Chapter 2

Stabilization of Bioactive Molecules Through the Spray-Drying Technique: Current Applications and Challenges

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Abstract

Spray-drying is an old technology that is used in the cutting edge of science. From a drying technique used in the front lines of the Second World War to the most promising encapsulation techniques in drug delivery systems.

The most beneficiaries of this technique are usually the food and the pharmaceutical industry as the stability of active molecules is a key factor to the success of their application into the final formulations. Spray-drying provides a range of processes that can be optimized according to the final objective such as the operating conditions, the use of carrier agents, the drying gases, all of them having a direct impact in the final powders/particles.

This technology has changed over the years, it now takes advantage of mathematical modelling to optimize spray-drying of compounds. Countless extracts, molecules, drugs, and other compounds have been spray-dried over the last few decades, making the spray-drying technique one of the cornerstones of many industries.

In this chapter, the history, technical aspects, examples, and general usage are addressed, focusing on the food and pharmaceutical industries. Trends and challenges of this technology are also focused.

Key words Spray-drying, Operating conditions, Stabilization, Bioactive molecules, Industrial application

1 Introduction

1.1 Spray-Drying: What and Why?

Spray-drying is the transformation of a feed (that is pumpable) from a fluid state to a dried one by spraying the particles through a hot drying medium [1]. This technology's inception dates back to the 1870s, having been invented by Samuel Percy who filed a patent to the U.S. Patent Office named "Improvement in Drying

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Andrea Gomez-Zavaglia (ed.), *Basic Protocols in Encapsulation of Food Ingredients*, Methods and Protocols in Food Science, https://doi.org/10.1007/978-1-0716-1649-9_2,

and Concentrating Liquid Substances by Atomizing" [2]. Although the technology did suffer some improvements, its use was limited until World War II started. The military used the technology to reduce the weight of the food being transported to the front lines and distant battles. The major use was in powdering milk for soldiers, due to it being a reasonably complete nutritious and inexpensive food but had the drawback of its weight when in liquid state [3]. Since this war, improvements to the technology increased, and it disseminated into many industries, namely for the production or transformation of foods, pharmaceuticals, soaps, fertilizers, clays, ceramics, polymers, and many other products [3].

1.2 Featured Advantages and Disadvantages

In recent years, the food industry has become the major user of this technology, transforming millions of tons of ingredients and foods. According to Technavio, in 2016, the spray-drying market was valued at 1.2 billion dollars, and expected to rise to 1.5 billion by 2021, with just the spray-drying of milk representing 420 million dollars of the total amount. Still, by 2020, this global market had already reached a size of 4.5 billion dollars and expected to rise to 6 billion by 2025 [4].

Spray-drying represents considerable advantages when compared to other transformative technologies, namely the fact that it can be fully automized and work in a continuous manner with very low human intervention, reducing contamination of sensible products like food or pharmaceuticals.

This technology also has short residence times and is suitable for both heat-sensitive and heat-resistant foods and other products, with a wide variety of applications, provided they are pumpable. It allows a tailored approach and specific conditions for each of the products it is used with, accommodating the specific needs of a products. It can be used as an encapsulation technique, resulting in a homogenous product, resistant to thermal degradation and allowing a controlled release, being especially important for the pharma industry, and to encapsulate bioactive substances for foods [3, 5]. The disadvantages of this technology should not be overlooked, and one of the most significant is the price of a spray-drier, both for laboratorial and industrial use. Although the investment is quite high, a spray-drier, over time, will probably offset, but the initial investment might not be accessible to all. Furthermore, there are also considerable maintenance issues that increase the overall costs of the equipment. Another important drawback is the yield of particles, which can be as low as 20%, and tends to be lower in smaller, laboratorial sized spray-driers due to the particles remaining stuck to the walls of the drying chamber. In some cases, small particles, under 2 μm, can usually pass into the exhaust air and be removed. Another disadvantage, found especially for microencapsulation, is limited types of wall materials, and these must have a good solubility in water to be used [5, 6].

2 Spray-Drying Operating Processes

There are four primary steps, namely the atomization, followed by the droplet-to-particle stage, the moisture evaporation, and finally the particle collection (Fig. 1). The atomization stage is one of the most important, in which the liquid is atomized or divided into small droplets and become ready to undergo the next steps. In terms of atomization, there are several different atomizers that are adjusted to different products. Rotary atomizers, for instance, are used with low viscosity fluids and rely on centrifugal energy by discharging the fluids at a high velocity (200 m/s) from the edge of a wheel or disc. Two-fluid nozzle atomizers use kinetic energy and feature the impact of the droplets at high velocity with gaseous flows, allowing the production of particles with a relatively greater size. Hydraulic atomizers discharge the fluid under pressure through an orifice of variable sizes and can reach pressures of 250–10,000 PSI but produce less homogenous and coarser particles. The ultrasonic atomizers force the liquid through two piezoelectric disks that vibrate at high frequencies and ensure the vibration of the atoms of the droplets, reducing the surface tension. This type of atomization is intended for low-viscosity Newtonian

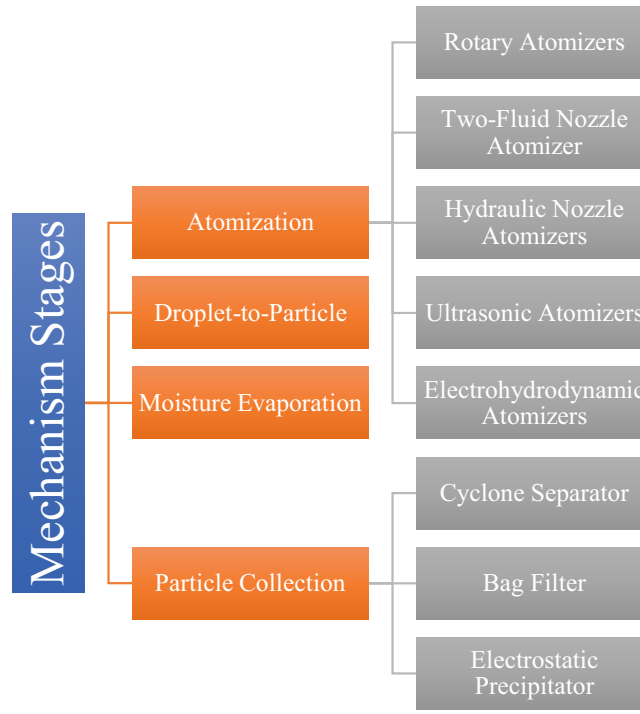

Fig. 1 Stages of the spray-drying procedure and different variations of the technology

fluids. Finally, the electrohydrodynamic atomizers pass an electric current through the fluid enabling the production of droplets of narrow particle sizes.

In terms of the particle collection, there are three types of collectors, namely the cyclone separators that use a centrifugal force to separate the solid particles from the carrier gas, bag filters that separate the particles by retaining them inside the bag and allowing the carrier gas through the bag material, and the electrostatic precipitators that retain the particles by using electrostatic forces to ionize the air and make the particles cling to collecting plates [1, 7].

3 Stabilization of Bioactive Molecules

Stability is a factor of great importance when it comes to the exploration of natural products [8]. Natural products have poor stability when compared to products obtained synthetically, namely by chemical synthesis. In order to enable their use by different industries, new approaches are constantly being researched to overcome these problems and make this possibility real [9]. There are several factors that affect the stability of molecules of natural origin, such as light, temperature, pH, the presence of oxygen, among others. This occours due to the recover the molecules it is necessary to remove them from their surroundings, leaving them unprotected and susceptible to various factors that can somehow affect their molecular structure and destabilize it, causing them to lose or modify properties of interest [10]. After the extraction process, the simple fact of removing the extractor solvent is in itself a process of stabilization, since a greater physical and chemical stability is achieved in the solid state [11]. Due to this there are several process to remove solvents, namely freeze drying, convective hot air drying, spray drying [12], among others, all with different costs, efficiencies, and sustainability.

In recent years, the pharmaceutical and food industries have expressed a preference for the spray-drying technique, as this is a methodology that, despite effectively removing the extractor solvent, is still capable of encapsulating the molecules of interest [13] and thus increase their stability in a fast and relatively cheap process.

During the spray-drying/encapsulation process, stability is achieved due by creation of a protective barrier against various factors that interfere with molecular stability. This is done in a fast process, where the small particles are formed while the solvent is extracted. For instance, dehydrated fruits, with a high content of organic acids and low molecular weight sugars, during the storage period tend to present a rubbery structure. To overcome this problem, some compounds can be added during the spray-drying process, known as carriers [14]. This example outlines the

versatility of the technology to adapt to various situations and different solvents and carriers, which is one of the strongest advantages. With spray drying-carriers, it is possible to increase stability and, depending on the proportion in which it is added, achieve the encapsulation, where the carrier becomes the actual wall material.

Some examples of carriers are high molecular weight biopolymers such as maltodextrins, modified starch or gums, or steric function biopolymers, such as fibers, proteins, or some inorganic compounds. The spray-drying process can be applied to a huge range of products for the food, pharmaceutical, and other industries [15–22]. Considering the food industry, spray-drying has been used in dairy products, essential oils, aromas, coloring compounds, phenolic compounds, probiotics, and others [23–28].

From Table 1, it is possible to see that the spray-drying technique is a highly inclusive technique regarding the type of samples that can be processed. It is possible to perform drying or encapsulation by spray-drying on natural compounds, bioactive molecules, color-holding molecules, probiotics, essential oils, molecules with pharmacological activity, among others [23–25, 28, 34]. Carrier molecules can be luteolin, maltodextrins, gum arabic, modified starches, and simple sugars such as trehalose and inulin [15, 29]. Oils are also an example of carrier agents [19, 22, 25, 31, 36, 37, 44, 53, 59, 64, 68, 78]. In the case of oils, the technique of spray-drying is of great importance, because, considering their composition, they are very susceptible to oxidative decomposition and have a volatile portion that besides having interesting biological activities can be protected. Encapsulation in the case of oils helps to provide a barrier against deterioration processes, increase stability, and suppress unpleasant aromas. The spray-drying technique is capable of much more than protecting molecules against deterioration processes and camouflaging unwanted aromas/flavors.

The added value of this technique is to increase the stability of the molecules of interest, and thus, enable different industries to resort to new alternatives to incorporate in their products. It allows to make products more natural and to develop new products for the food industry, since it offers a whole new panoply of substances, for example with regard to molecules to be explored as colorants of natural origin [14, 15, 34, 39, 45, 61, 66, 80], probiotics, and bioactives [12, 23, 24, 49, 54, 57].

In the pharmaceutical industry, this technique is used to increase molecular stability, producing small-sized particles, which are easier to transport and thus allow the use and approach of new therapies. With spray-drying, it is possible to encapsulate active ingredients that have some difficulty in expressing their beneficial effect, such as solubility problems. The pharmaceutical industry takes advantage of all the possibilities that the spray-drying technique offers, such as encapsulating the active ingredients, increasing

Table 1
Molecules stabilized through the spray-drying technique

Sample	Auxiliary molecules		Operating conditions				Stability	Destination	References
	Molecule	Acting as	Air flow	Feed rate	Inlet	Outlet			
Citrus paradisi var. star ruby juice	Gum arabic Maltodextrin Whey protein isolate	Carrier agent	473 l/h	9 ml/min	148 °C		Relative humidity, exposure to light, and time	Food industry	[14]
Lutein	Maltodextrin Gum arabic Modified starch	Encapsulating agent	50 m^3/h	4 ml/min	185 ± 5 °C	100 ± 5	Temperature and relative humidity	Food industry	[15]
	Trehalose Inulin Modified starch	Encapsulating agent	–	7 ml/min	180–200 °C	75 and 85 °C	Temperature degradation kinetics		[29]
Flaxseed-peptide fractions	Chitosan	Encapsulating agent	0.54 m^3/h	5 ml/min	130 ± 1 °C	73 ± 2 °C	Thermal stress and dehydration	Food industry	[21]
Bioactive compounds of *Bidens pilosa* L.	Microcrystalline cellulose MC102: Aerosil:	Encapsulating agent	1.67×10^{-2} m^3/s	1.49×10^{-4} kg/s	155 °C	–	Relative humidity temperature sampling time	Food and pharmaceutical industry	[24]
Juglans regia L. and *Salvia hispanica* L. oils	Maltodextrin: hydroxypropyl methylcellulose	Encapsulating agent	–	279 l/h	163 °C	–	Oxidative stability	Food industry	[25]
Salvia hispanica L.	Maltodextrins DE10, DE20, whey proteins Gum arabic	Encapsulating agent	–	7 ml/min	160 ± 2 °C	60 ± 5 °C	Oxidative stability	Food industry	[30]
Sour cherry seed oil	Gum arabic Maltodextrin	Encapsulating agent	600 ml/h	8 ml/min	195 °C	–	Thermal and oxidative stability.	Food industry	[31]
Enzalutamide	Hydroxypropyl methylcellulose Acetate succinate	Carrier agent	6.83 l/min	3 ml/min	100 °C	70 °C	Physical stability	Pharmaceutical industry	[32]
Cocoa hull waste phenolic extract	Chitosan Maltodextrin	Coating agent Encapsulating agent	5 cm^3/min	2.5 cm^3/min	170 °C	75–80 °C	Physic-chemical stability	Food industry	[33]
Probiotics (*Lactobacillus acidophilus*)	Maltodextrin: Gum arabic	Encapsulating agent	–	8 ml/min	–	55 ± 3 °C	Physic-chemical stability	Food industry	[23]

Probiotic (*Lactiplantibacillus plantarum* 299v; *Pediococcus acidilactici* HA-6111- 2)	Maltodextrin (in the orange powder)	Encapsulating agent	25 ml/min	–	150 °C	70 °C	Cell viability over time	Food industry	[12]
Beta vulgaris L. extract	Maltodextrin Inulin Whey protein isolate	Carrier agents	35 l/min	0.8 l/h	150 °C	96 ± 4 °C	Adsorption isotherms, thermogravimetric analysis, and accelerated storage	Food industry	[34]
Moringa stenopetala extract bioactive compounds	Maltodextrin: Dextrose: high methoxul pectin	Encapsulating agents	–	–	–	–	Temperature, time	Food and pharmaceutical industry	[16]
Immunoglobulin G	Threalose + (leucine, phenylalanine, arginine, cysteine, and glycine)	Carrier agent	–	–	−50 °C	–	Temperature and relative humidity	Pharmaceutical industry	[35]
Euphausia superba oil	Whey protein concentrate, maltodextrin, and gum arabic (8:2:0.5)	Encapsulating agent	2.5 m^3/min	5 cm^3/min	130 °C	71–75 °C	chemical stability of krill oil in terms of oxidative stability	Food industry	[36]
Fish-oil	Hydroxy propyl cellulose	Encapsulating agent	600 l/h	1 ml/min	200 °C	–	Temperature, time light and oxidative stability	Food industry	[37]
Physalis peruviana (carotenoids) juice	Maltodextrin Modified starch Inulin Gum arabic Alginate	Encapsulating agents	473 l/h	–	140 °C	70 ± 4°C	Time, temperature, relative humidity.	Food industry	[38]
Blackberry pulp	Arrowroot starch: gum arabic (1:1.78)	Encapsulating agent	0.6 m^3/h	–	143 °C	105.43 ± 3.13 °C	pH	Food industry	[39]
L-Lactic dehydrogenase	Trehalose	Carrier agent	150 l/min	0.2 ml/min	120 °C	–	Temperature and shear stress	Pharmaceutical industry	[40]
Conjugated linoleic acid	octenyl-succinic anhydride:starch: xanthan gum	Encapsulating agent	–	–	160 ± 5 °C	75 ± 5 °C	Oxidative stability	Food and pharmaceutical industry	[17]

(continued)

Table 1
(continued)

Sample	Auxiliary molecules		Operating conditions				Stability	Destination	References
	Molecule	Acting as	Air flow	Feed rate	Inlet	Outlet			
Nilotinib hydrochloride	–	–	–	–	120 ° C	75 °C	Thermal	Pharmaceutical industry	[41]
L-ascorbic acid	Taro starch spherical aggregates	Encapsulating agent	–	19.5 g/min	145 °C	80 °C	Relative humidity	Food, pharmaceutical, and cosmetic industry	[18]
Vanillin	Whey protein isolate β-cyclodextrin	Encapsulating agents	–	20 ml/min	110 ± 2 °C	60 ± 2 °C	Temperature	Food industry	[42]
Lysozyme	–	–	35 m^3/h	2.3–2.6 ml/min	130 °C	69–75 °C	Protein	Pharmaceutical industry	[43]
Red palm oil	Sodium caseinate: maltodextrin: sou lecithin	Encapsulating agents	150 l/h	15 ml/min	165 ± 2 °C	60 ± 2 °C	Storage and oxidative	Food industry	[44]
Beta vulgaris juice	Maltodextrin	Encapsulating agent	450 l/h	6 ml/min	170 ± 5 °C	65 ± 5 °C	Temperature	Food industry	[45]
Novel structured lipids enriched with medium- and long-chain triacylglycerols	Whey protein isolate: maltodextrin: inulin	Encapsulating agent	300 nl/min	14–15 ml/min	180 ± 5 °C	80 ± 5 °C	Oxidative stability	Food industry	[46]
Pseudomonas phages, (PEV2 (Podovirus) and PEV40 (Myovirus))	Threhalose:leucine	Encapsulating agent	0.742 m^3/h	1.8 ml/min	–	40–45 °C	Temperature, time	Pharmaceutical industry	[47]
Oil / milkfat	Sodium caseinate: lactose	Encapsulating agent	–	–	180 °C	80 °C	pH, physical	Food industry	[48]
Lacticaseibacillus casei LK-1	Skim milk Trehalose Maltodextrin	Encapsulating agent	–	320 ml/h	–	70 °C	Temperature, physical	Food industry	[49]
Therapeutic (or monoclonal) antibodies (mAbs)	Trehalose: amino acids	Carrier agents	10 l/min	3 ml/min	120 °C	55–60 °C	Temperature, time	Pharmaceutical industry	[50]

Infant milk formula	Lactose: maltodextrin	Carrier agents	–	–	180 °C	90 °C	Physic-chemical stability	Food industry	[51]
Lime and rosemary essential oils and α-tocopherol	Maltodextrin	Encapsulating agent	40 l/h	600 ml/h	140 °C	–	Light, temperature	Food industry	[52]
Vitamin D2	Casein micelles	Encapsulating agent	6.7 kg/min	203 g/min	180 °C	80 °C	Storage	Food industry	[53]
Polyphenols-rich grape marc extract	Maltodextrin: whey protein isolate: pea protein isolate	Encapsulating agent	–	21.5 g/min	140 °C	–	Temperature, time	Food industry	[54]
Tadalafil	Glycyrrhizin	Carrier agent	–	3 ml/min	80 °C	60 °C	Storage	Pharmaceutical industry	[55]
Curcuma longa	Skim milk powder	Encapsulating agent	–	–	160–165 °C	88–93 °C	Temperature, time	Food industry	[26]
Cinnamomum zeylanicum proanthocyanidins	Maltodextrin	Carrier agent	–	40 ml/min	130 or 160 °C	–	Temperature, time	Food industry	[56]
Lactiplantibacillus plantarum B21 and A6	Whey protein isolate	Encapsulating agent	70 m^3/h	6.6 ml/min	110 °C	68 °C	Temperature, time	Food industry	[57]
Allium cepa extract	Maltodextrin	Encapsulating agent	–	0.39 l/h	160 ± 2 °C	90 ± 2 °C	Storage	Food industry	[58]
Strawberry flavour	Maltodextrin Gum arabic Modified starches Xanthan Cyclodextrins	Encapsulating agents	–	2.5 ml/min	180 ± 2 °C	90 ± 2 °C	Temperature, time	Food industry	[27]
Moringa oleifera oil	Maltodextrin Gum arabic Whey protein concentrate	Encapsulating agent	73 m^3/h	10 g/min	180 °C	85 °C	Oxidative	Food industry	[59]
Tamarillo juice	Maltodextrin n-octenyl succinic anhydride modified starch Low viscosity gum arabic Resistant maltodextrin Gum arabic	Encapsulating agent	–	6–10 rpm	140–170 °C	60–90 °C	Physical and storge	Food industry	[60]

(continued)

Table 1
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Sample	Auxiliary molecules		Operating conditions				Stability	Destination	References
	Molecule	Acting as	Air flow	Feed rate	Inlet	Outlet			
Vaccinium spp. (anthocyanin extract)	Maltodextrin DE20: hi-maize	Encapsulating agent	–	–	120, 140 and 160 °C	79.75 °C, 100 °C and 108.25 °C	Time	Food industry	[61]
Lactiplantibacillus plantarum CIDCA 83114	Amorphous and crystalline inulins	Carrier agent	–	–	160 °C	65 ± 5 °C	Temperature	Food industry	[62]
Food-grade solid lipid particles and nanostructured lipid carriers containing ω-3 fish oil	Maltodextrin types (DE 6 and DE 21)	Encapsulating agents	–	6 cm^3/min	140 to 170 °C	65 to 95 °C	Storage, temperature, time	Food and pharmaceutical industry	[19]
Peptide fractions (flaxseed protein)	Polysorbate 80 (Tween-80): maltodextrin (MD)	Encapsulating agent	0.54 m^3/h	5 ml/min	110 ± 1 °C	60 ± 2 °C	Physicochemical	Food and pharmaceutical industry	[20]
Emulsion containing ultrahigh oil content	Whey protein	Encapsulating agent	–	10 l/h	105 ± 2 °C	65 ± 2 °C	Mechanical and oxidative	Food, pharmaceutical, personal care and home care industries	[22]
Ciprofloxacin hydrochloride	Sucrose Lactose Trehalose Mannitol L-leucine	Carrier agent	700 l/h	2 ml/min	120 ± 2 °C	60 ± 2 °C	Relative humidity, protein physical stability	Pharmaceutical industry	[63]
Matcha-tuna oil and matcha-maltodextrin-tuna oil emulsions	Maltodextrin	Encapsulating agent	–	12 g emulsion/min	185 °C	80 °C	Oxidative	Food industry	[64]
Alginate-coated chitosan-stabilized Pickering emulsion	Maltodextrin	Encapsulating agent	–	120 ml/h	150 ± 2 °C	95 ± 2 °C	Oxidative	Food industry	[65]

Lycopene	Maltodextrin Whey protein isolate Modified starch	Encapsulating agent	700 l/h	34 ml/min	160 ± 2 °C	80 ± 2 °C	Storage time	Food industry	[66]
D-limonene ethyl hexanoate	Yeast cells (*Saccharomyces cerevisiae*) Maltodextrin	Encapsulating agents	110 kg/h	25 ml/min	160 °C	97 to 108 °C	Oxidative	Food industry	[67]
Anguilla anguilla oil	European eel protein isolate	Encapsulating agent	35 l/min		175 °C	80 °C	Oxidative	Food industry	[68]
Sulforaphene	Hydroxypropyl-β-cyclodextrin Maltodextrin Isolated soybean protein Chitosan	Encapsulating agent	–	–	180 °C	–	Temperature	Food industry	[69]
Lutein *Quillaja saponaria Molina* saponin extract	Glucose syrup	Encapsulating agent	–	50 ml/min	180 °C	68–70 °C	Colour	Food industry	[70]
Norbixin	Gum arabic: Maltodextrin	Encapsulating agent	600 l/h	0.39 l/h	150 °C	75 °C	Temperature	Food industry	[71]
Donkey milk	–	–	–	–	190 °C	90 °C	Temperature	Food industry	[28]
Liposomes	Calcium alginate	Encapsulating agent	–	–	–	–	–	Pharmaceutical industry	[72]
Paeonia sect *Moutan* DC seed oil	Whey protein isolate: corn syrup: soy lecithin	Encapsulating agent	500 l/h	5 ml/min	180 ± 5 °C	90 ± 5 °C	Oxidative	Food industry	[73]
Lactococcus lactis ssp. cremoris and Lactobacillus acidophilus NCFM	Reconstituted skim milk	Protectant/ encapsulating agent	–	0.85 ± 0.08 g/min	97 ± 5 °C	58 ± 2 °C	Temperature	Food industry	[74]
Small interfering RNAs	Mannitol	Encapsulating agent	35 m^3/h	473–742 l/h	80 to 200 °C	60 to 125 °C	Temperature	Pharmaceutical industry	[75]
Antidesma puncticulatum Miq. anthocyanin-rich extract	Maltodextrin	Encapsulating agent	473 l/h	6 ml/min	140 °C	–	Temperature	Food industry	[76]

(continued)

Table 1
(continued)

Sample	Auxiliary molecules		Operating conditions				Stability	Destination	References
	Molecule	Acting as	Air flow	Feed rate	Inlet	Outlet			
Chicorium intibus and *Brassica oleracea* var. capitata f.rubra poliphenols	Modified starch	Encapsulating agent	40 m^3/h	5 ml/min	140 ± 3 °C	70 ± 3 °C	Temperature	Food industry	[77]
Trypsin	Trehalose	Encapsulating agent	260 ± 5 l/min	–	180 ± 3 °C	90 ± 3 °C	Temperature	Pharmaceutical industry	[78]
Vaccinium macrocarpon Ait. Phenolic compounds	Gum arabic: maltodextrins (M1, 10–13 DE; M3, 17–20 DE)	Encapsulating agents	600 l/h	–	185 °C	105 °C	Storage, temperature	Food industry	[79]
Grape skin anthocyanins extract	Sodium alginate	Encapsulating agent	4.2 m^3/h	0.85 ml/min	120	70	Light, temperature	Food industry	[80]

its stability, and altering its bioavailability in the organism. Through this technique, it is possible to obtain particles with a gradual and controlled release of the active principle. This is of great importance as it allows a gradual dosing of the same and that it remains constant during therapy [63, 75, 78].

Mainly due to these characteristics, the spray-drying technique is progressively a viable resource for different industries, which is constantly being improved, by varying the molecules, the carriers, and the operating conditions, allowing to explore a whole new range of molecules and products. This technique allows to explore and develop the industries, more precisely the food and pharmaceutical industry.

3.1 Spray-Drying Operational Conditions

The spray-drying operating conditions must be chosen considering the chemical features of the material that will be spray-dried. The use of the spray-drying is increasing due to its ability to protect molecules from deterioration and volatile losses, allowing the protection of the target compounds from adverse factors such as light, moisture, oxygen, among others [81].

Furthermore, this technology also allows the encapsulation of bioactive compounds, leading to the increase in their solubility, their affinity with the destination matrix, or to allow a controlled release [81]. Bearing this in mind, the deep knowledge regarding the chemical features of the material to be spray-dried, as well as the final desirable particles, are crucial to establish the most efficient operating conditions. The secret to a successful spray-drying operation is the choice of the operating conditions, namely inlet/outlet temperature, drying air flow rate, feed flow rate, speed of the atomizer, carrier agent, and respective concentration [82, 83].

3.1.1 Temperature

One of the most important parameters to be considered is the temperature. This technology needs high temperatures that can cause thermal degradation of the target molecules. In fact, the material to spray-dry has a very short contact with high temperatures, namely the inlet temperature that is commonly in the range of 150–220 °C and the outlet temperature between 50 and 80 °C. In general, there are several factors directly affected by the inlet temperature such as the final size of the produced particles which is directly related with the inlet temperature; high temperatures lead to faster solvent evaporation, causing the faster production of spheres without the ideal shrinkage, thus producing larger particles [84].

Also, the solubility of the final powders is affected by the inlet temperature. Daza et al. [84] described that an increase in the inlet temperature from 120 to 160 °C improved the solubility of samples. For instance, the outlet temperature is a crucial parameter and must be controlled to assure that this temperature is lower than the thermal degradation temperature of the constituents, to avoid the powder degradation by high temperatures [85, 86].

Several studies suggest that the outlet temperature is the most relevant to control the droplet drying temperature or droplet drying speed. The outlet temperature is directly related and increases with the increase of the inlet temperature and drying flow rate and decreases with the decrease in the feed flow rate and atomizing air flow rate [87]. High outlet temperatures cause the reduction in moisture contents, increasing the process yields, while low outlet temperatures improve the sphericity of particles, causing higher retention of some compounds such as anthocyanins, thus being a key factor on the physicochemical properties of the final powders [87]. Nevertheless, this temperature cannot be too low, as it can lead to water accumulation in the final product, resulting in a significant decrease in the product stability and shelf life.

The direct contact of the material with inlet temperature causes significant heat and mass transfer during the droplet process and affects the particle formation caused by the high rate of solvent evaporation. Singh et al. [85] analyzed these effects and described that this leads to a pressure gradient inside, but also outside the droplet, causing morphologic alterations in the final powder, namely surface roughness.

Thus, a thermal equilibrium must be found in order to maintain the particles stability during the process, without compromising the final stability.

3.1.2 Carrier Agents

Carrier agents are very important to overcome some drawbacks of spray-drying. For instance, samples with high concentrations in sugars mostly cannot be spray-dried without a carrier agent, due to their stickiness, leading to serious drying problems and consequent low yields [86]. The use of carrier agents decreases the stickiness of samples and their hygroscopicity allowing the obtention of dried powders.

Arabic gum, maltodextrins, starches, pectin, alginates, and combinations of these agents are the most used carriers [88], used for their high solubility, low viscosity, high molecular weight, capacity to decrease stickiness, and protect the material from external factors such as heat, oxygen, humidity, pH, among others [86].

Regarding the concentrations of carrier agents and analyzing the results from the literature (Table 1), significant different amounts of carrier agents are applied even for the same samples; thus the concentration of the carrier agents must be applied accordingly to each different sample.

3.1.3 Feed Concentration and Rate

The feed flow rate corresponds to the atomizer speed. Specifically, it relies on the concentration of the feed solutions; higher concentrations have high solid contents and lead to the presence of less solvent in the droplets, causing short evaporation times and the formation of agglomerates constituted of porous final particles with low density [89].

Another important factor is the feed rate that basically corresponds to the speed of the atomizer system. If the feed rate is high, the systems will need more energy to evaporate the solvent from the droplets, and it does not allow an ideal interaction between the feed droplets and the hot air, producing wet particles that stick on the wall of the drying chamber and leading to a less effective heat and mass transfer, corresponding to high moisture contents in the final particles, and low processed yields [87, 90].

According to the available literature, high feed rates lead to lower yields in the spray-drying process, and they increase the particle size and bulk density [91]. Nevertheless, there are also some exceptions such is the case of the same authors [91] thar described that the spray-drying process of orange juice with high feed rates lead to less moisture in the final particles and less bulk density.

3.1.4 Atomization Parameters and Drying Gases

Probably the most important parameter of the spray-drying process is the atomization step; it is crucial to the final particles size, density, velocity, among other important characteristics of the final powders. The main objective of the atomizer is the maximization of the surface volume of liquid area of the feed solution for an efficient drying step. Therefore, choosing the ideal atomizer system is crucial to the final particles and to their physicochemical parameters, since their properties are directly related with the atomizer design and performance features [92].

Concerning the atomizer conditions, the pressure is also an important parameter and also influences the final product features. According to the available literature, higher pressures in the range of 1–2.5 bar create smaller particles and larger surface areas, increase the total solid percentage and bulk density, in turn increasing the drying process efficiency [86, 93]. In another study, Tee et al. [92] reported that increasing the atomizer pressure from 80 to 100% produced smaller particles and decreased the moisture content, while also increasing the process yield and hygroscopicity.

Nevertheless, the use of excessive pressures also leads to an enormous energy consumption without bringing additional benefits regarding the particle size and yields of the process.

Particular attention must be given to the atomizer choice; the most commonly used are the rotary atomizer, pneumatic, ultrasonic, and hydraulic nozzles. When comparing the efficiency of these different atomizers, the literature describes that rotary atomizers create larger particles when comparing with nozzle atomization, and two-fluid nozzle atomizer usually produces the smaller particles [86].

The speed of the atomization is another parameter that directly influences the final product characteristics. For instance, higher atomization speeds (10,000 to 25,000 rpm) usually lead to a

decrease in the moisture contents and a reduction in the final size. As the increase in the atomization speed results in the increase in the flow rate, creating tiny particles, resulting in a higher area of contact that allows for a faster drying procedure, and an increase in the yields [86–94].

Different gases are commonly used in the spray-drying process, being compressed air, CO_2, and N_2 the most common ones. These gases and their properties also represent key factors to the success of the spray-drying products. For instance, the use of low-density gases such as nitrogen, an inert gas, which is commonly used in solutions with high concentrations of organic solvents and in solutions with easily oxidable compounds, produces smaller particles with different surface morphologies [85]. On the other hand, CO_2 that presents higher density properties produces larger particles. Several authors reported the effect of the atomization gas type and concluded that the crystallinity of the final particles is directly influenced by the type of gas, describing that N_2 allows the production of higher crystallin particles than CO_2 and compressed air [95]. On the other hand, the atomization with CO_2 means higher temperature and mass transfer during the process, obtaining higher efficiency in the drying process, resulting in 20% faster drying, which offers 4% energy savings on the heat input according to Kudra and Poirier [96].

As stated above, all the spray-drying parameters are strongly related with the final particle's characteristics, namely in terms of particle distribution, moisture, yields, particle size, and morphology. According to the final applications, the operating conditions can be adjusted and optimized to target different morphologies, yields, particle sizes, and distribution.

Furthermore, these parameters can be optimized using mathematical models such as the response surface methodology that can predict the ideal operating conditions to the desirable target particle characteristics, a technology based on reduced experimental data that is already applied to the spray-drying processes, namely by the pharmaceutical industry to increase particle yields [86, 97].

4 Challenges, Trends, and Conclusions

Considering that published papers in 2003 with the keywords "spray-drying" were about 200 and had risen to over 1000 in 2017, it is clear that this technology has improved over time, and pondering the consistent growth until today, it is expected to continue into the next decade [98]. Although spray-drying technology is centuries old, it is still developing, and important developments have been introduced in the past years, with some important ones that are previewed for the near future. With

globalization, the cost of the equipment has seen some important reduction in their price, allowing more businesses and research centers to use them, thus creating a bigger potential audience for improvements which in turn encourages more improvements and breakthroughs. Sosnik and Seremeta [5] stated that the trends in spray-drying would include the production of finer particles, narrowing of the size distributions, and the improvement of yields by reduction of product loss on the walls of the drying chambers. The improvements in polymer chemistry and nanotechnology are also important for the miniaturization of encapsulation techniques, allowing for the encapsulation of smaller and smaller products, which result in finer powders that are suitable for broader applications. Another improvement that is envisioned for the near future is the stability of the dried or encapsulated products over a longer period, as well as the improvement of nano-spray driers. Special emphasis is also considered in the food industry, due to the higher need for encapsulation of natural food additives. These natural compounds have seen increasing demand by consumers due to the concomitant increase of distrust of synthetic additives and the need of higher stabilization from the natural additives [86, 98, 99].

Overall, the contribution of spray-dryers to the food and pharmaceutical industries is undeniable. From a simple method of drying and encapsulating food during the end of the twentieth century to a technology that allows controlled release of ingredients and active compounds in drugs, spray-drying is an essential technology in the twenty-first century. With the previewed enhancements to the technique, longer shelf-lives are expected in foods, better efficacy in drugs, nano-spray driers, and an overall reduction in the cost of the equipment which will democratize its use, leading to a broader use.

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