

Scale-up methodology for pharmaceutical spray drying

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ABSTRACT: The use of spray drying in the pharmaceutical industry is growing at a fast pace. The need for robust scale-up methods is essential in order to control critical quality attributes and improve powder properties during drug development. Moreover, poor scale-up is likely to lead to considerable losses of expensive materials. Process understanding and simulation is a very powerful tool to support the scale-up of spray drying processes. A scale-up methodology based on scientific principles is proposed in this study. The method is divided in two steps: thermodynamic and atomization & particle formation. The method is relatively straightforward to apply and has been tested in numerous spray-dried formulations across all production scales. An illustrative example is also shown covering the main steps of the proposed methodology.

INTRODUCTION

Spray drying is presently one of the most interesting technologies in the pharmaceutical industry. The process shows a remarkable capability in manipulating powder/particle attributes such as size, morphology, density and level of residual solvents. This flexibility led to its application in a variety of powder formulations and advanced solid forms: from very fine powders for inhalation to large particles for direct compression, and from solid dispersions for enhanced bioavailability to microcapsules for drug protection or controlled release. Moreover, the technique is also applied to process difficult-to-crystallize materials and temperature sensitive compounds (the relative short exposure to temperature makes it a gentle process, suitable for handling most sensitive materials).

Spray drying is a unit operation in which a liquid stream (solution, suspension or emulsion) is continuously divided into very fine droplets (a process known as atomization) into a chamber where they are contacted with a hot gas and dried into particles, which are separated from the drying gas using a cyclone or a bag-filter. Hence the spray drying process can be described as consisting of four events: i) atomization of the liquid into droplets, ii) contact of the droplets with the hot drying gas, iii) drying of the droplets into particles and iv) separation of the particles from the drying gas.

Spray driers can operate in open cycle mode (where the drying gas is passed through the chamber and vented to the appropriate waste stream) or in closed-loop mode (where the drying gas is recycled typically via a condenser or a scrubber unit).

A key feature in any spray drying process is the atomization system since it controls droplet size and hence particle size. Rotary, pressure, two-fluid and ultrasonic nozzles are the most common systems. For each type of atomizer, a wide range of designs were developed to handle the diversity of feed materials and to meet specific dried-product characteristics. In the pharmaceutical industry pressure and two-fluid nozzles are the most common, due to their simplicity (and easy cleaning), flexibility and ability to handle most feedstocks (1). Spray dryers in the pharmaceutical industry are available in a wide range of scales: from lab units where milligrams of material can be produced to very large commercial units capable of handling several tons per day. One particular concern during development of pharmaceutical spray dried materials is the effect of scale-up on critical quality attributes. Moreover, a less careful scale-up strategy may lead to considerable losses of very expensive materials and jeopardize the timelines of a clinical program. Mathematical modelling is a very powerful tool to support the scale-up of spray drying processes.

Process simulation has been used in chemical and oil industries since the early of 1960s and more recently pharmaceutical development scientists have also begun to make use of it during development, scale-up and manufacturing (2). The use of process simulation should result in more robust processes, faster development at a lower cost and in higher quality products (3). This enhanced understanding is also in line with the Quality by Design initiative and the *Desired State* of the industry.

This paper describes a scale-up methodology for spray drying processes based on scientific first principles simulation models and process characterization techniques. Such methodology aims to ensure that scale-up is as straightforward and predictable as possible.

SCALE-UP METHODOLOGY

The scale-up of spray drying processes has been mainly conducted based on experimental experience. Among the reasons are the complexity of the drying process (characterized by rapid and simultaneous heat and mass transfer between the droplets and the drying gas) and the unavailability of model parameters, often not readily measured. Furthermore, the whole process is extremely dependent of the feed properties and equipment scale and design. Nevertheless, some fundamental engineering models approaches for up-scaling spray drying processes can be found in the literature.

Berman et al. (4) considered the humidity of the exhaust air from the spray dryer a critical process control parameter. Thermodynamic modelling was used to estimate the humidity of the exhaust air for a particular set of processing conditions. However, this methodology was not able to predict most particle/powder related attributes such as particle size and moisture level.

More recently, Thybo et al. (5) investigated the ability to produce identical powders in different scales by matching the droplet size distribution produced in the two atomizers. The methodology was not successfully implemented, for the applied formulation, because the differences in droplet temperature and residence time histories between the spray drying units was not accounted for.

Dobry et al. (6) proposed a methodology that encompasses thermodynamics, droplet drying kinetics, particle formation and atomization principles. The events were discussed qualitatively and the methodology, based on engineering models and process-characterization tools, was used as an alternative to traditional empirical spray-drying process-development methods.

The purpose of the present work is to present a pragmatic approach to process scale-up based on thermodynamic, fluid dynamics and drying kinetics considerations.

Thermodynamic

In the thermodynamic step, the aim is to understand how process parameters such as the temperature profile in the drying chamber (T_{in} and T_{out}), the condenser temperature (T_{cond}), drying gas and feed flows (F_{drying} and F_{feed}) will scale-up from any smaller unit to a larger unit. Note that this step disregards most phenomena concerning atomization and particle formation. The proposed method is based on energy and mass balance equations (see (1) for details), together with the liquid-vapour equilibrium models to describe the condenser unit, drying gas flow corrections (due to variations

in gas density) and process/product related restrictions (such as glass transition of the material being spray dried). Such thermodynamic models require no detailed knowledge of the equipment geometry nor the drying mechanisms involved. However, if possible, the heat loss should be measured experimentally since this is affected by unit design, construction materials and environment conditions (in general, heat loss becomes less significant as the scale increases). Also, some important and not readily measurable process parameters can also be calculated in this thermodynamic space. For example solving the thermodynamic model for the relative concentration of the gas phase at outlet conditions, i.e. concentration of solvent in the gas phase in relation to its concentration at saturation (Cr_{out}), the following expression is obtained:

$$Cr_{out} = \frac{1}{P_{air}(T_{out})} \times \frac{(F_{feed} \cdot x_{solvent} - \%Solv \cdot F_{solids} + y_{cond}^* \cdot F_{drying}) \cdot MW_{solvent}}{(F_{feed} \cdot x_{solvent} - \%Solv \cdot F_{solids} + y_{cond}^* \cdot F_{drying}) \cdot MW_{solvent} + F_{drying} \cdot (1 - y_{cond}^*) \cdot MW_{gas}} \quad (1)$$

Cr_{out} can thus be manipulated either by the feed flow (F_{feed}), outlet temperature (T_{out}) or condenser temperature (T_{cond} , which affects the equilibrium condition at the condenser, y_{cond}^*), as illustrated in the above equation.

Moreover, Cr_{out} is closely related with the residual solvent level in the dried material (%Solv) through the applicable desorption kinetics. Therefore, a common scale-up condition, which can be seen as a conservative/safe approach, is to maintain the relative saturation at the exit of the drying chamber (Cr_{out}) at a similar level.

This is particularly important when producing amorphous materials since the residual solvent level in the solid strongly affects its glass transition temperature (T_g). This represents another constraint to the scale-up of a spray drying process (the outlet temperature, T_{out} , should be kept below T_g).

Atomization and particle formation

In the atomization and particle formation step several key events occur in sequence. The droplets formed come into contact with the hot gas leading to evaporation of the solvent and solute precipitation. Efforts to understand these processes were intensified in the last decade with the aim of improving powders attributes.

Feed properties (like viscosity, density and surface tension) and atomization conditions (such as nozzle orifice diameter, spray angle and atomization energy) are well known to affect droplet size (and hence the final particle size of the product).

The droplet size obtained from an atomization process is commonly predicted through empirical correlations. However, those correlations are often product and nozzle-dependent and may not describe adequately the complex fluid dynamic processes (7). Extrapolation should therefore be done carefully since they may be valid only in the local experimental space.

On the other hand, Computational Fluid Dynamics can not currently handle the dynamics of liquid break-up (8) and require droplet size as an initial condition to do further process simulations. The most accepted theoretical approaches for droplet size estimation are based on the stability and collapse of liquid jet and sheet systems. They assume that prior to liquid break-up, unstable waves develop with a distinct wavelength that dictates the droplet size (see (9) and (10) for detailed descriptions of the models for pressure and two-fluid atomization, respectively).

These theories provide a qualitative description of the physical mechanisms involved in the jet/sheet breakup and were able to describe quantitatively experimental data (9, 11-15). However, some complex phenomena, such as droplets coalescence, are still most often neglected which may lead to additional errors in the estimation of the final droplet size distribution. Nevertheless, the mean droplet diameter provided by instability theories is still a good approximation and can be of a good guidance for scale-up purposes.

Regarding particle formation, by far the most complex physical mechanism to describe mathematically, two pragmatic approaches may be considered. The first approach assumes a constant shrinking ratio, i.e. a characteristic ratio between droplet size and particle size. This requires some prior knowledge of product/drying behaviour. For example, the shrinking ratio observed at a smaller scale (and using similar drying conditions) can be used to model larger scale processes. Alternatively, one can use the shrinking ratio of a similar product (for example in formulations using large proportions of the same polymer).

In the second approach, there is need to measure or estimate the apparent density of the particles, which can then be used to estimate particle size using equation 2 (16). A good estimation for the apparent density of a spray dried material is the value obtained from preliminary work at a smaller scale

and similar drying conditions. In the absence of this information, the values obtained with similar products or those reported in the literature can be useful. For example for spray dried lactose, particle apparent densities of 0.26-0.39 g/cm³ have been measured (15).

$$\frac{\bar{d}_{droplet}}{\bar{d}_{particle}} = \sqrt[3]{\frac{\bar{\rho}_{particle}}{\rho_{droplet} \times C_{feed}}} \quad (2)$$

Nozzle selection will depend on the target quality attributes and on feed properties. In most pharmaceutical applications pressure nozzles are preferred to two-fluid nozzles, mainly because they provide powders with a narrower particle size distribution. The main exceptions are when feeds have very high viscosities or large suspended materials (which may block the nozzle orifice) or when very fine powders are required. In the latter case, the greater ability to manipulate and control particle size in the fine range favours two-fluid nozzles.

It is noteworthy that during scale-up there is a great opportunity to improve powder properties. This results from the greater ability to produce and dry larger droplets in the larger drying chambers of the commercial units. This is an advantage if the purpose is to obtain large and denser particles for solid oral dosage forms. For particles for inhalation, however, the scale up challenge is to keep particle properties unchanged. An overview of the methodology described above is illustrated in Figure 1.

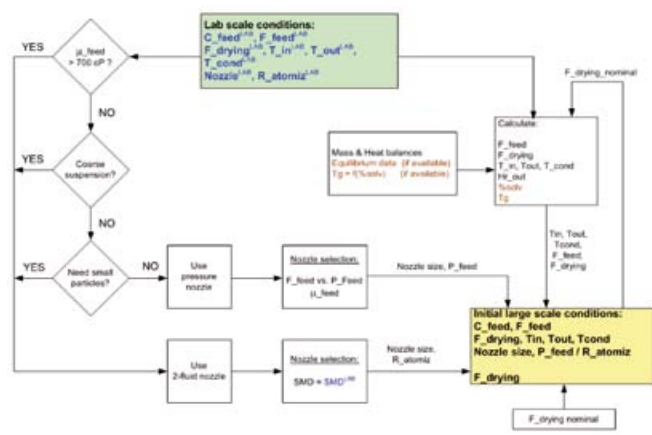


Figure 1. Scale-up methodology.

ILLUSTRATIVE EXAMPLE

A process developed at the laboratory scale (40 kg/h of nominal drying gas flow) was transferred to a commercial unit (1250 kg/h nominal drying gas flow).

The feed solution used methanol as the solvent and had a concentration of 20% w/w (150 g/ml). The basic data taken from small scale work is shown in Figure 2.

| Process parameter | Unit | Commercial scale |
|------------------------------------|------|--------------------|
| F _{drying nominal} | kg/h | 1250 |
| F _{drying} | kg/h | 1500 ^{a)} |
| C _{feed} | %w/w | 20 |
| T _{in} | °C | 107 |
| T _{out} | °C | 55 |
| T _{cond} | °C | -12 |
| F _{feed} | kg/h | 78 |
| C _{rout} | %w/w | 7.9 |
| Viscosity at 5°C | cP | 13 |
| Surface tension | mN/m | 22.5 |
| Concentration (C _{feed}) | g/l | 150 (20%w/w) |

^{a)}A higher drying gas flow was used to maintain the pressure drop in the air distributor at similar (nominal) level.

Table 1. Main process parameters for commercial scale production.

In order to guarantee acceptable stability of the spray dried product it was required to achieve a T_g ≥ 60°C. Using Figure 2, it can be seen that for a T_g of 60°C the solvent level in the spray dried material will be approximately 9.3% w/w. At lab scale this residual solvent level was obtained when operating with a relative concentration of 8.0% w/w.

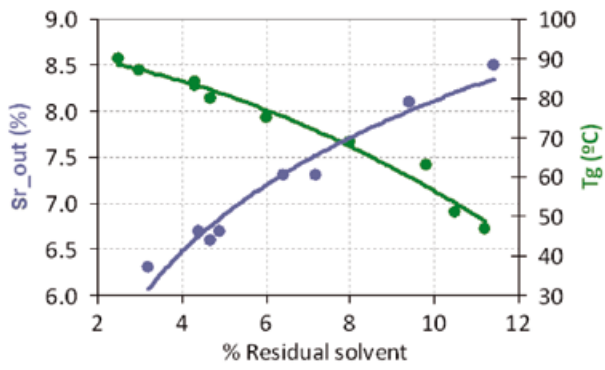


Figure 2. Relationships between: i) relative saturation (at lab scale) and residual solvent level (blue), ii) glass transition temperature and residual solvent level (green).

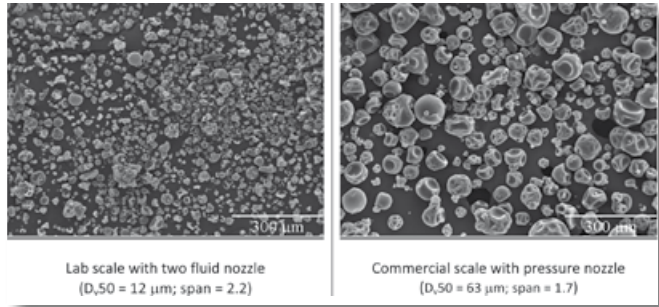


Figure 4. Scanning electron micrographs of the powders.

- Feed flow (F_{feed}) = 78 kg/h
- Predicted droplet size = 92 µm
- Predicted particle size = 62 µm

This compares relatively well with the experimental data. A particle of 63 µm was obtained. The span obtained, 1.7, is typical for a pressure nozzle. In Figure 4 the powders obtained from both scales are compared by SEM.

CONCLUSIONS

A scale-up method was proposed for spray drying processes. The method is divided in two steps – a thermodynamic step and an atomization and particle formation step. The scale-up approach proposed, based on maintaining the relative concentration of the drying gas at constant level, uses only lab scale data and reduces significantly the risk of failure during the initial

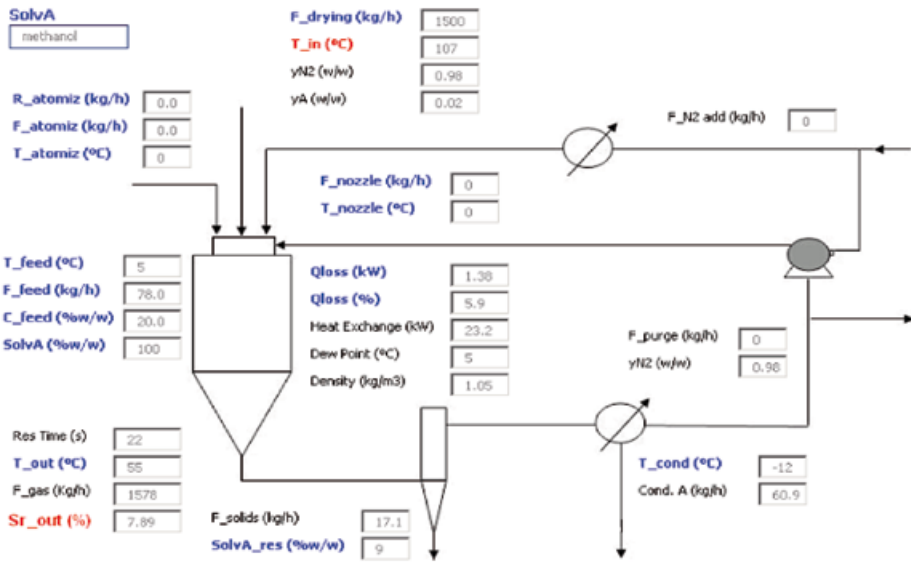


Figure 3. Process simulation for a commercial spray dryer.

A conservative scale-up approach was used by keeping the relative concentration at a similar level. (Note that the extended residence time in the larger drying chamber provides a safety margin to the assumed relationship between concentration level in the gas phase and solvent level in dried powder). The mass and energy balance were therefore used to find out the operating conditions at the commercial scale. Table 1 summarizes the main process parameters taken from the process simulator illustrated in Figure 3.

After establishing the thermodynamic space, it is time to define the atomization conditions. The product being processed was a powder for oral administration and the target was to significantly improve powder properties, namely by increasing particle size (from 12 µm to ~50-100 µm) and by reducing the span of the distribution (2.2 at lab scale). The atomizer used at lab scale, a typical two-fluid nozzle, was therefore replaced by a pressure nozzle in the commercial scale. Note also that the feed properties (see Table 1) did not present any limitation to the use of a pressure nozzle. We have estimated an apparent particle density of 0.5 g/ml (value obtained from a similar product at large scale). A droplet size between 70 and 140 µm is therefore required.

With a feed flow of 78 kg/h, the properties of the feed summarized in Table 1, and using pressure nozzles from SS (Spraying Systems), the following conditions and estimations were obtained:

- Nozzle diameter = 0.71 mm
- Feed pressure (P_{feed}) = 85 bar

scale-up of the process. However, this conservative method will result in a non optimized throughput of the process. Regarding atomization and particle formation, a mechanistic model was used to describe the former and estimate droplet size and this was then coupled with experimental data (using the apparent density of the particles) to estimate particle size. The approach is simple to use but requires prior knowledge on the product/drying behaviour. A good agreement was found between predictions and experimental results.

NOMENCLATURE

T_{in} – Gas inlet temperature

T_{out} – Gas outlet temperature

T_{cond} – Condenser temperature

F_{drying} – Drying gas flow rate

F_{feed} – Feed flow rate

Cr_{out} – Relative outlet concentration

P_{sat} – Saturation vapour pressure

$x_{solvent}$ – Solvent mass fraction

$\%SOV$ – Mass fraction of residual solvent in the dried solid

F_{solids} – Dried solid flow rate

$MW_{solvent}$ – Solvent molecular weight

MW_{gas} – Gas molecular weight

y_{cond}^* – Solvent mass fraction at equilibrium in the condenser

Tg – Glass transition temperature

$\bar{d}_{droplet}$ – Average droplet diameter

$\bar{d}_{particle}$ – Average particle diameter

$\bar{\rho}_{particle}$ – Average particle apparent density

$\rho_{droplet}$ – Droplet density

C_{feed} – Concentration of the feed solution

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