process and loss of product. Nozzle assembly procedure should be carefully followed as per instruction and thoroughly tested before use.

8.1.3.3 Chemical Stability

The product purity profile is a very important attribute for any product. During spray drying operation, chemical degradation may occur:

- When the product is dissolved in the solvent prior to spray drying. This is particularly true at commercial scale, as the holding time may be long. It is therefore critical to define the solution storage conditions, especially the temperature and duration.
- When the freshly spray-dried product is still hot and not fully dried. In particular, some deposits of product may remain for a long time in the spray drying chamber, exposed to hot temperature (the walls of the chamber typically exhibit temperature close to the exit temperature of the drying gas).

Aforementioned chemical stability risks will be discussed below using a solid dispersion (API to excipient ratio of 1:4), where the solvent system used was a mixture of dichloromethane to ethanol ratio (97.5:2.5, % w/w), as an illustration.

8.1.3.3.1 Degradation of the Feed Solution

The degradation kinetics of a feed solution, at three different temperatures, is shown in Fig. 8.4. In order to determine accurate degradation rates, the timescale in this study was much longer than typical holding time. Although the formation of multiple impurities was observed, depicted in Fig. 8.4 is only the main (and most critical) impurity, for which an upper limit of 0.1 % was set.

As shown in Fig. 8.4, the kinetics show a linear increase over time, more pronounced at higher temperature. Using a simple Arrhenius equation, the activation energy (Ea) can be calculated, from which a mathematical expression capable of describing the growth of the impurity can be obtained. Equation can be readily used to construct a two-dimensional plot of temperature versus hold time (see Fig. 8.5).

Obtaining this type of representations enables the selection of the most appropriate feed solution temperature, in agreement with the target run time; for example, for a

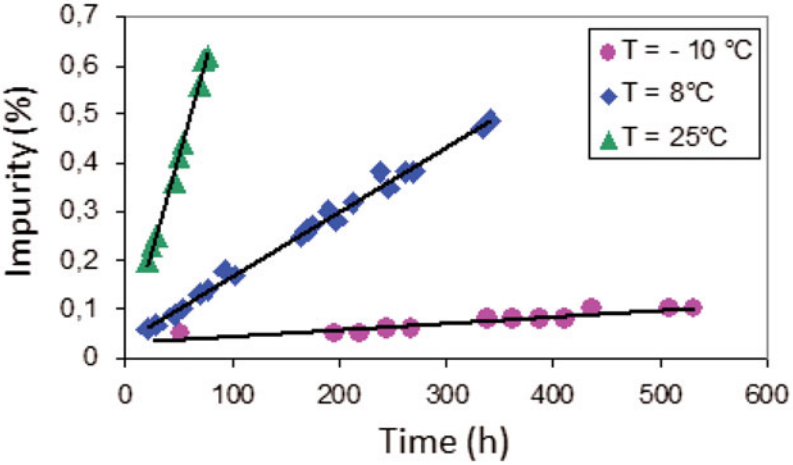


Fig. 8.4 Main impurity formation over time, as a function of the feed solution temperature

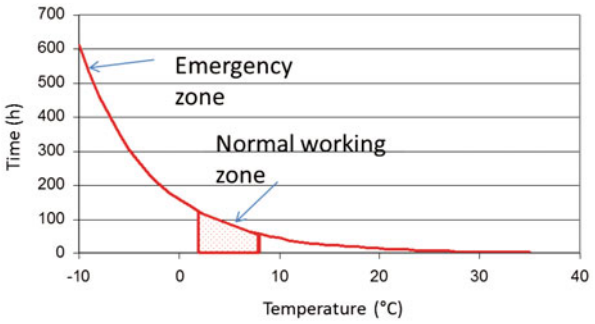


Fig. 8.5 Maximum (hold time vs. temperature), considering the main impurity formation

target spray drying time of about 24 h, a hold temperature range of 2–8 °C keeps the degradation level well below the 0.1 % limit. Additionally, in the case of emergency (e.g., equipment failure, requiring full process stop in order to allow for maintenance), Fig. 8.5 plot also shows that feed solution could be kept for more than 1 week (168 h) in case hold temperature is lowered to − 10 °C.

8.1.3.3.2 Degradation Inside the Spray Dryer Chamber

The spray-dried product accumulated in the chamber is exposed to harsh conditions (solvent vapor and high temperature) for an extended period of time and, therefore, it is expected to show a less favorable purity profile. Considering a worst-case scenario, where the entire amount of powder deposited on the walls would suddenly fall into the main product container, the entire batch could be jeopardized; therefore, it is important to evaluate the degradation of the deposited material as a function of its age (e.g., to define the optimal cleaning frequency of the spray dryer: too frequent would

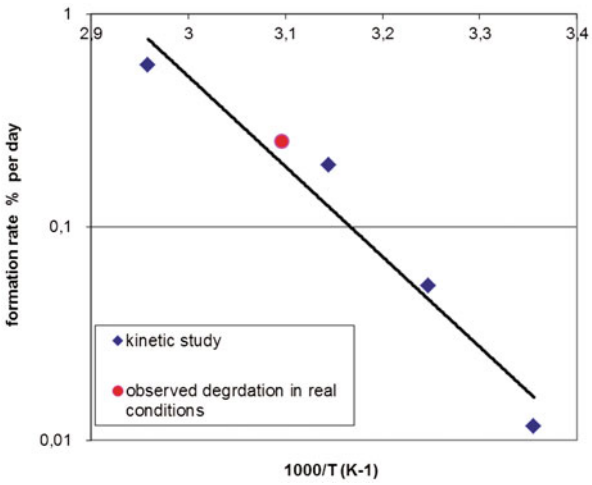


Fig. 8.6 Arrhenius plot for main impurity formation of the powder (lab kinetic results vs. spray drying data)

impact cycle time, whereas too rare would imply a risk of product contamination). These types of studies can be conducted using a two-step approach (the same example previously used to address the feed solution chemical stability is being considered):

- Acquisition of the degradation kinetics using a sample of freshly spray-dried product. In this illustrative case, a product with 3 % of residual solvents (the typical value obtained at normal operating conditions) was enclosed in containers and kept at four different temperatures (25, 35, 45, and 65 °C).
- Verification of the degradation kinetics at the real spray drying scale. In this illustrative case, a spray drying run (using a PSD3 unit, with an inlet and outlet drying gas temperatures of 95 and 50 °C, respectively) was performed for about 1 h (with a feed rate of 50 kg/h of feed solution), in order to obtain some product deposited on the walls; afterwards, the spray drying of pure solvent (at similar flow rate and thermal profile) was maintained for 24 h, in order to keep the product on the wall under normal degradation conditions. At the end of the trial, the powder deposited on the walls of the chamber was manually recovered (scrapped) and analyzed.

The results obtained for the current illustrative example are shown in Fig. 8.6.

As shown in Fig. 8.6, the rate of impurity growth observed in the laboratory is typically comparable to the degradation observed in the powder deposited on the spray dryer; considering the good alignment of the data, the degradation in real manufacturing conditions can be estimated from lab data (in this case 0.25 %/day). Therefore, by knowing the overall amount of deposited solids during a typical run (in this case known to be less than 1 % of the batch size) and considering that the drug product is typically homogenized and sieved, it is possible to anticipate the maximum impact for a given time window (e.g., 0.01 % of degradation during 4 days) and define the cleaning frequency (e.g., every 4 days of production would be, in this case, a good compromise).

8.1.4 Modeling Tools and Mechanistic Interpretation

The scale-up of spray drying processes has been primarily conducted based on actual experimental data and experience mainly because the process, characterized by rapid and simultaneous heat and mass transfer between the droplets and the drying gas, is difficult to describe mathematically, and some of the parameters are often not readily measured. Furthermore, the whole process is extremely dependent on the feed properties and equipment scale and design. Despite this, fundamental modeling approaches for process characterization have been proposed in the literature. Among these are thermodynamic models to estimate the humidity of the exhaust air (Berman et al. 1994), atomization models to predict droplet size (Lefebvre 1989; Senecal et al. 1999), or drying kinetics studies to anticipate the morphology of the particles (Larhrib et al. 2003; Littringer et al. 2013).

In this section, several tools, which will serve as the basis for the scale-up method, are presented: (1) a thermodynamic model to predict the outlet conditions of the spray drying, viz. relative saturation and temperature of the outlet gas; (2) an atomization model to predict the droplet size; and finally (3) a simplified model for droplet drying to define the general trends of particle size and morphology.

8.1.4.1 Thermodynamic Modeling

The thermodynamic model allows the characterization of the process in terms of drying gas flow (F_{drying}); relative saturation at the outlet of the drying chamber (RS_{out}); inlet, outlet, and condenser temperatures (T_{in}, T_{out}, T_{cond}); dew point of wet drying gas (T_{dew}); and feed flow (F_{feed}). A multivariate relationship of such variables can be used to define the process operation range that respects the desired outlet conditions (T_{out}, T_{dew}, and RS_{out}). The determination of such variables plays a role in the development of the spray drying process in several distinct ways. T_{out} is one of the most important process parameters since it has an impact on particle and powder properties such as density, surface area, mechanical strength, and physical stability. RS_{out} is the main driving force in the drying process and, therefore, has direct impact on the level of residual solvents in the final powder. The latter is of particular importance when producing amorphous materials since the level of residual solvent in the solids strongly affects its glass transition temperature (T_{g}). Dew point temperature (T_{dew}) is also an important parameter to have in mind in order to prevent solvent condensation in the equipment.

Essentially, the thermodynamic modeling consists in a set of equations that relate process parameters through mass and heat balances and liquid–vapor equilibrium equations. Below are the critical equations:

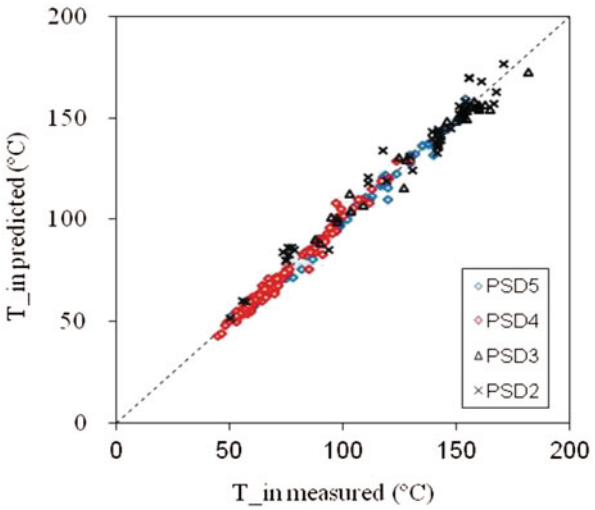


Fig. 8.7 Accuracy of the thermodynamic model. (Data from 386 batches, using multiple solvent systems and four scales of Hovione's Niro spray dryers)

$$F_{\text{drying}} \cdot \overline{Cp_{\text{drying}}} \cdot (T_{\text{in}} - T_{\text{out}}) = \sum_{i=A}^{B} \left[\overline{Cp_i} \cdot (T_{\text{out}} - T_{\text{feed}}) \cdot \dot{m}_i^1 \right] + \sum_{i=A}^{B} \left[\overline{\Delta H_{\text{vap\_}i}} \cdot \dot{m}_i^2 \right] + Q_{\text{loss}} \tag{8.1}$$

$$Q_{\text{loss}} = U \cdot A \cdot (T_{\text{out}} - T_{\text{room}}) \tag{8.2}$$

$$y_i \cdot P = x_i \cdot \gamma_i \cdot P_i^{\text{sat}}. \tag{8.3}$$

The accuracy of the thermodynamic model can be significantly improved by measuring experimentally the heat loss of a particular unit. Figure 8.7 depicts the accuracy of the model by comparing experiment with model inlet temperatures.

The development of a thermodynamic model is of utmost importance for modeling and scale-up purposes and provides an expeditious way to anticipate process conditions at any scale. Figure 8.8 below shows the typical information that is obtained through this model.

8.1.4.2 Droplet Size Estimation

The second stage of process modeling consists in applying a reliable correlation between atomization parameters, liquid properties, and droplet size. Numerous experimental studies have been carried out, and several equations have been proposed to relate droplet size to nozzle design, atomization energy, and physical and flow properties of the gas and liquids employed. Although some published models have proved

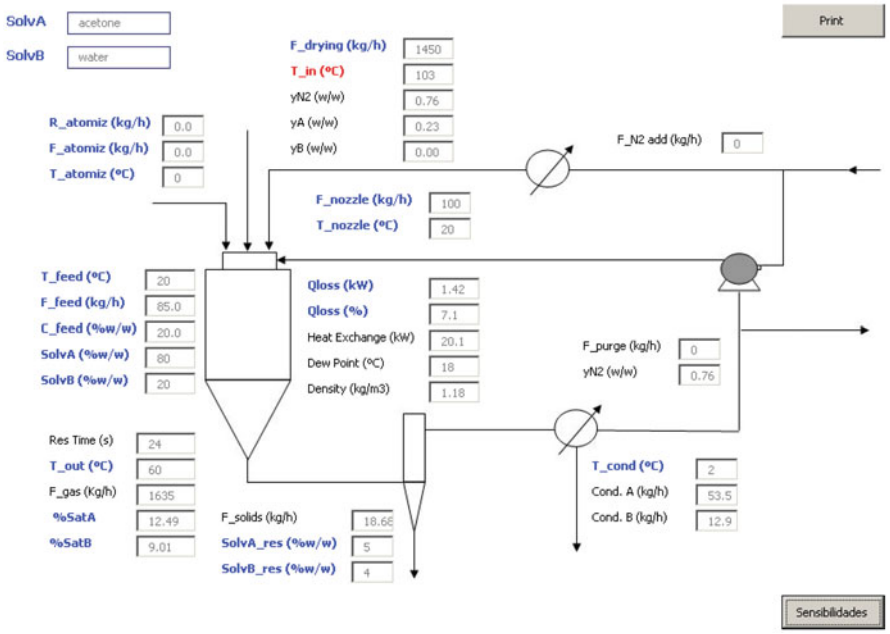


Fig. 8.8 Output of thermodynamic modeling for a process using pressure nozzle

good predictive capabilities, it is worth noting that these models were developed for specific nozzle geometry, and extrapolation to other nozzles needs to be done with care. An example of such correlations is shown in Eq. 8.4 below. The correlation was developed based on data from 12 nozzles from Spraying Systems (Maximum Free Passage, SK Series SprayDry®) with different geometric dimensions.

$$d_D = 2.41\sigma^{0.25}\mu^{0.25}F_{feed}^{0.25}P_{feed}^{-0.450}\rho_g^{-0.25}. \tag{8.4}$$

Figure 8.9 shows that despite many influences of process and formulation variables on the particle formation process, droplet size is still the major factor controlling the particle size, and it can be estimated by Eq. 8.4. The atomization model is a valuable tool for scale-up since it can be used to select the nozzle that best suits the targets for process throughput and particle size.

8.1.4.3 Particle Formation

To describe the particle formation process, several authors (Vehring 2008) emphasize the usefulness of the Peclet number (ratio between droplet evaporation rate and diffusional motion of the solutes) as a mean to predict the morphology of spray-dried powders. For low Peclet numbers, the diffusion motion of the solutes is fast compared to the velocity of the receding droplet surface and the droplet is allowed

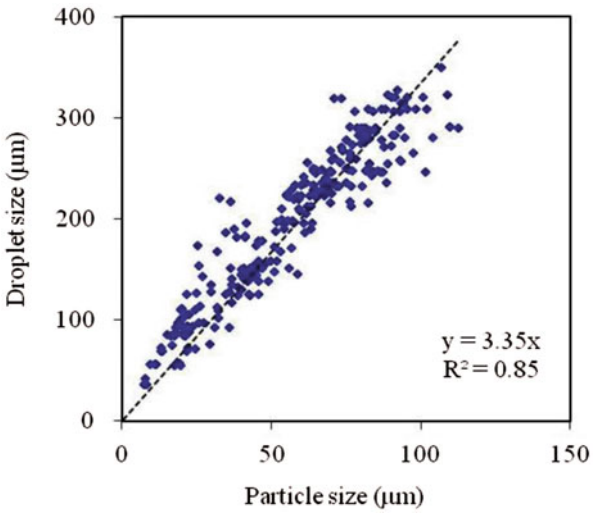


Fig. 8.9 Dv50 is highly correlated with the droplet size produced during the atomization process. Trendline was forced to pass through the origin

to shrink while solutes migrate to the droplet center. At a critical supersaturation level, dense and solid particles are produced. For high Peclet numbers, on the other hand, the evaporation predominates over diffusion and the surface becomes rapidly enriched in solutes that precipitate. In these cases, an outer layer is formed almost instantaneously at the droplet surface leading to hollow, light, and porous particles.

Often in pharmaceutical applications, viscous feeds are obtained as a result of the formulations used (e.g., polymers, proteins, carbohydrates among other large molecules) and particles tend to be hollow. However, the plasticity of the pharmaceutical materials during drying has resulted in greater morphologies diversity (Walton 2000). Due to the low diffusivity, most pharmaceutical particles form a shell earlier during drying and the rate of evaporation decays gradually as the shell becomes thicker. At this point, the shell mobility is determined not only by the diffusion of the dissolved solids but also by their solubility and, more importantly, by the mechanical properties of the formed shell (Vehring et al. 2007). If the drying rate is high, the critical thickness, i.e., the thickness that assures the mechanical stability of the shell, is reached very early in the drying process and the resulting particles sustain the spherical form of the droplet. On the other extreme, if the drying is slow, the thin shell formed in the early stages of drying will recede until its thickness is stable enough to sustain the particle structure. So by controlling the evaporation rate and drying time, one can exert control over particle morphology (see Fig. 8.10). The mechanism of evaporation in a still gas, based on boundary-layer theory, can be justifiably applied to many spray drying conditions (Masters 2002) and used to estimate the drying time of the droplets. While the constant evaporation rate is applied, the drying time can be expressed by the following equations:

$$t = \frac{\rho_L}{8D_v\left(P_{wb} - P_{out}\right)}\left(d_D^2 - d_P^2\right) \tag{8.5}$$

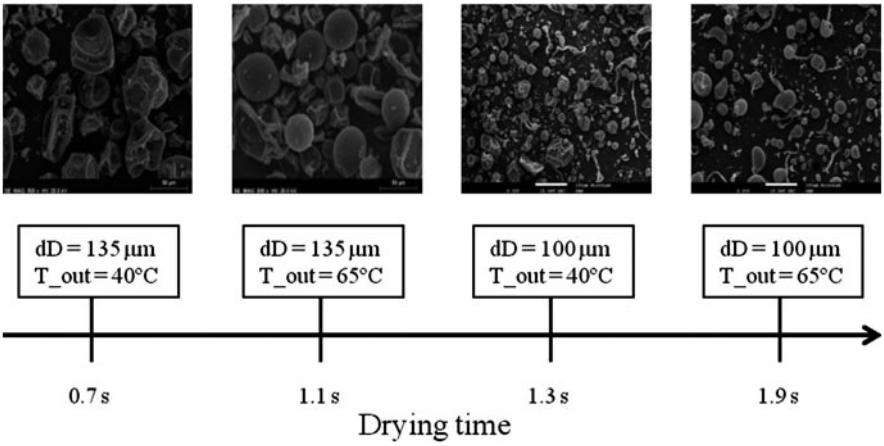


Fig. 8.10 Illustrative relationship between drying time and the sphericity of the spray-dried particles

$$Dv = \frac{0.00143T^{1.75}}{MW_{AB}^{1/2}\left[(\Sigma_v)_A^{1/3} + (\Sigma_v)_B^{1/3}\right]^2} \tag{8.6}$$

$$T_{wb} = 137\left(\frac{T_b}{373.15}\right)^{0.68} \log\left(T_{out}\right) - 45 \tag{8.7}$$

In Eq. 8.5, the vapor pressure at wet bulb temperature can be calculated from the Antoine equation, while the solvents concentration (P_{out}) in the drying gas can be determined in the thermodynamic step described previously. For example, fast evaporation and low drying times can be imposed by manipulating T_{out} and droplet size (d_{D}) and used to promote the production of smooth spherical particles.

The other feature throughout the formation of particles is the creation of internal pressure when droplets are dried at temperatures close or above the boiling point of the solvent. In this case, the vapor pressure inside the particles is higher than the outer surface and particles can, depending on the shell properties, inflate or break apart as the result of the pressure gradient. When particles expand, then particle size becomes a function of droplet size and outlet temperature (Fig. 8.11a). On the other hand, if the material is friable, the particles tend to break apart and the degree of breakage is typically more pronounced at higher temperatures. In those cases, particle size is still dependent on the droplet size, but the outlet temperature or relative saturation has a negative effect on particle size (Fig. 8.11b).

The tools presented throughout this section are intended to be used in all the steps of the scale-up to assure the production of powders with the desired quality, viz. particle size, particle morphology, and level of residual solvents. This enhanced understanding and mechanistic thinking, in line with the quality by design (QbD) initiative, will support the establishment of ample design spaces that are both unit and scale independent.

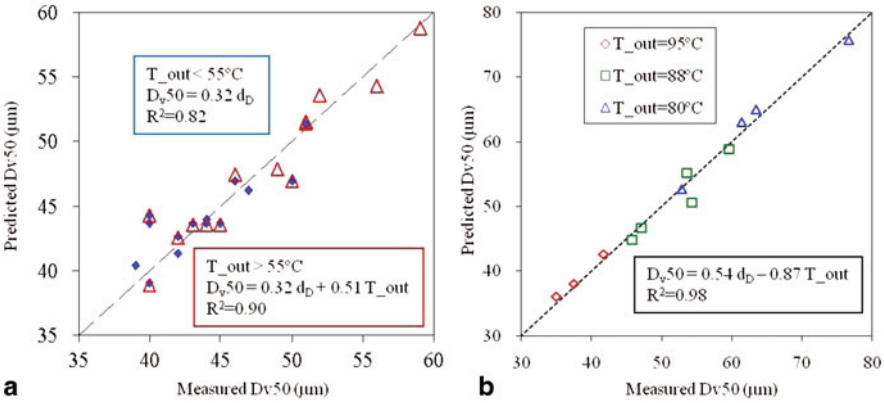


Fig. 8.11 **a** Particle inflation observed above boiling point; **b** typical behavior of a friable material

8.1.5 Scale-Up Methodology

As discussed in the Sect. 8.1.1, the spray dryer scale may have a significant impact on the properties of the spray-dried material and general scale-up procedures have to be established to assure an uneventful transfer to larger scales. Before embarking on the scale-up of any process, it is highly recommended to attain a stable and robust process at lab scale. Only then one can clearly understand how key process parameters such as temperature profile in the drying chamber (T_{in} and T_{out}), condenser temperature (T_{cond}), drying gas and feed flow (F_{drying} and F_{feed}), and atomization conditions should be set at the larger-scale unit. The present methodology is based on the mechanistic understanding described in the previous section and comprises three modeling steps: thermodynamic, atomization, and particle formation.

8.1.5.1 Thermodynamic Step

Through thermodynamic modeling (see Sect. 8.1.4), one can calculate the relative saturation of the drying gas. This combined with a small set of experiments at lab scale provides the relationship between the level of residual solvents in the product and relative saturation of the drying gas. This is particularly important when producing amorphous materials since their glass transition temperature (T_g) is affected by the residual solvent since solvent acts as a plasticizing agent. Figure 8.12a illustrates how these relationships can be used for scale-up purposes: If the target is to manufacture a spray-dried (wet) powder at a $T_g > 60\,°C$, then the level of residual solvent in the spray-dried material should not exceed 9 % w/w. At lab scale, this residual solvent level was obtained when operating with a relative saturation of 8 %. Therefore, a possible scale-up condition, which can be seen as a conservative or safe approach, is to maintain at the larger-scale equipment a relative saturation at the exit of the drying chamber (RS_{out}) at a similar level. If droplet size is maintained somewhat

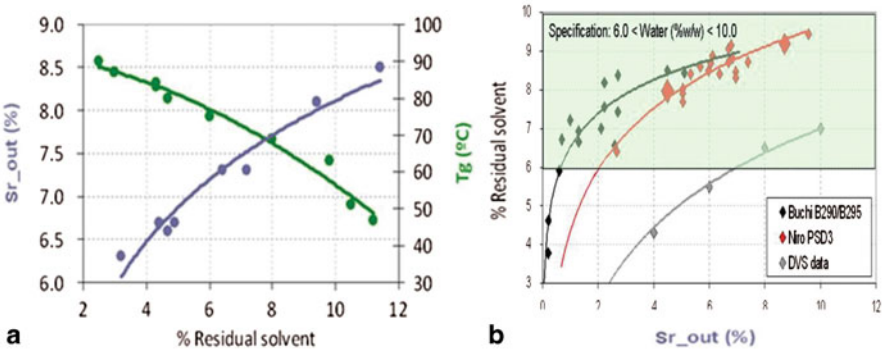


Fig. 8.12 **a** Effect of the relative saturation of the drying gas on the level of residual solvents and T_g and **b** effect of the scale on the desorption curves of a spray-dried product

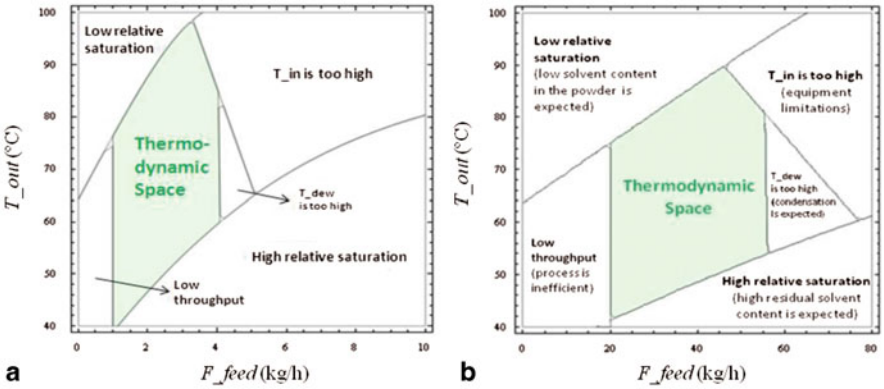


Fig. 8.13 **a** Thermodynamic space at pilot scale and **b** projection to commercial scale

unchanged, the extended residence time in larger scales will provide a safety margin to the assumed relationship between RS_{out} and level of residual solvents. As can be seen in Fig. 8.12b, the sorption curve approaches the equilibrium when increasing the scale (equilibrium data is obtained with dynamic vapor sorption studies).

The multivariate thermodynamic relationship of the process parameters with RS_{out} can also be used to define the process operation range that respects the imposed constraints. Apart from the limits imposed on the RS_{out}, the constraints usually include equipment limitations (e.g., maximum inlet temperature or minimum condenser temperature), product requirements (e.g., outlet temperature limited by the product degradation profile, physical stability, or stickiness behavior), and other process constraints (e.g., F_{drying} limited by the gas disperser or flow requirements, F_{feed} limited to avoid high dew points). These theoretical relationships provide a bridge between processes at different scales, as depicted in Fig. 8.13 below.

Fig. 8.14 **a** stable spray drying process, **b** product degradation in the cyclone, and **c** bad atomization leading to product accumulation in the bottom of the drying chamber

This thermodynamic analysis is a very powerful tool often replacing the need for experimentation at different scales. However, as mentioned before, product constraints should ideally be studied at lab scale to minimize development costs. Visual degradation of material, bearding, heavy accumulation due to inadequate temperature profiles, or poor atomization among other are all easier to understand and to solve at lab scale (see Fig. 8.14).

Some of the most common studies performed at lab scale include:

- Stability of the drug in the feed. This can be critical to the success of the scale-up. In larger scales, product may be held in solution for many hours or days, and therefore, the kinetics of degradation at different feed temperatures should be known. In some cases, the feed temperature needs to be reduced to prevent impurity growth.
- Process yield (expect $> 80\,\%$ for a sample of more than 5 g). The reasons for a low yield are very diverse (e.g., product stickiness or bad atomization) and should be solved at small scale before scale-up.
- Ability/ease of the secondary drying step. At lab scale, drying profiles and physical/chemical stability of the product can and should be evaluated.
- Process edge of failure by spray drying, for example, at elevated relative saturation (RS_{out}) can be very useful to understand the limits of the process and provide extra information for the scale-up process.
- When stable process conditions are found, it is recommended to run the process for an extended period to monitor the robustness of the process. Note, for example, that some processing issues (e.g., nozzle bearding or heavy product accumulation in the equipment walls) may not be obvious in very short tests.

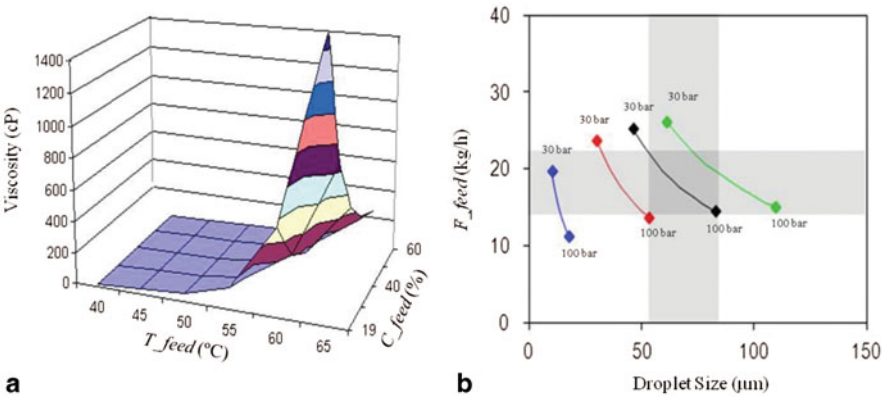


Fig. 8.15 **a** Feed solution characterization regarding the impact of C_{feed} and T_{feed} on feed viscosity and **b** simulation of four nozzles MFP (maximum free passage) SK series SprayDry nozzles from Spraying Systems; the core/orifice codes are –80/16, –70/20, –65/21, and –65/17

8.1.5.2 Atomization Step

Once the thermodynamic conditions have been established, there is a need to select the nozzle that best suits the targets of droplet size and process throughput. The most common nozzles used at lab scale are external two-fluid nozzles. However, during scale-up, there is typically the opportunity to improve powder properties by switching to a pressure nozzle. This results from the greater ability to produce and dry larger droplets in the larger drying chambers of the commercial units.

Feed properties like viscosity, density, and surface tension are well known to affect droplet size (and hence particle size). Therefore, for an accurate estimation of droplet size, it is recommended to characterize the solution regarding those properties. Frequently, all of these properties are dependent on the feed temperature (T_{feed}) and solids content (C_{feed}).

C_{feed} is a critical parameter which impacts the process viability and product quality in several manners, viz. process throughput, particle/powder density, or feed viscosity. Economic considerations of the process favor high C_{feed}, but concentrations close to the saturation point should be further studied to minimize the risk of product precipitation. Further, the use of high concentrations may lead to highly viscous feeds which may be difficult to atomize (Fig. 8.15a illustrates a typical relationship between feed concentration and temperature with feed viscosity). T_{feed} is rarely manipulated to obtain target powder properties. Nevertheless, it may affect solution stability and also influences viscosity and solubility. A strict control of T_{feed} is required, namely when operating close to solubility limits.

After determination of the feed properties, correlations like the one shown in the Sect. 8.1.4 (Eq. 8.4) are commonly used to predict the droplet size.

In the example given in Fig. 8.15b, the ranges of interest were 52–80 μm for droplet size and 14–21 kg/h for the feed flow rate. The most adequate nozzle, according to the feed properties measured and simulations performed, was the 65/21. The 65/21 nozzle fulfills both criteria within the typical operating conditions of pressure 30–100 bar.

8.1.5.3 Particle Formation Step

In order to establish a target for droplet size, it is required to study the effect of the drying condition on droplet drying and consequent particle formation. In the particle formation step, which is by far the most complex physical mechanism to describe, two approaches may be considered to estimate the final particle size.

The first approach assumes a constant shrinking ratio, i.e., a characteristic ratio between droplet size and particle size. When there is no information available about the product drying behavior, a pragmatic approach can consider a general shrinking ratio of about 3.3 (as seen in Fig. 8.9, most spray drying products follow the general trend of droplet size, independently of their nature and drying conditions).

A second approach is to use experimentally found shrinking ratio. This requires some prior knowledge of product/drying behavior. For example, the shrinking ratio observed at a smaller scale (and using similar drying conditions) can be used to model particle size at larger scale. In this approach, there is a need to measure or estimate the apparent density of the particles (measured, for example, by mercury intrusion porosimetry—Fig. 8.16), which can then be used to estimate particle size using a mass balance to the solids in the droplet and particle (Eq. 8.8).

$$\frac{d_{droplet}}{d_{particle}} \sqrt[3]{\frac{\rho_{particle}}{\rho_{droplet} \times C_{feed}}} \tag{8.8}$$

Besides particle size, the control of the particle morphology may also be critical for some applications. Surface area, particle density, and roughness or porosity are all known to affect the performance of spray-dried powders. Therefore, it is common during the development of a spray-dried product to explore the process to produce powders with distinct characteristics. This step of powder optimization can be conducted at pilot scale where a good compromise is achieved in terms of the range of particle/powders that can be obtained and the ability to target these ranges throughout the remaining of the scale-up process.

Particle properties are related to the drying kinetics of the droplets inside the drying chamber and are primarily dependent on the mechanical and chemical properties of the spray-dried material. These interactions are very complex to model, and therefore, process development is typically ruled by some general trends, as described below (see Fig. 8.17). The parameters that most influence particle morphology are T_{out} (or RS_{out}) and C_{feed}. Note that by adjusting the droplet size produced during the atomization process, one can control the particle size in such a way that size and morphology become almost independent of each other.

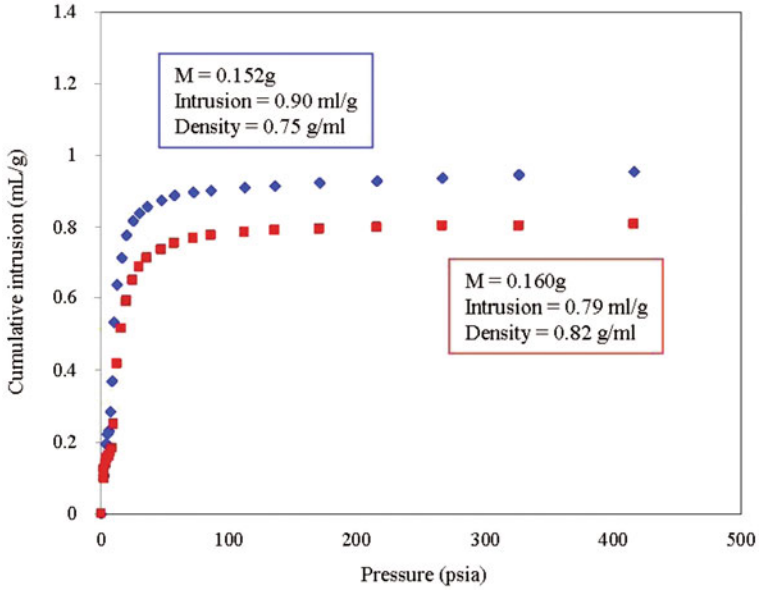
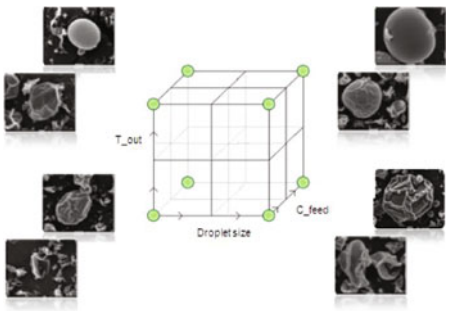


Fig. 8.16 Mercury intrusion in HPMCAS spray-dried particles manufactured at a Niro PSD4

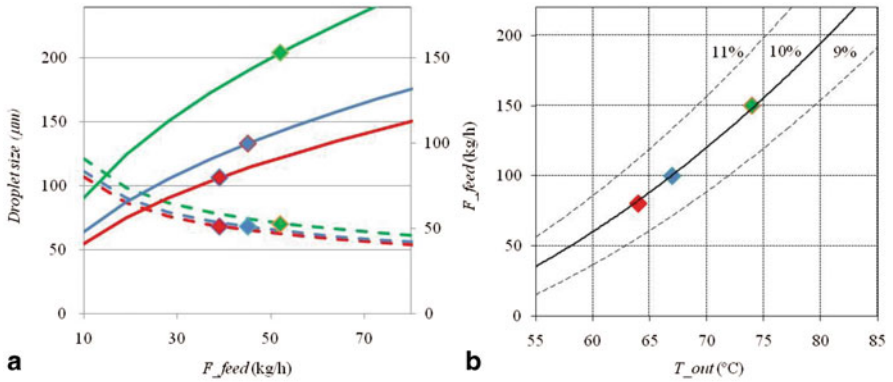


- Increase *T_out* to promote the production of smooth spherical particles
- Increase *C_Feed* to promote the production of dense particles
- Decrease *C_feed* to promote the production of shriveled particles (increased surface area)
- Size and morphology are roughly independent

Fig. 8.17 General guidelines to produce particles of different morphologies

8.1.6 Process Intensification

When moving to a full commercial scale, one of the main goals is to increase the process throughput while maintaining or improving the attributes of the powder. In other words, the goal is to increase F_{feed} and keep constant the RS_{out} and droplet size, already optimized at a smaller scale. Droplet size and throughput can be controlled by nozzle selection and atomization conditions, while RS_{out} is controlled by T_{out}, F_{feed}, and T_{cond}. This is achieved by using the thermodynamic and atomization models



nozzle	A	B	C
P_feed (bar)	39	45	50
d_D (µm)	66	66	69
F_feed (kg/h)	80	100	150
RS_out (%)	10	10	10

Fig. 8.18 Simulation of **a** nozzle performance and **b** relative saturation for three possible scenarios

described before. Figure 8.18 describes an illustrative example of how this can be simulated.

As depicted in the simulations of Fig. 8.18a, several nozzles can produce droplets within approximately the same size range but at very different feed flow rates. By changing from nozzle A to nozzle B or C, droplet size can be maintained while the process throughput is increased. With the feed flow defined, then, as can be seen in Fig. 8.18b, the heat requirements can be determined by the thermodynamic modeling in such a way that outlet temperature is defined in order to have approximately similar levels of relative saturation of those optimized in previous stages. It is schematized in Fig. 8.18; three different scenarios that, according to the developed models, have similar conditions of droplet size and relative saturation. It is expected that the three scenarios result in the production of powders with equivalent quality.

8.1.7 Conclusions

A scale-up method was proposed for spray drying processes. The method encompasses three steps: thermodynamics, atomization, and particle formation. A scale-up approach based on keeping the relative saturation of the drying gas at constant level can be derived using only lab-scale data to define the thermodynamic design space. The atomization condition and nozzle selection are decided based on target process throughput and droplet size considerations. The methodology presented here reduces the risk of failure during the initial scale-up of the process. The process can then be

Table 8.2 Summary of the scale-up methodology

Feed properties	
T_{feed}	Use the T_{feed} defined at lab scale. Keep a strict control over T_{feed}, mainly if operating close to the solubility limit
C_{feed}	Preferably defined at lab scale. May need adjustments for adjusting powder properties or for process intensification
F_{feed}	Work within the thermodynamic space defined by the target throughput and drying capacity of the equipment
Drying gas variables	
F_{drying}	Use the nominal flow of the equipment and adjust for drying gas density to keep pressure drop through gas disperser at nominal level
T_{out} and T_{cond}	Work within the thermodynamic space. Use initially a conservative scale-up approach; keep RS_{out} similar to the lab scale. Adjust at larger scale based on desorption/T_g data
Atomization variables	
Nozzle/P_{feed}	Pressure nozzle preferred for most applications. Very small particles (e.g., for inhalation powders), feeds with large suspended particles and very viscous feeds, may require other atomization systems, namely two-fluid nozzle. Use droplet size correlations to select the most suited nozzle and atomization conditions

T_{in} is a dependent variable that is limited by equipment constraints

gradually intensified to improve throughput while keeping material attributes roughly unchanged. Table 8.2 summarizes the methodology suggested.

8.2 Development of a Manufacturing Process of a Spray-Dried Dispersion Under a Quality by Design Approach

8.2.1 Methodology Overview

Pharmaceutical QbD is a systematic scientific risk-based holistic and proactive approach to pharmaceutical development that begins with predefined objectives that address product and process understanding. Successful product development relies on consistent application of a proven methodology. The key steps are the same, irrespective of the product or formulation being developed. One proven methodology is described within this chapter. The framework is shown in Fig. 8.19, while a short description of the main steps is given below.

Target Product Profile and Critical Quality Attribute The target drug profile consists of prospective and dynamic summary of the characteristics of a drug that should be achieved in order to reproducibly deliver the therapeutic benefit; the target product profile (TPP) sets an important number of performance parameters that will be the

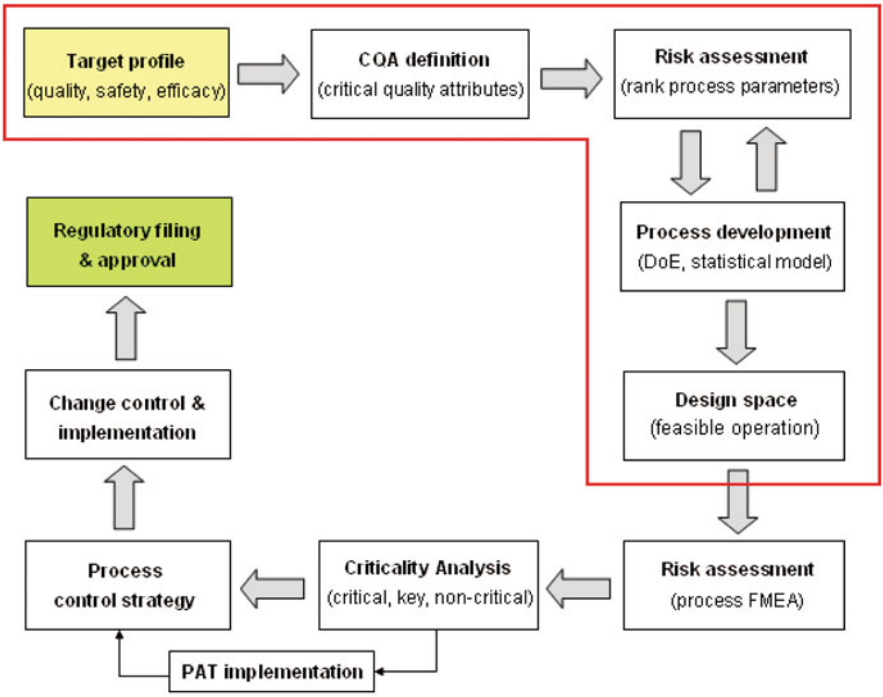


Fig. 8.19 Quality by design framework (main stages)

basis of the critical quality attribute's (CQA's) definition, that is, the attributes of the drug that must be kept within appropriate limits in order to ensure the desired product quality.

Risk Assessment (Development Phase) For each CQA, an analysis of the potential critical process parameters (pCPPs) and potential critical material attributes (pCMAs) is conducted. The aim is to evaluate, in each process step, which operating parameters or raw materials have the potential to impact a CQA, within the known ranges, and therefore should be monitored or controlled, in order to ensure the desired quality. Since the number of parameters is usually high, a risk assessment, based on prior knowledge of product/process, is used to rank the parameters in terms of perceived criticality; the ultimate goal is to keep the development process as lean as possible, by focusing the studies on those parameters and material attributes with a higher likelihood of having a critical impact.

Process Development The output of the previous risk assessment is a qualitative match between CQAs and pCPPs/pCMAs. To confirm the dependences and quantify the effects, a process development stage is conducted. If a statistical approach is followed, a sequence of design of experiments (DoE) is usually performed with different objectives: screening, optimization, and robustness studies. This development

stage constitutes the core of the QbD methodology since most of the specific process knowledge is generated during this stage. Although not mandatory, a model, either statistical and/or mechanistic, is a usual outcome of this stage. Process analytical tools can also to be considered at this stage; based on the need to improve, the CQA's monitoring as the process is scaled up.

Design Space and Normal Operating Range Once the impacts of the pCPPs/pCMAs are quantified on the CQAs, a feasible operating space can be defined. This space, known as the design space, will consider all the interactions between operating parameters and material attributes and will often be multidimensional. The normal operating range (NOR) is established within the design space, and can be thought of as the ranges where the process typically operates.

Risk Assessment (Manufacturing) After defining the design space and NOR, an exhaustive analysis of the process is conducted at the manufacturing scale. In this study, a failure mode effect analysis (FMEA) of all manufacturing aspects are reviewed, challenging the equipment operating ranges and procedures against the process knowledge gathered in the previous steps. The purpose of this study is to understand and quantify the risk of failure and to define actions to minimize it.

Criticality Analysis By knowing the feasible operating regions, the design space, and after evaluating the equipment/procedures at the manufacturing scale, directly evaluating the practical NORs, a final criticality analysis will take place in order to identify parameters and/or material attributes that will require tight monitoring or control; for example, all those for which the corresponding NORs are close to the boundaries of the design space.

Process Control Strategy Once the criticality around a process parameter and/or raw material attribute is confirmed, adequate control strategies will be set in place. The ultimate goal is to assure that operation is always taking place within the design space, therefore assuring the quality of the final product. For this purpose, and considering the dependence of a control strategy on a given monitoring capability, the final implementation of process analytical tools may be carried out at this stage.

The subsequent steps of this methodology are mainly focused on documentation aspects associated with the filing process and, given the purpose of this current article, will not be further discussed. This work focuses on the steps highlighted in Fig. 8.19, which will be discussed in detail in the sections below.

8.2.2 Case Study Overview

Two particular difficulties are generally recognized during the formulation of solid dispersions by spray drying: the need to dissolve both the drug and the polymer in a common solvent system and the need to prevent phase separation during the removal of the solvent. The selection/optimization of formulations will not be addressed in this chapter as the corresponding approaches/methodologies are extensively discussed

throughout this book by other authors; the formulation presented in this case study, optimized in previous stages of development, consisted of (1) a binary solvent system (methylene chloride and ethanol, 95/5 % w/w), (2) hypromellose phthalate (HPMCP) mixed with the drug at a ratio of 4:1, and (3) a solids concentration of 9 % w/w.

The solution is prepared in a reactor with a mechanical stirrer and a thermal circuit for temperature control. After complete dissolution, the solution is fed to the spray dryer. Droplet size is controlled by the liquid feed flow and by the type of atomizer and atomization conditions (pressure nozzles were used during this work). T_{out} is used to define the morphology of the particles and assure an efficient drying. The particles obtained were separated from the drying gas through a cyclone. The unit is operated in closed-loop mode, i.e., with recirculation of the drying gas. The solvent was removed by a condenser temperature within the gas recycling unit. Finally, the spray-dried material is collected and transferred to a double cone dryer for a secondary drying operation to fulfill the applicable limits for residual organic solvents.

8.2.3 Target Product Profile and Critical Quality Attributes

As introduced in Sect. 8.2.1, the roadmap of any QbD approach starts with the Target Product Profile (TPP) definition; this summary of drug characteristics (e.g., pharmacokinetic properties and stability) will serve as the basis for a set of performance parameters (e.g., immediate release drug: 80 % in $\leq$ 30 min, 36-month shelf life at room temperature, respectively) that, in turn, will be linked to a set of Critical Quality Attributes (CQAs; e.g., shelf life will depend on the amount of *residual solvents* due to its impact on chemical stability; release profile will depend on *particle size* for some drugs due to its impact on dissolution).

As one may expect, not all attributes of a drug will be classified as critical; Q6A (Conference and Harmonisation 1999) offers guidance on this matter, by distinguishing groups of attributes that should always be classified as critical regardless of the drug's end use (e.g., identification, assay, purity) from others whose classification (critical, noncritical) will depend on the final product nature (see decision trees in Q6A Conference and Harmonisation 1999). In order to conduct this exercise, it is therefore important to have the full picture of all manufacturing processes that are associated with a given product since, as depicted in Fig. 8.20, some of the attributes of an intermediate manufacturing step (e.g., density of the bulk powder) are established as critical due to their importance for subsequent manufacturing steps (e.g., by affecting tablet hardness during downstream operations).

For the sake of simplicity, the current case study will only focus in one of the manufacturing steps (the spray drying of the bulk powder, as previously introduced in Sect. 8.2.2) and, within this one, only show the application of the QbD methodology for two of the CQAs: particle size (Dv50) and bulk density (BD). The considered specifications for these CQAs (31–57 μm for particle size and 0.100–0.200 g/ml for BD) were set based on the interaction/interdependence with the downstream process

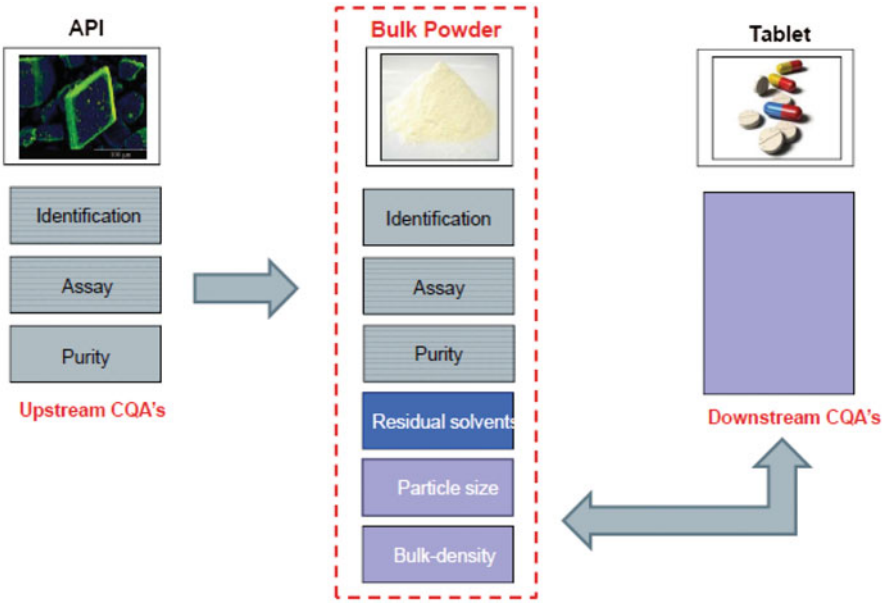


Fig. 8.20 Interactions between upstream and downstream processes during CQA definition

where, as introduced before, these attributes reveal a critical importance during manufacturing of the final oral dosage form.

8.2.4 Risk Assessment

The number of parameters involved in any spray drying process is relatively large, and evaluating the impact of each one, in all CQAs, would be difficult to manage (both from a cost and time perspective); therefore, one of the main goals of the risk assessment, as previously introduced in Sect. 8.2.1, is to reduce the number of pCPPs that will be studied in subsequent stages of process development. As shown Fig. 8.21, the procedure adopted considers the ranking, for each CQA, of all process parameters, according to the perception of criticality (that relates to the mechanistic understanding and relevant manufacturing experience with similar products).

Once a ranking of perception of criticalilty is obtained, the process parameters can then be divided into three groups: a first group (T_{out}, P_{feed}, D_{noz}, T_{cond}), that is considered to have a potentially relevant impact on the CQAs and, therefore, will be studied in detail in order to establish the design space; a second group (F_{drying}, C_{feed}), considered to have a lower potential of criticality—these parameters will not be optimized (they will be fixed at preestablished set point values based on prior knowledge of the process or similar processes) but will be used during the final evaluation of the process robustness (in order to confirm the assessment made); a

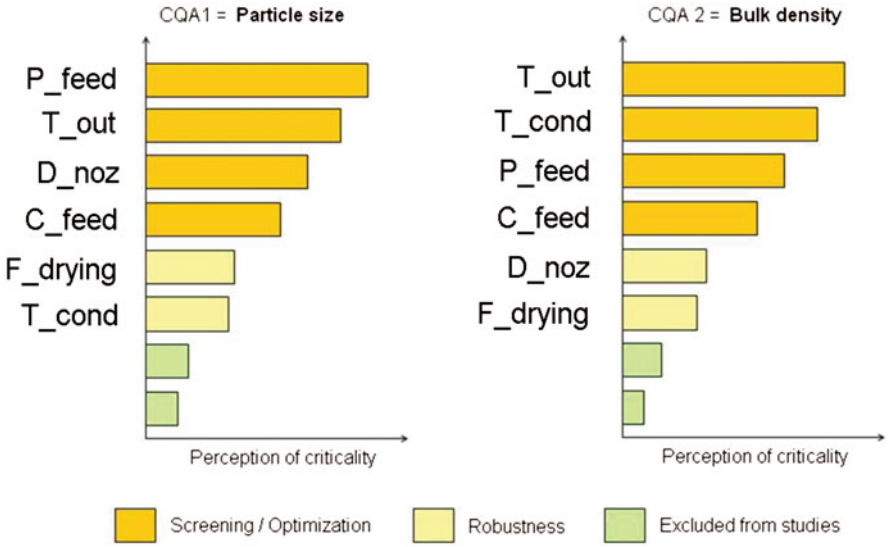


Fig. 8.21 Ranking of pCPP per each CQA

third group (the least ranked parameters), that are expected to have no impact on the process and that will be excluded from further studies. The rational for exclusion of these parameters needs to be appropriately justified in a QbD application.

8.2.5 Process Modeling

The outcome of the previous risk assessment is a qualitative match, based on perceptions, which needs to be confirmed and quantified during a subsequent process development stage. A mechanistic description of the process, as introduced in Sect. 8.1.5, can be used as a powerful tool to establish the design space with minimum need for experimentation at final scale. However, this type of description is not always readily available, and the use of a statistical approach constitutes a pragmatic alternative. The limitation of the statistical approach is its reliance on scale-dependent experimentation and the difficulty in extrapolating relationships to other scales or equipment. Selection of the most adequate approach (mechanistic or statistical) depends, therefore, on the (1) existence/reliability of the mechanistic understanding, (2) availability of material for experimentation, and (3) flexibility required on the design space. In this section, a statistical approach will be illustrated in order to quantify relationships between process parameters and product attributes; the three involved steps are described in Fig. 8.22.

The objectives of a screening stage, used to confirm the most significant factors, are to determine the ranges of process parameters to be investigated and to reduce the

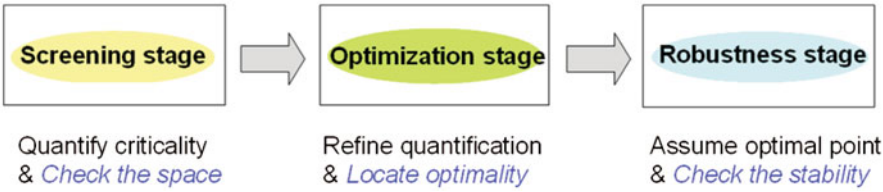


Fig. 8.22 Statistical modeling approach: structured sequence of design of experiments

number of parameters to be further studied. Since an accurate quantification of the effects is not crucial at this stage, low-resolution experimental designs can be considered. Hence, few experiments per studied factor are typically required. The second level of the experimental plan consists of the optimization of the process conditions over the most promising subregion found during the screening stage (considering only the parameters that have previously shown statistical significance). Since the ability of capturing interactions between process parameters may greatly influence the outcome of this stage, high-resolution experimental designs are advised. Finally, the robustness evaluation is conducted in order to determine the sensitivity of a CQAs toward small changes in some process parameters. Typically, the robustness evaluation is centered at the target operating point (defined during the optimization stage), by considering variations on parameters that have not been studied in detail.

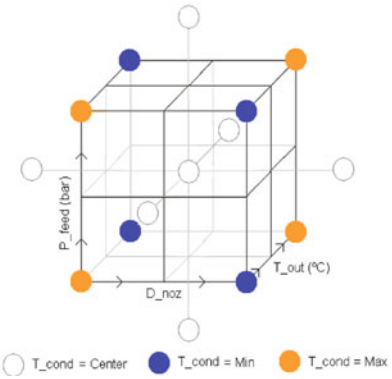
8.2.5.1 Screening Stage

Among the pCPPs of the spray drying step, the risk assessment identified feed concentration (C_{feed}), feed pressure (P_{feed}), outlet temperature (T_{out}), condenser temperature (T_{cond}), and nozzle orifice diameter (D_{noz}) as the highest-ranked ones.

For the screening stage, a DoE with resolution ≥ 4 is recommended in order to retrieve unconfounded relationships between first-order terms. The structure of the DoE is shown in Fig. 8.23. In order to study a broader range of process throughputs, six star points were added to a 2^{4-1} fractional factorial.

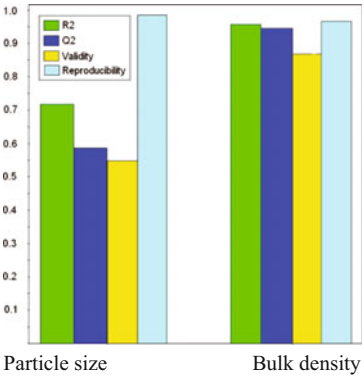
The results obtained, shown in Fig. 8.24, reveal that the response of BD seems to be well described by a linear function of T_{out}. For particle size, although a reasonable model has been obtained, a linear structure seems to be insufficient to explain the observed variance (as denoted by the relatively low R^2 and Q^2).

Additionally, this screening phase shows that two factors (T_{cond} and D_{noz}) were found to have no statistical significance (within the tested ranges) and, therefore, should be subsequently excluded from the optimization stage. Finally, the screening model also showed that a great share of the evaluated operational ranges is feasible (considering the target ranges for Dv50 and BD).



Input variable	Min	Center	Max
P_feed (bar)	50	85	120
T_out (ºC)	25	55	85
T_cond (ºC)	-10	-5	0
D_noz (mm)	1.01	0.91	0.78

Fig. 8.23 Screening study: DoE structure (*left side*) and ranges of variation studied (*right side*)



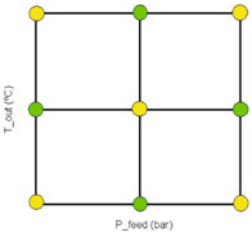
	p-value	
	D50	BD
P_feed	$6.72 \times 10_{-3}$	0.280
T_out	$8.93 \times 10_{-4}$	5.78x10-10
D_nozzle	0.846	0.381
T_cond	0.742	0.322

Fig. 8.24 Screening study: model adequacy (*left side*) and statistical significance data (*right side*)

8.2.5.2 Optimization Stage

During the optimization stage, the operating ranges were narrowed down and an experimental design (central composite face-centered design) was considered in order to support nonlinear interaction models. Only P_{feed} and T_{out} were selected as input variables at this stage, in agreement with the conclusions taken before. The center point assumed during the screening study was maintained since product attributes obtained at 85 bar and 55 °C were close to the target values. The DoE selected to support the optimization stage, as well as the considered ranges for the input variables, are shown in Fig. 8.25.

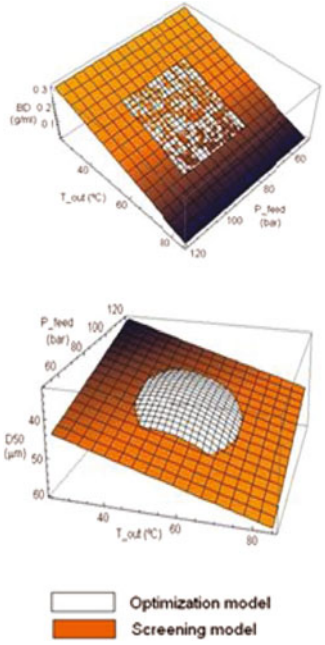
As shown in Fig. 8.26, the quadratic interactions improved the accuracy of the model for particle size prediction. For powder BD, the optimization study confirmed the suitability of a linear model (only function of T_{out}).



Input variable	Min	Center	Max
P_feed (bar)	70	85	100
T_out (ºC)	40	55	70

D_ nozzle = 0.91mm; *T_cond* = Cte = -5ºC

Fig. 8.25 Optimization study: DoE structure (*left side*) and ranges of variation studied (*right side*)



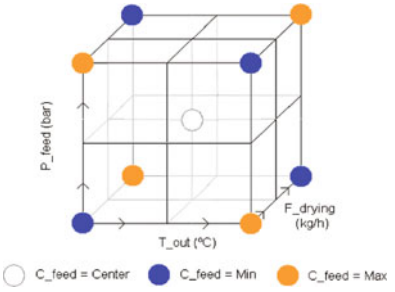
		D50 (□ m)	BD (g/ml)
Constant		141.2	0.449
P_feed	(bar)	-1.46	---
T_out	(ºC)	-1.35	-5.44 x 10^{-3}
P_feed · *T_out*	(bar ºC)	---	---
(*P_feed*) ^{2}	(bar)^2	7.64 x 10^{-3}	---
(*T_out*) ^{2}	(ºC)^2	1.47 x 10^{-2}	---
R^2	(-)	0.87	0.97
Q^2	(-)	0.79	0.96

Fig. 8.26 Model predictions: Dv50 (*left bottom*) and BD (*left top*), coefficients, and adequacy data

8.2.5.3 Robustness Stage

The DoE considered in this stage is shown in Fig. 8.27. The selected ranges for the input variables translate possible deviations around the parameters settings. The optimal values for P_{feed} and T_{out} were determined through the optimization model, considering the target values for product attributes.

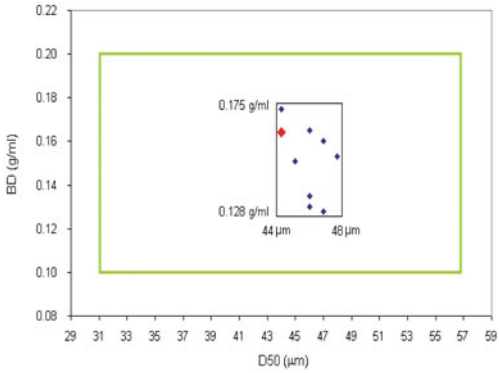
No reliable model was obtained for particle size prediction (a desired outcome, considering the nature of this study), which is in agreement with the small response of Dv50 observed in Fig. 8.28 (between 44 and 48 μm). For BD, however, it was still



Input variable	Min	Center	Max
P_feed (bar)	P_opt -5	P_opt	P_opt +5
T_out (ºC)	T_opt -2	T_opt	T_opt +2
F_drying (kg/h)	1300	1400	1500
C_feed (% w/w)	8.5	9.0	9.5

D_noz = 0.96 mm; *T_cond* = -5ºC

Fig. 8.27 Robustness study: DoE structure (*left side*) and ranges of variation studied (*right side*)



	p-value	
	D50	BD
P_feed	0.118	0.220
T_out	0.793	0.019
F_drying	0.433	0.395
C_feed	0.514	0.608

Fig. 8.28 Robustness study: results against targets in place (*left side*) and statistical significance (*right side*)

possible to obtain a model as a function of T_{out} (denoting an undesirably high sensitivity), confirming the strong dependence predicted by the screening/optimization models. Based on the results of Fig. 8.28, it can be concluded that (1) the process is robust towards the parameters F_{drying} and C_{feed} (thus validating the risk assessment) and that (2) although all obtained results are within the specification limits, T_{out} will need to be carefully monitored and controlled during the control strategy definition (due to its high potential of criticality via a high process sensitivity).

8.2.6 Design Space

The design space was defined as the multidimensional combination of the pCPPs where, according to the optimization model, all CQAs' values are obtained within the applicable target ranges. Although considering the intersection of the feasible operating ranges for each CQA, the final design space was mainly constrained by the BD target range, as shown in Fig. 8.29.

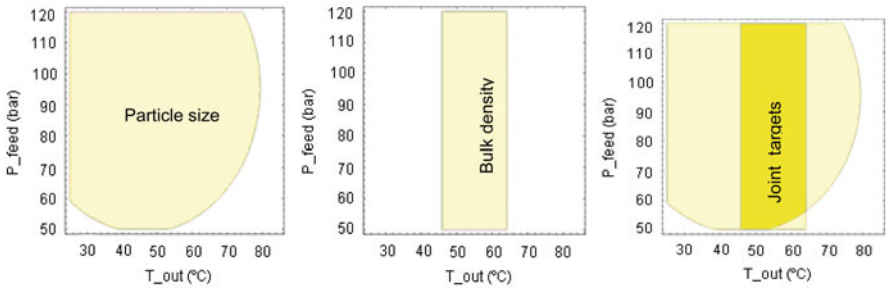


Fig. 8.29 Design spaces for Dv50, BD, and joint Dv50 and BD targets

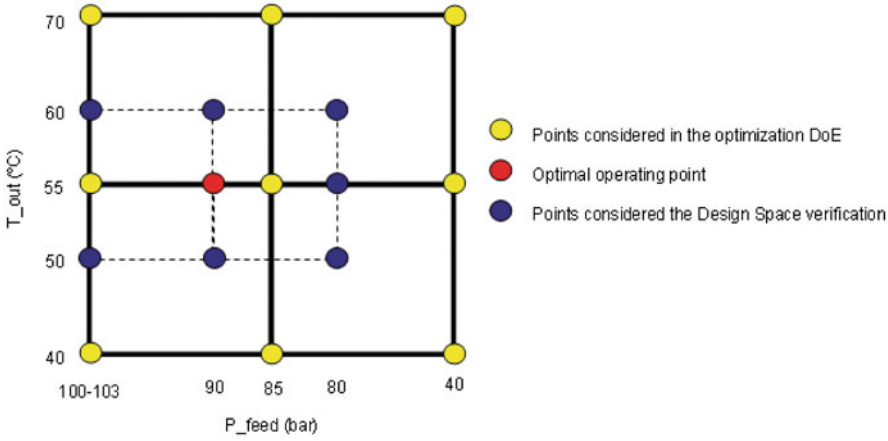


Fig. 8.30 DoE structure for design space validation

Regarding the validation of the design space, there is no universally recommended procedure for verification of a model, and there is limited literature or regulatory guidance that addresses the extent of verification required to justify a design space (Hallow et al. 2010). In the present work, eight additional runs were performed inside the design space and confronted with the predictions of the optimization model. A 3^2 DoE was centered in the optimized operation point (see Fig. 8.30). The results obtained showed very small errors (the root mean squared error was 0.06 μm for particle size and 0.003 g/ml for BD).

Nevertheless, this type of assessment can be misleading, as the magnitude of the model prediction errors (small or large, acceptable or unacceptable) can only be properly judged when confronted with the target specification ranges, during an uncertainty evaluation exercise (García-Muñoz et al. 2010; Peterson 2008). In fact, all models will have a corresponding error distribution, causing the boarders of the design space to be a less safe operating region. These error distributions are the sum of all the variability that cannot be explained or controlled (e.g., sampling errors, analytical method variability, influence of unknown factors, etc.) and should

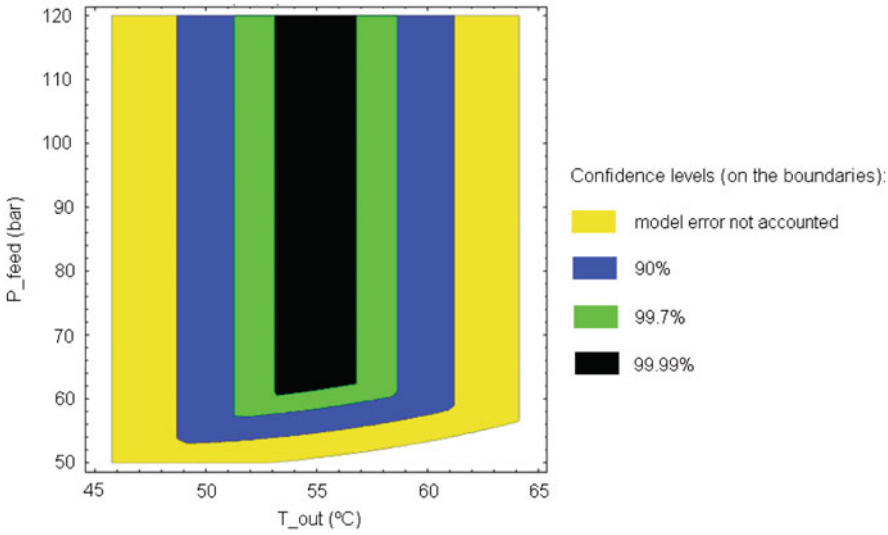


Fig. 8.31 Design space boundaries as a function of the imposed confidence level

be accounted during definition of the design space limits. In this work, the error distribution was calculated using the residuals of the optimization model and the eight runs performed for the design space validation. A normal distribution was fitted to the data (17 points in total) through a nonlinear parametric regression. The error distribution was then used to estimate error intervals at different confidence levels. By accounting the errors intervals on the limits of the CQAs' target ranges, it was possible to establish the design space in a true risk-based approach where broader operating ranges for the pCPPs imply greater risks of excursions outside the CQAs' target ranges. As shown in Fig. 8.31, the 90 % confidence boundaries lead to a significant reduction of the original design space. However, if the operating point is properly selected ($P_{\text{feed}} = 90$ bar and $T_{\text{out}} = 55\,^{\circ}\text{C}$), a temperature variation of $\pm 3\,^{\circ}\text{C}$ and a pressure variation ± 30 bar will have a very low likelihood of threatening the target CQAs' ranges (as the 99.7 % confidence boundary is not crossed), an observation that is in agreement with the outcome of the robustness study.

8.2.7 Mechanistic Understanding

The design space reported in the previous section was built based on statistical models; however, the ultimate goal of any QbD framework should be the enhanced understanding of the process, and this is ultimately achieved when a mechanistic interpretation of the underlying phenomena is derived. Theoretical description of the process of particle formation comprises two sequential steps: the atomization

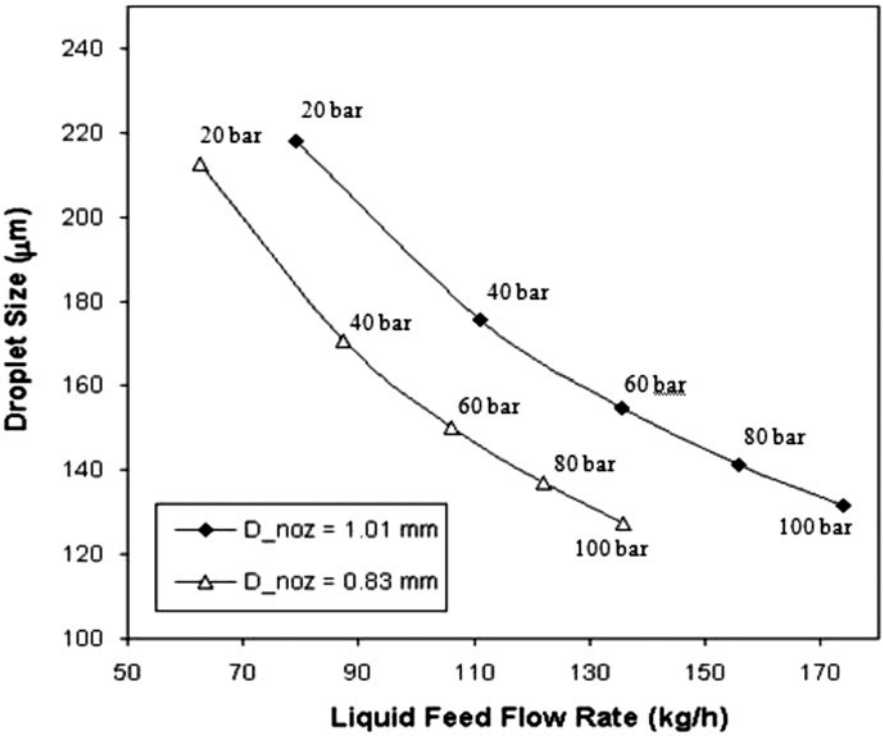
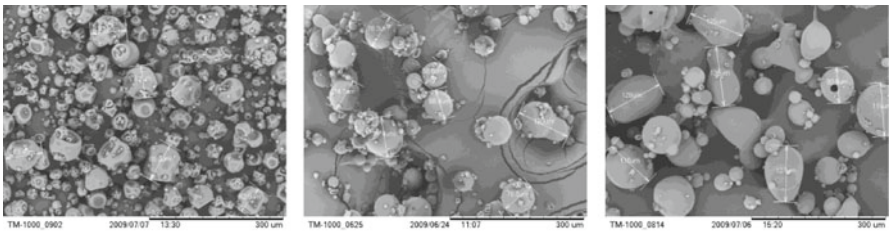


Fig. 8.32 Atomization model predictions: Influence of nozzle orifice diameter on droplet size and throughput, P_{feed}, ranged from 30 to 100 bar in both nozzles

process to describe the liquid breakup and drying kinetics to explain the final particle morphology.

In the present work, droplet size was calculated using the atomization model introduced in Sect. 8.1.5, and the obtained simulations (Fig. 8.32) were used to support the final nozzle selection, considering all relevant production goals (i.e., process throughput and target particle size). As forecasted by the theoretical simulations (and confirmed by the screening statistical studies of Sect. 8.2.5), the nozzle orifice diameter has little impact on droplet size. However, it is one of the most important factors that determine the process throughput; changing the diameter of the orifice is actually the most expeditious way to control the process throughput and keep the droplet size roughly unchanged.

Regarding the particle morphology, the maximum structural stability of the spray-dried particle is in a spherical form; however, the interactions between several process parameters, which are related to the mass and heat transfer of the droplet, can result in different particle morphologies. From the theoretical point of view, the evaporation begins as soon as the droplets are ejected from the nozzle. Consequently, the droplet



T_out = 25ºC → Dv50 = 43□ m | T_out = 55ºC → Dv50 = 44 □ m | T_out = 85ºC → Dv50 = 59□ m

Fig. 8.33 SEM pictographs: Influence of T_{out} on particle size, at the same conditions ($P_{feed} = 85$ bar; $D_{noz} = 0.96$ mm; $T_{cond} = -5$ °C)

surface rapidly becomes enriched in solutes. At a certain supersaturation level, precipitation will occur and a rigid particle will be formed with a given particle diameter. From this standpoint, it is expectable that particle size closely follows droplet size. However, at low temperatures, the mechanisms of solvent evaporation are slower, allowing more time for particle surface to deform, shrink, or collapse. On the other hand, at temperatures close or above the boiling point of the solvents, the increased internal vapor pressure may lead the particles to inflate. Both phenomena could be observed during the current work, being more notorious when the experimental data is grouped in two sets: drying temperatures below and above boiling point. Two models for particle size were built with different sensitivities towards T_{out}. Below the boiling point, particle size is only dependent on the droplet size; above boiling point, particle size is dependent on both droplet size and T_{out}. Both models of the particle size showed good correlation coefficients (see Fig. 8.11a), and, together with the different morphologies shown in Fig. 8.33, it is therefore possible to consolidate and bridge the current mechanistic interpretation with the statistical model derived for particle size in Sect. 8.2.5.

Since the atomization process is not affected by the drying condition (T_{out}, T_{cond}, and F_{drying}), the droplet size distribution produced by a given nozzle is mainly dependent on P_{feed}. Hence, since the same applies to the mass distribution of the droplets (at constant C_{feed}), particles produced at high temperatures have lower densities. Thus, powders dried at low temperatures have relatively high BD, because the individual particles are shriveled and not very porous; on the other hand, powders dried at high temperatures have relatively low BD, because the individual particles preserve their inflated state and are, consequently, very porous (Langrish et al. 2006). Both interpretations are well aligned with the statistical model derived in Sect. 8.2.5 for BD, where T_{out} shows up as the most important operating parameter.

Therefore, through the development of mechanistic analyses, it is therefore possible not only to predict and control particle size but also to understand the main physical phenomena that rule particle morphology and powder BD.

8.3 Conclusions

In the current work, a QbD methodology was applied during the development of a spray drying process for the manufacture of a pharmaceutical solid dispersion. The risk assessment stage (where mechanistic knowledge and past experience play an important role) was found to be of major importance in order to keep development as lean as possible (by focusing on the most important parameters). Although not mandatory, the development of predictive models is strongly advisable to establish a reliable design space where model uncertainty should be addressed. Statistical approaches are a pragmatic way of establishing these relationships; however, a fundamental mechanistic understanding will always be advantageous as this one portrays the physical principles that rule the process and, therefore, enables more general considerations. For the current spray drying process, the combination of statistical and mechanistic information enabled to conclude that (1) particle size depends mainly on the droplet size and outlet drying temperature, (2) nozzle diameter dictates the throughput and does not affect particle size significantly, and (3) BD can be controlled just by manipulation of the outlet drying temperature due to its strong influence on the porosity of the particles.

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