Chapter 2

Spray Drying: An Overview

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Abstract

Spray drying is a well-known method of particle production which comprises the transformation of a fluid material into dried particles, taking advantage of a gaseous hot drying medium, with clear advantages for the fabrication of medical devices. In fact, it is quite common the production of microspheres and microcapsules designed for drug delivery systems. This review describes the different stages of the mechanism of the spray-drying process: atomization, droplet-to-particle conversion and particle collection. In particular, this work addresses the diversity of available atomizers, the drying kinetics and the importance of the configuration of the drying chamber, and the efficiency of the collection devices. The final properties of the dried products are influenced by a variety of factors, namely the spray dryer design, the feed characteristics and the processing parameters. The impact of those variables in optimizing both the spray-drying process and the synthesis of dried particles with desirable characteristics is discussed. The scalability of this manufacturing process in obtaining dried particles in submicron-to-micron scale favors a variety of applications within the food, chemical, polymeric, pharmaceutical, biotechnology and medical industries.

Keywords: spray drying, dry particles, atomizer, drying chamber, collector

1. Introduction

Spray drying is a well-known method of particle production which consists on the transformation of a fluid material into dried particles, taking advantage of a gaseous hot drying medium [1]. Its first observation is dated 1860 and a primitive spray dryer device was patented by Samuel Percy in United States in 1872 [1–3].

Ever since it was first discovered, the spray-drying technique has been improved concerning its operational design and applications. In fact, the primordial spray dryer devices lacked process efficiency and safety. After overcoming these issues, spray drying became an attractive method for food industry purposes, ending up to be used in milk powder production in the 1920s, remaining one of the most important applications until the current days. Spray-drying evolution was directly influenced by World War II, where there was an imperative need to reduce the weight and volume of food and other materials to be carried [3, 4]. As a result, spray drying has become an industry benchmark, namely in the dairy products' fabrication. In the post-war period, the spray-drying method continued progressing, reaching the pharmaceutical, chemical, ceramic and polymer industries [3, 5].

Even after more than a century of research, spray drying is still a target of study and innovation due to the increasing demand for complex particles with specific characteristics. This is considered a powerful technological process since it brings feasibility to the production of free-flowing particles with well-defined particle size. Besides, bearing in mind the ability to use different feedstocks as well as its high productivity and broad applications, makes this technique more and more attractive to the scientific community [2, 3].

Spray-drying mechanism is based on moisture elimination using for that a heated atmosphere to which the feed product is subjected. The process may be described by three major phases (atomization, droplet-to-particle conversion and particle collection), although some authors use four or five minor steps to describe it in more detail [2, 4, 6]. As shown in **Figure 1**, a solution is pumped to an atomizer, breaking up the liquid feed into a

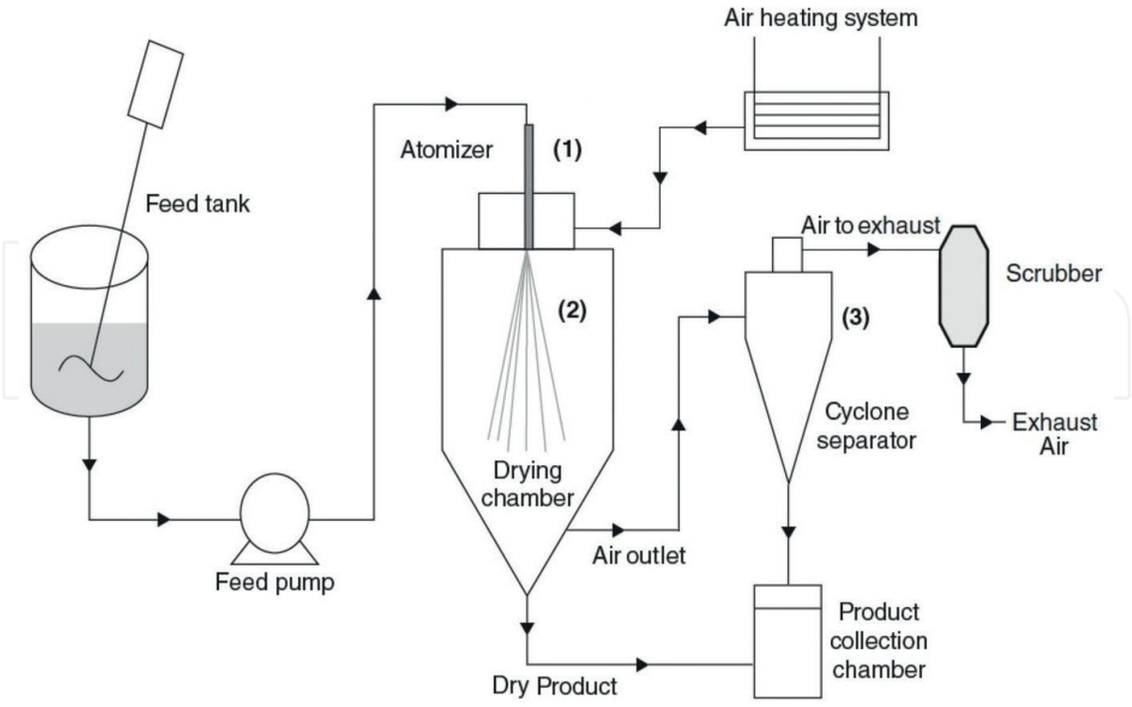

Figure 1. Schematic representation of spray-drying mechanism. (1) Atomization. (2) Droplet-to-particle conversion. (3) Particle collection. Adapted from [2, 7].

spray of fine droplets. Then, the droplets are ejected into a drying gas chamber where the moisture vaporization occurs, resulting in the formation of dry particles. Finally, using an appropriate device, the dried particles are separated from the drying medium, being then collected in a tank.

All of these stages, conjointly with the conditions, in which they are processed, play a crucial impact in the yield of spray-drying mechanism as well as in the final particle properties [1, 3]. Thus, every step of this mechanism will be meticulously described below.

2. Design and mechanism stages

2.1. Atomization

The spray-drying process is initiated with the feed solution atomization in small droplets due to a decrease of surface tension. This is considered a crucial step for the subsequent phases, namely during the drying chamber exposition. In fact, breaking up the initial solution into many droplets increases their surface area, optimizing therefore the heat and mass transfers between the heated drying gas and the liquid particles. In other words, this gathers the ideal conditions for evaporation process, which will be preponderant for the formation of dried particles [1, 6, 8].

The physical principle behind the atomization transformation process is based on the liquid disintegration phenomenon. Several authors have addressed different interpretations and analytical models to explain such event [2].

In 1873, Joseph Plateau was a pioneer in this issue, realizing that a liquid jet of constant radius, falling due to gravity, experiences a progressive increase of its length [2]. As soon as a critical value is reached, the cylindrical shape of the jet is disintegrated into small spherical droplets, which essentially takes place due to a decrease in surface tension (**Figure 2A**). Later, Lord Rayleigh (1878) [2] validated Plateau's work and postulated the "Liquid jet theory". In broad terms, he described the existence of perturbations waves in a simple laminar jet. For certain wavelengths, the optimum wavelength (λ_{opt} = 4.51d, where d is the initial jet diameter), such perturbations grow larger in time, causing the droplet formation (**Figure 2B**) [2].

Weber (1931) [2] and Ohnesorge (1936) [2] built a more complete model to describe the liquid instability. Besides the surface tension and inertial forces underlying the previous works, they

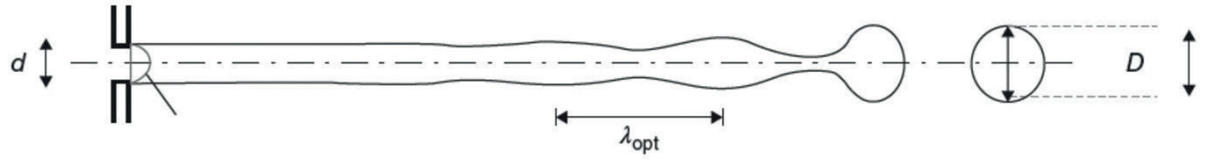

Figure 2. Schematic representation of droplet formation mechanism showing the optimum wavelength introduced by Rayleigh [2].

described the impact of other factors in the system, namely feed viscosity, the surrounding air and the atomization gas. Weber proved that the frictional forces of the surrounding air cause a decrease in the λ_{opt} for drop formation. Moreover, the increase of the relative velocity between the liquid jet and the surrounding air also provokes a decrease in the λ_{opt}, and consequently a reduction in the final droplet size. Regarding Ohnesorge's contribution, he reported the propensity of a liquid jet to breakup into droplets through a relationship (Eq. (1)) between its viscosity, density, surface tension and jet size [2].

$$Oh = \frac{\sqrt{We}}{Re} = \frac{\mu}{\sqrt{\rho \cdot \gamma \cdot L}} = \frac{Viscous\ forces}{\sqrt{(inertia \times surface\ tension)}} \quad (1)$$

Oh is the Ohnesorge number (dimensionless) that expresses a ratio between the Weber number (*We*) and the Reynolds number (*Re*). μ, ρ and γ are the viscosity, density and surface tension of the feed solution, respectively. *L* is the volume per unit area of the feed droplet.

The atomization process into droplet form may be accomplished by pressure, centrifugal, electrostatic or ultrasonic energy, using specific devices called atomizers [6, 8]. There are different atomizers (**Figure 3**), which are used according the desired product characteristics (shape, structure and size) as well as depending on the nature of the feed solution. The most common devices used in the majority of atomization processes are explained below and summarized in **Table 1** [1, 2]. In fact, there is a mathematical equation (Eq. (2)) which expresses the relation between the droplet diameter (D_d), the atomizer type and feed solution properties (surface tension (γ), viscosity (μ) and density (ρ)) [6].

$$D_d = K_f \cdot Q^n \left[\rho^a \cdot \gamma^b \cdot \mu^c\right] \quad (2)$$

K_f, Q and n are the equipment constant, feed solution volumetric flow rate, and the power constant of volumetric flow rate, respectively. The power constants of solution properties are represented by *a*, *b* and *c*.

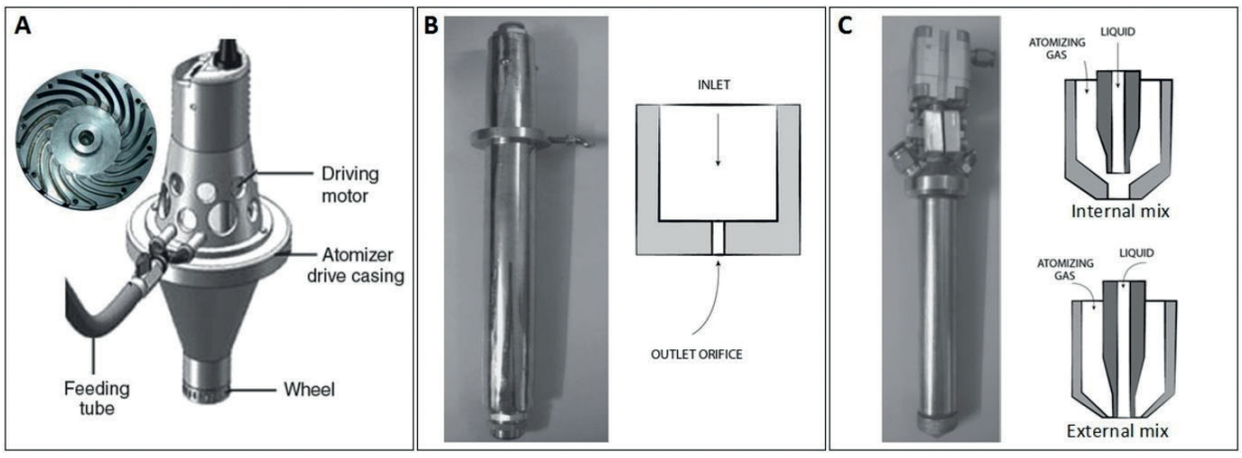

Figure 3. Schematic representation of conventional atomizers used on spray drying. (A) Rotary atomizer with respective disc atomizer in detail. (B) Hydraulic nozzle atomizer, (C) pneumatic nozzle atomizer—internal and external two-fluid nozzles. Adapted from [1, 2, 7, 9, 10].

	Rotary atomizer	Hydraulic nozzle atomizer	Pneumatic nozzle atomizer
Atomization energy	Centrifugal	Pressure	Kinetic
Atomization parameters	Disc speed 10,000–30,000 rotations per minute (rpm)	Nozzle pressure 250–10,000 PSI	Nozzle pressure 250–10,000 PSI
Type of spray	Fine, medium, coarse	Coarse, less homogeneous	Medium coarseness, poor homogeneity
Mean droplet size	30–120 μm [2] 10–200 μm [11]	120–250 μm [2] 30–350 μm [11] 20–600 μm [4]	30–150 μm [2] 5–100 μm [11] 10–200 μm [4]
Relation between D_d and the feed solution properties	$D_d \alpha Q$ $D_d \alpha \mu$	$D_d \alpha Q$ $D_d \alpha \mu$	$D_d \alpha Q$ $D_d \alpha \mu$
Relation between D_d and atomization	D_d is inversely proportional to disc speed and diameter	D_d is inversely proportional to atomization pressure	D_d is inversely proportional to atomization pressure
Advantages	Handle high feed rates without clogging; formation of uniform size particles; low pressure operation; high efficiency	Low price; formation of particles with little occluded air (i.e. particle production of higher density); enables the use of narrow drying chambers	Better control over particle size than in the hydraulic nozzle; useful for feeds of high viscosity; ideal to laboratory scale since it requires small drying chamber; good efficiency
Drawbacks	High price; not suitable to viscous feed; Inability to use a horizontal and small spray dryer chambers	Not suitable to high viscous feed; high feed rates cause coarse and less homogeneous sprays (i.e. broad particle size distribution)	High operation costs due to the need of high amounts of compressed gas for atomization; production of particles with high occluded air; Downstream turbulence

Adapted from [1–3, 7, 11].

Table 1. Conventional atomizers used on spray drying.

2.1.1. Rotary atomizers

The rotary atomizers have a horizontal wheel or disc, and the feedstock solution is driven to its center. There, a centrifugal force is applied which accelerates the feed solution to the periphery, forming a spray of droplets. It is common to find grooves in the atomizer disc, since these structures maximize the control over the solution dispersion caused by the rotary high velocities [1, 2].

2.1.2. Hydraulic nozzle atomizers

Also known as one-fluid nozzles, the operation principle of the hydraulic nozzles consists on the conduction of the feed solution, under pressure, through a pipe with gradually decreasing diameter. The fluid emerges from a small nozzle orifice (usually ranging from 0.4 to 4 mm in

diameter) at high velocity with a simultaneous loss in its pressure, undergoing atomization, and thus it is disintegrated in the form of droplets [1, 2].

2.1.3. Pneumatic nozzle atomizers

Pneumatic nozzles are also called multi-fluid nozzles. The most common configuration of these devices is based on a two-fluid nozzle atomizer, where two phases are fed into the nozzle, namely the feedstock solution and the compressed gaseous atomizing medium. The gas flows separately from the feed solution, meeting it whether within or outside the nozzle. Due to the high frictional forces over the liquid surface caused by the high gas velocity, atomization takes place and the feedstock solution is broken down into a cloud of droplets, as stated by Weber. Similarly to the previous atomizers, atomization is influenced by feed properties. Herein, gas velocity and density, as well as its direction and the ratio liquid/gas, also have an important effect in the atomization process [1–3].

2.2. Droplet-to-particle conversion

After atomization, the spray-drying mechanism proceeds with the particle formation phase, a crucial stage marked by two events: spray-air contact and droplet drying step, resulting, as a whole, in the removal of the droplets' solvent content and consequently on their transformation into dried particles [4, 6].

2.2.1. Droplet-air-contact

Atomized droplets are exposed to a hot gas within the drying chamber, resulting on first rapid moisture evaporation. Usually, this drying gas is heated (and filtered) atmospheric air, although in some cases there is a need to use other inert gases to avoid eventual instabilities between the gas and the droplets [2]. In what concerns drying chamber's size and shape, it should be consistent with the spray dryer setup, that is, it should be chosen according the used atomizer and the pretended particle properties. Thus, there are different sized drying chambers (smaller or taller), though they should be big enough to guarantee that particles have the necessary time to dry before reaching the chamber's walls (otherwise they would deposit in the chamber walls, which is undesirable). The majority of vertical chambers are cylindrical, ending with an inverted cone on its base, as depicted in **Figure 4** [1].

There are different drying chamber configurations, in which the flow pattern between the hot gas and the spray of droplets is distinct: co-current flow, counter-current flow and mixed flow [1].

In the co-current flow (**Figure 4A**), both the atomized spray and the heated gas enter at the top of the drying chamber, flowing through it in the same direction. The dried particles are dropped at the bottom of the chamber, where they are released together with the gas. In such configuration, there is no time for the drying gas to exchange some of its heat with the surroundings, and thus the atomized droplets meet the highest temperatures inside the drying chamber. However, this implies an instantaneous high rate of solvent evaporation (thermal energy of hot air is utilized for evaporation, cooling it), enabling the dried particles to contact with moderate temperatures which avoid undesirable thermal degradation [1, 2, 8].

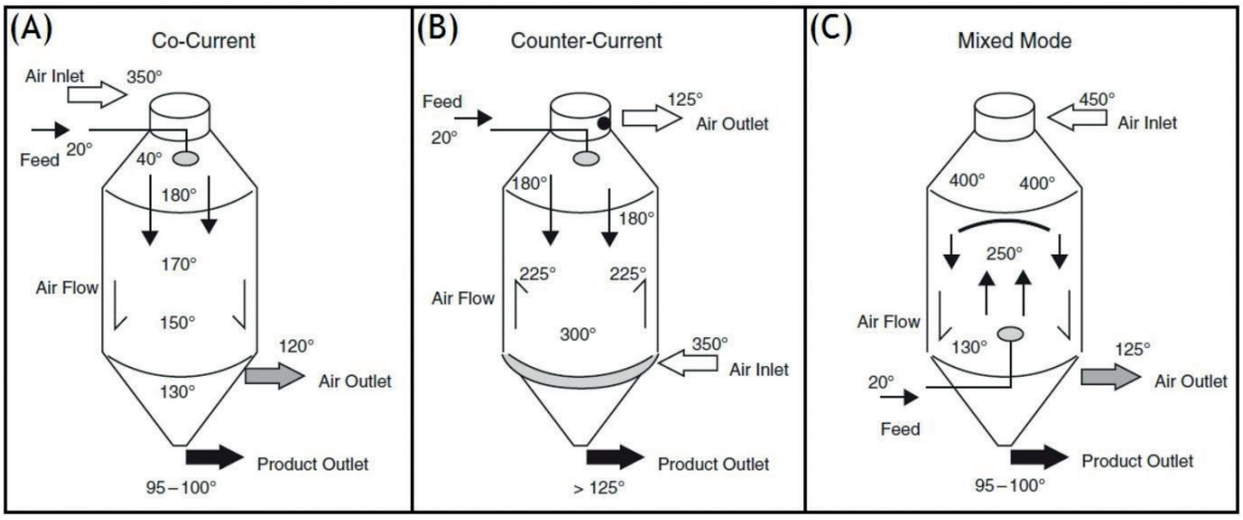

Figure 4. Air-droplet flow patterns within the drying chamber. An exemplificative temperature profile is also represented. (A) Co-current flow. (B) Counter-current flow. (C) Mixed flow [7].

In the counter-current design (**Figure 4B**), spray and hot gas are introduced at opposite ends of the chamber, being the atomizer positioned at its top and the air supplied from the bottom. This flow pattern is considered the most efficient use of the chamber's heat since the upward streamline of the hot gas will reduce the downward flow velocity of the atomized spray, subjecting it to a longer period of time inside the chamber [3]. However, in contrast with what happens in the co-current flow, during the upward flow of the hot gas some of its heat is released to the surroundings. Thus, atomized droplets with high amounts of solvent will hit the gas at lower temperatures, whereas the driest particles will contact with the highest temperatures of the drying medium at the bottom of the chamber, limiting the application of this process to heat resistant materials. The dried particles are released at the bottom of the chamber while the gas leaves it through its upper part [1].

Mixed flow dryer construction (**Figure 4C**) combines both co-current flow and counter-current flow, that is, atomized droplets are fed from the bottom of the chamber in counter-current relative to the downward streamline of the drying gas which is supplied from the top. The dried particles as well as the drying gas are then released at the bottom of the chamber. First, the atomized spray experiences an upward flow, and due to the impact of the downward flow of the drying medium, there is a reversion on its path, ultimately falling in the bottom of the chamber. Hence, the residence time of spray inside the chamber is maximized, being this method preferential to dry coarse droplets, even in small chambers [3]. This arrangement is also appropriated only for heat resistant materials.

2.2.2. Droplet drying: moisture evaporation

As introduced above, as soon as the aerosol droplets contact with the drying medium within the chamber, they undergo evaporation and solute condensation, resulting in solvent removal. This phenomenon reflects a heat and mass balance problem driven by the difference between the solvent's vapor pressure and its partial pressure toward a gas phase. Thus, the hot gas

temperature triggers a heat exchange from it to the droplets, whereas the vapor pressure difference causes a moisture transfer in the opposite direction. As a result, dried particles are obtained [5, 8].

Drying kinetics of the spray-drying process comprise several steps with different durations and specific events, as shown in **Figure 5** [2, 12].

Immediately upon gas-droplet contact, heat transfer from the gas to the droplet causes an increase of droplet's temperature, from its initial temperature (T_i) to a constant value, the equilibrium evaporation temperature (T_{eq}) (**Figure 5AB**). The drying process proceeds at a constant evaporation rate, that is, a fast water diffusion from the droplet core to its surface allows a constant moisture removal. Thus, the droplet surface remains sufficiently cool and saturated with moisture, keeping its temperature constant at the wet-bulb temperature (**Figure 5BC**). Wet-bulb temperature is the name given to the temperature of the gas when it gets saturated with vapor from the liquid. This is the lowest temperature that the drying gas can reach due to the evaporative cooling phenomenon, that is, the gas is cooled as it spends latent heat of vaporization. This stage of intense moisture evaporation is also marked by droplet shrinkage, as represented in **Figure 6**—step 1 [2, 12].

During the constant drying rate period, the evaporation of a liquid droplet with a given diameter d, is proportional to its surface area. This is reflected in the "d^2 law" (Eq. (3)), a mathematical model that expresses how the drying process is mainly controlled by the Peclet number (Pe) [2, 13].

$$\frac{\partial C}{\partial r} = Pe \cdot C \tag{3}$$

C and r are the mass concentration of solid fraction and droplet radius, respectively. Peclet number is defined by (Eq. (4)) [2, 13].

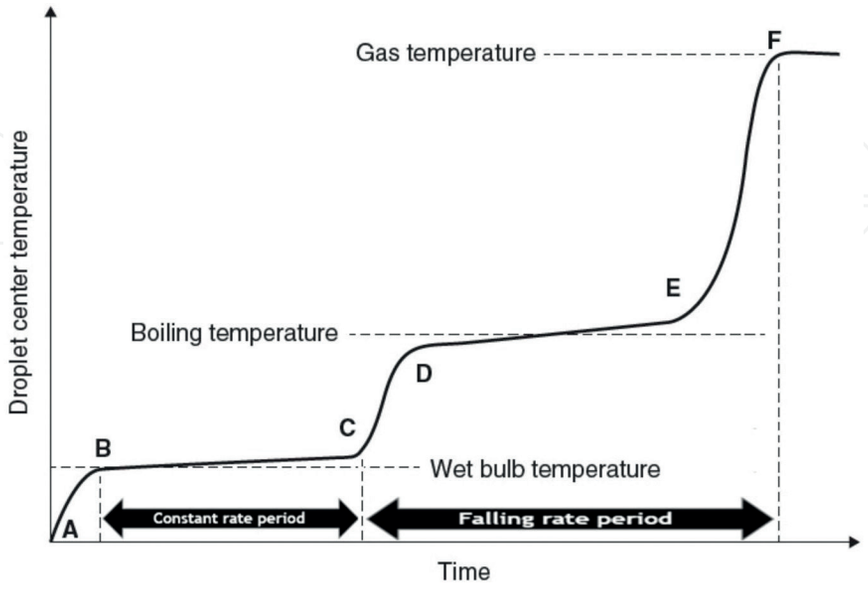

Figure 5. Temperature evolution during drying kinetics of a sprayed liquid droplet. Adapted from [12].

$$Pe = \frac{K}{D} \approx \frac{evaporation\ rate}{diffusion\ rate} \tag{4}$$

Moisture evaporation occurs at a constant rate until a critical value of the droplet water content is reached. In other words, when the solute dissolved in the liquid reaches almost its saturation, a thin shell (also known as crust) is formed at the droplet surface (**Figure 6**—step 2), and, as a result, evaporation slows down and becomes dependent on the water diffusion rate through such surface shell [2, 3]. This marks the beginning of the drying kinetics' falling rate period, being immediately noticeable an increasing particle temperature (**Figure 5CD**). When droplet temperature reaches the moisture boiling point, vaporization takes places, a transition which requires a large amount of energy (**Figure 5DE**). This means there is no longer a sensible heating of the particles and thus, the drying process proceeds driven by external heat transfer from the air to the particle. Once again, there is an increase of particle temperature until it becomes equal to that of the surrounding gas, marking the end of the drying process (**Figure 5EF**) [12]. Along the falling rate period, when the partial pressure of moisture vapor at the droplet core overcomes the ambient pressure, bubble formation inside the droplets may occur (**Figure 6**—step 3) [2].

In order to achieve a successful droplet-to-particle conversion, an optimization of the process conditions is required. Regarding the drying mechanism, two major aspects have a huge impact in the final products: the minimum temperature (T_G) which allows a completely solvent removal and the minimum residence time (t) of the particles inside the chamber that ensures a sufficient drying time. T_G can be predicted from (Eq. (5)), an Antoine equation [6].

$$T_{wb} = K_1 \cdot \left(\frac{T_b}{K_2}\right)^m log\left(T_G\right) + K_3 \tag{5}$$

T_{wb} and T_b are the wet-bulb temperature and the boiling temperature, respectively. K_1, K_2, K_3 and m are Antoine constants.

Regarding t calculation, a mathematical mass balance can be defined through (Eq. (6)) [6].

$$C_m = C_0 \left(1 - \frac{t}{\tau_D}\right)^{-\frac{3}{2}} \tag{6}$$

C_m, C_0 and τ_D are the desired final concentration of the main component of the dried particle after spray-drying process, the initial concentration and the maximum droplet drying time,

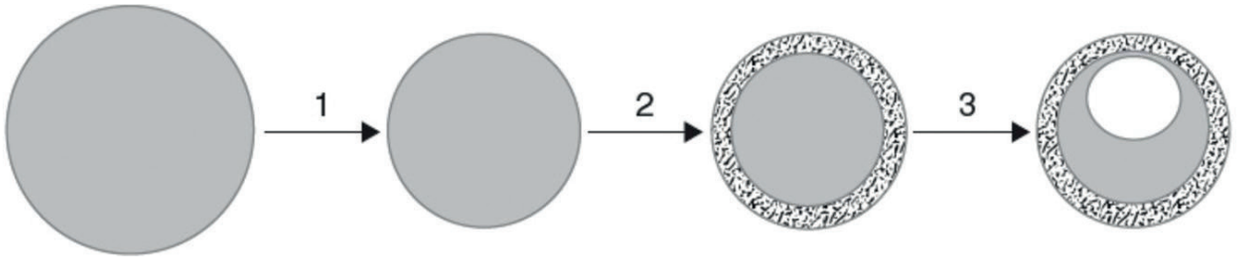

Figure 6. Schematic representation of droplet morphological changes during spray drying. Adapted from [2].

respectively. τ_D can be extrapolated from (Eq. (7)) [6], where D_d is the initial droplet diameter and K is the evaporation rate, as stated above in (Eq. (4)).

$$\tau_D = \frac{D_d^2}{K} \tag{7}$$

2.3. Particle collection

Once the droplet-to-particle conversion is concluded, it is necessary to collect the dried particles. This implies a separation procedure, in which the dried particles are disassociated from the drying gas. Such separation occurs in general in two phases, called primary and second separation. In the primary separation, the most dense particles are recovered at the conical bottom of the drying chamber, as they settle on it [2, 8]. On the second separation, the finest or smallest particles are transferred to external devices, where they are separated from the humid air. The most common dry collectors include the cyclone separator, the bag filter and the electrostatic precipitator (**Figure 7**); equipment with different efficiencies and which are

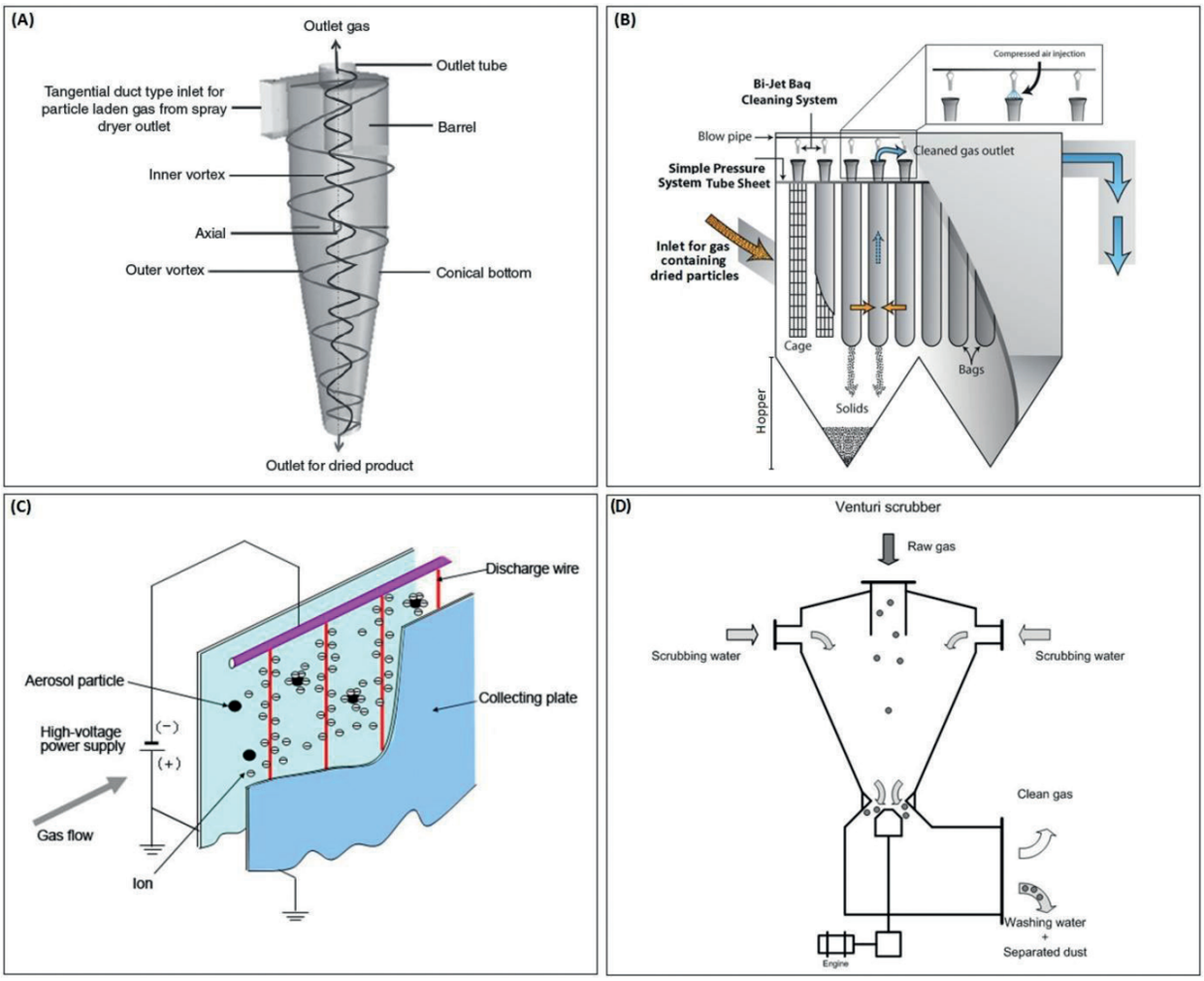

Figure 7. Typical collectors used on spray drying. (A) Cyclone separator. (B) Bag filter. (C) Electrostatic precipitator. (D) Venturi wet scrubber. Adapted from [14–17].

used according to the size of particles exhausted with the humid gas and the desired characteristics of the final product [6]. Moreover, it is also common to use wet scrubbers after the dry collectors in order to perform an extra gas cleaning step, as it will be explained below [2].

2.3.1. Cyclone separator

The separation mechanism of the cyclone separator is based on centrifugal force. This device presents a cylindrical upper part, the barrel, and a conical part on its bottom, the cone (**Figure 7A**). The streamline of air containing the dried particles coming from the drying chamber is supplied into the cyclone at its top, namely tangentially to the barrel. Then, this streamline follows a downward flow, creating an outer vortex. The high velocities of the outer vortex create a centrifugal force on the particles, allowing the particles-gas stream separation. As soon as the gas reaches the cone, an inner vortex is created in the opposite direction. Thus, the gas is expelled from the cyclone at its top, whereas the particles settle into a collection chamber placed on its bottom [2].

2.3.2. Bag filter

Filtration based on bags is extensively used in the spray-drying process. Herein, the air streamline containing the dry particles enters the bag filter under pressure or suction by its hopper and is passed through a fabric, which halts the particles path (**Figure 7B**). This means that the dry particles are retained on the bag surface while the clean air passes through it, being expelled from the device. The accumulated particles on the bag surface are then collected due to pulses of compressed air injected in counter-current flow inside the bags [2, 18]. Bag filters present high operation efficiency, especially when they are arranged in filtering units with decreasing fabric pores diameter [1].

2.3.3. Electrostatic precipitator

Electrostatic precipitation is a method of particle collection whose principle is based on electrostatic forces. A high voltage is applied to discharged wires, forming an electric field between them and the collecting plates that constitute the precipitator (**Figure 7C**). As a result, the gas around these wires is ionized, being capable of charging the particle content of the drying air flowing around this area. Due to Columbic forces, the charged particles converge to the collecting plates and thus the air becomes devoid of dust [2]. Electrostatic precipitators are also very efficient but seldom used taking into account the high equipment costs [1].

2.3.4. Wet scrubbers

In a spray-drying process, it is usual to find some particles escaping in the air stream after the dry collection. Owing to this, it is quite common to install an additional collecting system after the dry collectors, the wet scrubbers. These devices are economical and effective alternatives which perform a final gas cleaning step, being thus capable of minimizing the particle content or even some odor intensity before releasing the gas streamline to the atmosphere [2, 18].

Venturi wet scrubbers (**Figure 7D**) are well studied devices of easy cleaning or maintenance, being therefore one of the most used equipment in the spray-drying process. They present a converging section, a throat (narrowest part) and a divergent section (diffuser). The inlet air carrying fine particles enters the scrubber and is mixed up with the scrubbing liquid (usually water). This mixture flows throughout the converging section, reaching the throat at high velocity. As a result, a spray of droplets is formed with the dust particles entrapped inside them (scrubbing liquid could also be injected at the throat level). Lastly, the fluid content is separated from the clean gas, being the former discharged and the latter released into the atmosphere [16, 18].

3. Process parameters

As it could be noted above, the final properties of the dried products are directly influenced by a set of equipment parameters, such as the atomization devices, the drying chamber configuration and the collector type choice. Additionally, a variety of feedstock specificities and process parameters also play a crucial role in the final particle characteristics, conferring different morphologies, sizes or residual moisture amounts. It is thus fundamental to realize how these variables influence the spray-drying mechanism in order to achieve an optimized operation [2].

3.1. Atomization pressure

Atomization stage is carried under pressure, namely when nozzle atomizers are used. The pressure involved during this process has an impact on droplet size. For a given atomizer device and feed solution, droplet size decreases with increasing pressure, as expressed in the following mathematical correlation (Eq. (8)) [1, 2]:

$$\frac{D_f}{D_i} = \left(\frac{P_f}{P_i}\right)^{-0.3} \tag{8}$$

D_i and D_f are the initial and final droplet sizes when the atomization pressure changed from P_i to P_f, respectively.

In the particular case of rotary atomizers, droplet size exhibits an inverse relationship with wheel rotation speed and wheel diameter [2].

3.2. Feed flow rate

Feedstock solution is pumped into the atomizer at a controllable rate. Keeping the atomization pressure constant, there is an increase in the droplet size with increasing feed flow rates. This is easily understandable bearing in mind that the nozzle would have the same energy amount to spend in the atomization process of higher feeding volumes. Thus, the droplet fissions are minimized, provoking a small reduction of its size [2].

3.3. Feed viscosity

When feed viscosity is increased, a great percentage of atomization energy supplied to the nozzle is used to overcome the large viscous forces of the solution. Hence, a small amount of energy is left for the droplet fission, resulting in larger droplet sizes. This mechanism follows (Eq. (9)).

$$\frac{D_f}{D_i} = \left(\frac{\mu_f}{\mu_i}\right)^{0.2} \quad (9)$$

D_i and D_f are the initial and final droplet sizes when the solution viscosity changed from μ_i to μ_f, respectively. Feed density also follows this principle [2, 7].

3.4. Feed surface tension

As stated above, atomization occurs due to the disruption of the feed surface tension. This means that a feedstock solution with higher surface tension hinders the atomization process. In that sense, before starting the spray-drying process, feedstocks are usually emulsified and homogenized in order to reduce their surface tension [2].

3.5. Inlet temperature

The inlet temperature refers to the heated drying gas temperature, measured right before its entry into the drying chamber. The thermal charge of inlet drying gas reflects its capacity to dry the humid atomized droplets and, thereby, higher inlet temperatures enable higher solvent evaporation rates. Nevertheless, the inlet temperature should not just be increased to achieve better drying performances because it also has an impact in the wet-bulb temperature of the surrounding air. In fact, lower inlet temperatures lead to lower surrounding air wet-bulb temperature, preventing therefore thermal degradation of the final product. Hence, a wise choice of inlet temperature, balanced on these factors, should be done according the feedstock properties [1, 2].

3.6. Drying gas flow rate

Drying gas flow rate is the volume of drying gas which is supplied to the drying chamber per unit time. High gas flow rates will increase particle movements inside the chamber, minimizing air-droplet interaction time. Besides, it is also reported that the higher the drying gas flow rate, the greater efficiency will be obtained during cyclone separation. This means that the drying gas flow rate should be low enough to ensure a complete particle moisture removal, but on the other hand, it should be suitable for the subsequent separation procedure [1].

3.7. Outlet temperature

Outlet temperature is the temperature of the air containing the dried particles just before such content to be piped into the collection devices. Theoretically, the outlet temperature is the highest temperature to which the dried powder can be heated, although in the counter-current dryers the final product may present a higher temperature than the outlet air (**Figure 4B**) [1, 2].

Outlet temperature results from all heat and mass exchanges inside the drying chamber, and thus is not directly regulated by the operator. However, this is a function of parameters like the inlet temperature, the drying gas flow rate, as well as the feed properties (solvent evaporation enthalpy and droplet solid concentration) [1].

3.8. Residence time inside drying chamber

Residence time refers to the exposition period of the atomized droplets inside the drying chamber, being another important factor with a direct influence on the final product quality. Residence time should be long enough to guarantee that the main goal of the drying stage is accomplished, that is, to obtain dried particles. On the other hand, it is fundamental to keep the product characteristics and when the dried particles are subjected to longer residence times, thermal degradation may occur, especially upon heat-sensitive materials. It is hard to experimentally predict the minimum residence time to be used, although it could be approximately calculated using the (Eq. (6)), defined above. Notwithstanding, it should be remarked that the residence time is usually in the order of a few seconds (e.g. in general, fine particles should not stay more than 10–15 s inside the drying chamber) [2, 19].

3.9. Glass transition temperature (T_g)

Glass transition temperature is an important thermophysical property of amorphous polymers. Above T_g, the material changes from a rigid glassy state to a more rubbery state. Hence, this could be related somehow with the material stickiness on the drying chamber, being therefore an obstacle to the spray-drying process. Product agglomeration problems are, for example, one of the major undesirable issues. The T_g of a feed solution is dependent on its solute constituents. (Eq. (10)), the Gordon-Taylor equation, expresses the T_g of a given feed solution consisting of more than one solute [2, 20].

$$T_g = \frac{w_1 \cdot T_{g1} + k \cdot w_2 \cdot T_{g2}}{w_1 + k \cdot w_2} \tag{10}$$

w_1 and T_{g1} are the weight fraction and the glass transition temperature, respectively, of the blend component with the lower T_g. w_2 and T_{g2} are the weight fraction and the glass transition temperature, respectively, of the blend component with the higher T_g. k is the ratio of specific heat change of component 1 to component 2 at the glass transition temperature.

Summing up, the importance of processing parameters on the spray-drying efficiency is clear. Therefore, the advantages and drawbacks of each parameter should be weighed in order to produce products with desirable characteristics. The trade-off between some of the spray-drying parameters is summarized in **Table 2**.

Throughout this review, the importance of the spray-drying technique is evidenced. It enables the production of particles with high yield and made up of several raw materials on an industrial scale, thus proving to be a cost-effective process. Spray drying is preferred over conventional particle production approaches, such as emulsion/solvent evaporation method, due to its unique properties: rapid, continuous and single-step method that displays great versatility and reproducibility [22]. Additionally, spray drying does not require a final drying step, as is the case of the majority of conventional methods, and allows to deal with heat-sensitive materials. Considering these ideas, the use of the spray drying in the production of several drug particles or polymeric carriers with well-defined particle size and good flowability (in opposition to the conventional methods) comes as no surprise. Some examples are detailed below [22].

However, spray drying presents some challenges as it was being explained in the previous sections. It is worth highlighting issues like product loss associated to particle deposition

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INCREASING THESE VARIABLES		OUTLET TEMPERATURE	PARTICLE SIZE	FINAL PRODUCT MOISTURE	EFFICIENCY
	Drying air flow rate	Lower heat losses of the inlet energy ↑	---	Lower partial pressure of evaporated water ↓	Better separation in cyclone ↑
	Air humidity	More energy contained in moisture ↑	---	Higher partial pressure of drying air ↑	More moisture may lead to adherence of the product to chamber walls ↓
	Inlet Temperature	Direct proportion ↑↑	---	Lower relative humidity of air ↓	Eventually dryer product prevent adhering ↑
	Atomizing air flow	Higher amount of cold air to be heated ↓	Higher amount of available energy for atomization ↓↓	---	---
	Feed rate	More solvent to be evaporated ↓	More liquid to disperse ↑	Higher amount of water leading to its higher partial pressure ↑	Depends on application ↑↓
	Solid concentration in feed	Less water to be evaporated ↑	More solid available for particle formation ↑↑	Less water evaporation, lower partial pressure ↓	Bigger particles are easier to separate in cyclone ↑
-----	**Organic Solvent (instead of water)**	Less energy required for evaporation ↑↑	Lower surface tension. More available energy to spend on particle fission ↓	Lack of water in feed leading to very dry product ↓↓	Lack of hygroscopicity results in easier drying ↑

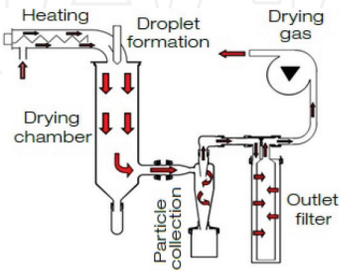
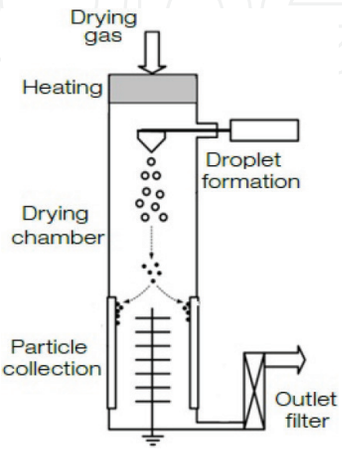
↑ Minor increase ↑ Moderate increase ↑↑ *High increase* ↓ *Minor decrease* ↓↓ *Moderate decrease* ↓↓↓ *High decrease*

Table 2. Relationships between spray- drying parameters. Adapted from [1, 21].

inside the walls of the drying chamber, as well as due to the inability of the separation devices to collect the smallest particles. As a result the process yield tend to decrease, while in optimal conditions would be close to 100%. Moreover, it is important to note that it is very challenging to obtain very small particles (nanometer scale) by spray drying, not only due to the inefficiency of the collecting devices but also due to the inherent difficulty of disintegrating the feedstock solution (atomization step) into submicron droplets [22].

4. Spray dryers

Spray-drying mechanism can be carried out in a pilot-spray dryer developed on a laboratory scale or performed in commercially available instruments. The best spray dryer configuration depends on the purpose for which the instrument is used, that is, the equipment must be

	Mini Spray Dryer B-290	Nano Spray Dryer B-90 HP
Schematic representation of the equipment		
Needed sample amount	30–1000 mL	1–200 mL
Sample viscosity limit	Up to 10 cps	Up to 10 cps
Droplet formation (atomization device)	Two-fluid nozzle	Ultrasonic nebulizer
Atomization principle	Fine droplets are formed using compressed gas. Nozzle tip diameter: 0.7, 1.4 or 2.0 mm	Piezoelectric actuator with a thin stainless steel membrane which vibrates at ultrasonic frequencies. Membrane micro sized holes: 4.0, 5.5 or 7.0 μm
Droplet size distribution	Broader	Narrow
Drying chamber temperature (inlet temperature)	Up to 220°C	Up to 120°C
Mean residence time	1.0–1.5 s	1–4 s
Particle collection	Cyclone technology	Electrostatic particle collector
Process speed	High	Low
Particle diameter range	1–25 μm	200 nm–5 μm
Yield	Up to 70%	Up to 90%
Applications	Pharmaceutical industry, life and material sciences	
Special remarks	Already used in more than 700 publications and 400 patents	Newest generation of laboratory scale spray-dryers provided by Büchi

Adapted from [22, 28–31].

Table 3. Major properties of Mini Spray Dryer B-290 and Nano Spray Dryer B-90 HP commercialized by Büchi.

compatible with the feedstock solution and meet the processing conditions, which lead to the desirable particle specificities.

Büchi (Switzerland) have been developing reliable and versatile spray dryers, which have been used for various intents [22–27]. Mini Spray Dryer B-290 and Nano Spray Dryer B-90 HP are two of those instruments and thus, their major characteristics and benefits are organized in **Table 3** [22].

5. Spray-drying applications in the biomedical area

Spray drying medical applications are mainly focused on the production of microparticles designed for encapsulation purposes and drug delivery systems, which can be then administered orally, pulmonary, ophthalmologically, parenterally, nasally or even vaginally [22]. The fact that this technological process enables to dry heat-sensitive components, like enzymes or proteins, without compromising their biological activity makes the production of such systems possible [32, 33]. As a result, within the biomedical field, spray drying is primarily used to produce dry powder aerosols and to tune active pharmaceutical compounds, making them useful and suitable for drug delivery [11, 32]. In that sense, different strategies have been used to tailor the sprayed products according to the desired goals.

Regarding the spray-drying approach aiming drug encapsulation and delivery systems, it usually takes advantage of a complex initial system containing the active drug substance and an aqueous/organic phase (solution, emulsion or suspension) to produce either microspheres or microcapsules [11, 32].

The fabrication of biodegradable microspheres filled with an active drug is one of the most common strategies of spray drying. Polyesters gather important requirements, such as good biocompatibility, biodegradability and easiness to process, and thus they are usually chosen for the manufacturing of such products. As a result, it is possible to control the drug release over time as the polymer fraction is gradually degraded toward the physiological environment [32, 34]. There are several studies which have reported the production of a wide variety of polymeric microspheres using spray drying. Exemplificative findings involve the use of co-poly (D,L-lactic/glycolic acid) (PLGA) encapsulating a drug designed to fight solid tumors [34], polylactide (PLA) and poly(lactide-co-glycolide) (PLG) entrapping antigens [35], and a mix of PLGA and poly(ε-caprolactone) (PCL) incorporating a specific chemotherapy agents used in the treatment of ovarian and breast cancer [36].

The incorporation of hydrophilic domains in the spray-dried particles is an alternative way of controlling the drug release behavior. In fact, the hydrophilicity of the polymers used to encapsulate the drug has a direct impact on the behavior it, as a more hydrophilic polymer enables fast gelation, consequently slowing the drug release rate. On the other hand, a low concentration of hydrophilic polymeric coating can enhance the drug release rate of poorly water soluble drugs, since it will improve the wettability of the surrounding fluids. Derivative cellulose polymers such as sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose and methylcellulose are just three examples of hydrophilic polymers which have been purposed for these endings [11, 32, 37].

A singular method focused on the encapsulation of sensitive bioactive compounds (e.g. peptides, proteins) or other drugs can be also achieved through spray-drying technology associated to sol-gel polymerization process. In other words, sol-gel process is carried under soft conditions, and when combined with spray drying can deal with the production of microspheres with sensitive molecules entrapped on them [32, 38]. Spray-dried silica gel microspheres are reported in the literature as a promising system to be administered in the form of a drug injectable [38, 39].

Some literature findings are assembled in the following subsections, which have reported the use of spray drying for different applications within the medical area.

5.1. Pulmonary drug delivery

Pulmonary drug delivery route is considered an interesting alternative to the oral drug delivery system, as the lung presents a high surface area covered by a rich blood supply. Thus, a targeted delivery to the lungs enables the use of reduced doses, consequently minimizing the side effects associated with systemic drug administration [24, 40]. Notwithstanding, this strategy implies the use of aerosol drugs, whose production is indeed feasible through the spray-drying technology. As reported in the literature, spray drying has revealed to be a powerful tool in fabricating an inhalable powder suitable for lung delivery, since it allows the production of dried, stable and well-defined solid particles within the "respirable size range for pulmonary delivery" [25, 26, 41, 42].

Adi et al. [43] used spray-drying method to produce dry powders for inhalation-containing doxycycline or ciprofloxacin or even a combination of these two chemicals. The cospray formulation of doxycycline and ciprofloxacin (1:1 ratio) has proved to be more efficient for lung delivery than each one of the single spray-dried antibiotic since it exhibited improved physical stability which favored the drug deposition profile.

Beck-Broichsitter et al. [24] investigated the release profile of phosphodiesterase V (PDE-5) (a drug prescribed in the treatment of severe pulmonary hypertension) encapsulated within spray-dried polymeric particles. In that sense, they produced particles from organic PLGA solutions and also composite particles obtained from aqueous PLGA nanosuspensions. They concluded that both spray-dried products were aerodynamically suitable for deep lung deposition but the particles produced from the organic solution are preferred over the composite ones to work as pulmonary drug delivery vehicles as they exhibited an extended drug releasing profile.

Grenha et al. [44] developed microencapsulated protein (insulin)-loaded chitosan/tripolyphosphate nanoparticles by spray drying. In particular, by taking advantage of the ionotropic gelation of chitosan with the tripolyphosphate, they prepared the nanoparticles and then incorporated the protein content within such particles using aerosol excipients (mannitol and lactose). As a result, suitable microspheres for lung protein delivery were produced. In fact, the microspheres presented a good protein loading capacity, being released in a matter of a few minutes toward the lung environment. Nevertheless, the authors realized that the mannitol/protein ratio impacts the microspheres morphology, namely spherical shapes are obtained in the presence of higher amounts of nanoparticles.

5.2. Nasal drug delivery

Similarly to the pulmonary drug delivery, nasal drug delivery present some remarkable advantages when compared to drug delivery using the central nervous system, standing out the rapid onset action. Nasal surface presents a large surface area with rich porous vascularized epithelium, favoring the drug adsorption. Dry powder-based mucoadhesive products are ideal for nasal administration and thus, spray-drying technique has been used for such purposes [26, 45, 46].

Tadwee et al. [46] prepared, by spray drying, hydoxypropyl methylcellulose microspheres loading carbamazepine, an antiepileptic drug which is used in epileptic seizures. Along this study, they found in this system a promising strategy to allow the drug absorption by the mucosal membrane. This is of extreme importance considering that carbamazepine has a poor aqueous solubility which hinders its use by oral administration.

Alhalaweh et al. [45] developed zolmitriptan-chitosan microparticles by spray drying. Zolmitriptan is a drug prescribed to fight the migraine symptoms (pain, nausea, photophobia and phonophobia). In the present days, it already exist a tablet and a nasal spray (based on zolmitriptan drug) solutions used to treat such health condition. Nevertheless, in both alternatives, the absolute bioavailability of this drug does not exceed 40% [47]. In that sense, Alhalaweh et al. intended to use chitosan in the preparation of a zolmitriptan powder, considering that the mucoadhesive property of chitosan may have an important impact on increasing the bioavailability of the drug in the nose. Some important notes can be drawn from this study, such as: spray drying allowed the production of chitosan spherical particles entrapping good amounts of zolmitriptan; zolmitriptan dispersion around the chitosan matrix is dependent on the chitosan quantity; zolmitriptan release is also affected by proportion and molecular weight of chitosan.

Recently, Zadeh et al. [48] used spray drying to produce insulin loaded microspheres for intranasal delivery application, which is indeed an alternative route of insulin administration that has been tested in the treatment of diabetic mellitus. For that purpose, Zadeh et al. used spray drying to produce microspheres of chitosan and polyvinyl alcohol (PVA) working as the carrier vehicle of insulin. As expected, the properties of the microspheres varied upon different material ratios. In what concerns the rate and drug release from the microspheres, it is important to highlight that chitosan microspheres led to an initial fast insulin release, followed by a slower release rate, but with effective insulin absorption, while the microspheres made up of chitosan and PVA allowed rapid insulin release but without absorption effectiveness.

5.3. Orthopedic field

Spray-drying mechanism can also be used in the materials production focused in the orthopedic field, as it will be hereafter explained. Aiming bone repair purposes, Quinlan et al. [27] proposed the development of a collagen-hydroxyapatite scaffold enhanced with spray-dried alginate particles loading vascular endothelial growth factor (VEGF). In other words, VEGF was primarily encapsulated in the alginate particles which were then incorporated within the collagen-hydroxyapatite matrix. Upon this biomaterial implantation in a bone damage site, it was registered VEGF release for 35 days. As a result, there was an effective vessel formation with consequent improved bone regeneration outcomes, which did not happen at all in the presence of a scaffold without the growth factor.

Sequeira et al. [49] pointed the use of two inorganic oxides, zirconia and alumina, as potential candidates to be used in the orthopedic implantology field. A biocompatible material for such purpose may be obtained combining these two materials, since the stiffness and long-term stability of alumina is merged to the chemical stability and mechanical strength of zirconia. Herein, different zirconia-toughened alumina and alumina-toughened zirconia composite granules were produced by spray drying. Both composites exhibited good mechanical properties as well as allowed osteoblastic cytocompatibility.

Ceramic powders are of major importance in bone tissue engineering. Innovative approaches like 3-D printing makes use of calcium phosphate ceramic powders to shape complex and precise products aiming the regeneration of bone defects. Nevertheless, conventional powder fabrication procedures are far from being ideal for the subsequent 3-D printing usage, as they lack flowability and dispersity which cause agglomeration and irregular morphology issues [50]. Following along with this idea, spray drying has proved to be a credible method to overcome those problems, and thus being suitable in the production of such powders. Ben et al. [50] used spray drying to fabricate monodispersed and spherical β-tricalcium phosphate (β-TCP) powders to be used in 3-D printing. They obtained ceramic materials with good dispersity and flowability, satisfying a high density and uniform porous architecture, meeting therefore important requirements for bone regeneration.

Cholas et al. [51] embedded spray-dried hydroxyapatite (HA) microspheres within a collagen matrix. HA microspheres presented a mesoporous structure which in combination with the collagen matrix formed a good composite scaffold for human bone tissue engineering. Moreover, the authors realized that promising outcomes may be obtained using a simple modification of this system. These HA microspheres could be loaded for drug delivery purposes or even to control the pore structure of the ceramic particle.

6. Spray drying patents in the biomedical area

Due to the increasing interest of spray-drying technology as well as the numerous applications that spray-dried products can hit, specially within the medical field, several patents were issued until these days. **Table 4** compiles some of those patents of the past 10 years.

Title and number of the patent	Technical field	Brief description/main goal	Publication year	Ref.
Thermostable spray-dried rotavirus vaccine formulation and process thereof (US20170173145)	Vaccine development (pharmaceutical)	Provide an enhanced spray-drying process to obtain said rotavirus vaccine formulation. In particular, it was obtained a vaccine with improved heat-stability, ease-of-use, ease-of-transportation and affordability features	2017	[52]

Title and number of the patent	Technical field	Brief description/main goal	Publication year	Ref.
Inhalable epinephrine (US20170119699)	Inhalable drug delivery	Development of particles for delivery of epinephrine to the respiratory system. It was intended to spray-dry particles exhibiting aerodynamic characteristics that enable targeted delivery of epinephrine to the site of action	2017	[53]
Pharmaceutical composition with improved bioavailability (US20170000764)	Solubility and bioavailability enhancement	It was intended to use spray drying to get improved bioavailability (good solubility/dissolution rate), safety and tolerability of a compound for therapeutic endings	2017	[54]
Method for improving the pharmaceutical properties of microparticles comprising diketopiperazine and active agent (US20160101049)	Pharmaceutical formulations for pulmonary delivery	Spray drying was used to fabricate diketopiperazine-insulin particles, improving the aerodynamic performance, active agent stability and efficiency delivery, when compared to diketopiperazine-insulin particles obtained by lyophilization	2016	[55]
Spray drying vancomycin (US20150231197)	Injectable antibiotic (pharmaceutical)	As an alternative to lyophilization, spray-dried vancomycin (an injectable antibiotic to fight bacterial infections in the body) was proposed. Spray-dried antibiotic demonstrated favorable reconstitution times and water content	2015	[56]
Spray drying of high molecular weight hyaluronic acid (US20140155347)	Spray drying of polysaccharides	Hyaluronic acid is commonly used in several medical applications due to its single physical and biological properties. This invention allows a minimal molecular weight loss of the spray-dried polysaccharide	2014	[57]
Liposomal formulations of lipophilic compounds (US20130259922)	Liposomal preparation for drug delivery	Liposomes have been used in the pharmaceutical industry for drug delivery purposes, being usually administrated by injection. Long-term stability and preparation procedures of liposomes involve dehydration and rehydration steps, which can be accomplished by spray drying	2013	[58]
Adhesive containing microparticles (WO2012158483)	Medical devices for skin delivery	A liquid containing active agents was spray dried, resulting in microparticles which can be subsequently incorporated in an adhesive	2012	[59]

Title and number of the patent	Technical field	Brief description/main goal	Publication year	Ref.
Nanoparticle carriers for drug administration and process for producing same (US20110033550)	Nanoparticle carriers for oral administration	Herein, a double emulsion of water-oil-water emulsion was spray dried to form spherical nanometric particles loaded with a specific drug. It is worth mentioning that the nanoparticle carrier itself is made up of polymeric material, the drug is delivered into one of the emulsion phases and the oil-phase or the outer-water phase was doped with a carbohydrate	2011	[60]
Method of producing porous microparticles (US20100092453)	Production of porous microparticles	The production of porous particles is feasible using spray drying under specific conditions. In particular, combining desirable organic compounds with a volatile solvent system.	2010	[61]
Pulmonary delivery of polyene antifungal agents (US20090081302)	Spray-dried polyene compositions	Polyenes (e.g. amphotericin) are efficient antifungal compounds, but lack solubility, either in water or organic solvents. In that sense, the current invention deals with complex issues to get a chemical stable and dispersible powder polyene antibiotic. Nevertheless, the obtained particles are good candidates to be administered by inhalation to the lung to fight pulmonary fungal infections	2009	[62]
Inhalable powders comprising protein, phenylalanine, and other protein stabilizers (US20080089849)	Production of phenylalanine-containing powders	This invention deals with the production of spray-dried powders containing a phenylalanine fraction and other active substance to serve as an inhalative pharmaceutical composition. The resulting powders revealed good aerodynamic characteristics and stabilization of the extra active agent	2008	[63]

Adapted from [52–63].

Table 4. Some patents about spray-drying technology in the past 10 years.

7. Conclusions

Spray drying is considered a powerful technological process since it brings feasibility to the production of free-flowing particles with well-defined particle size. This is indeed a cost-effective

manufacturing process capable of producing dried particles in submicron-to-micron range [2, 3]. Moreover, the ability to use different feedstocks and the high productivity and broad appli cations of this technique makes it more and more attractive to the scientific community [2, 3]. It was noticed that the spray-drying conditions form a network of mutual relationships which have a direct influence on the spray-drying efficiency. The advantages and drawbacks of each parameter should be weighed in order to produce products with desirable characteristics. Such parameters should not be analyzed separately, but rather looked as a complex model, which as a whole contributes to the success of the spray-drying process [2, 64]. The scalability and the cost-effectiveness of this manufacturing process in obtaining dried particles in submicron-to-micron scale favors an increasing variety of applications within the food, chemical, polymeric, pharmaceutical, biotechnology and medical industries.

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