Drug Delivery and Translational Research (2020) 10:1–12
https://doi.org/10.1007/s13346-019-00648-9

REVIEW ARTICLE

Spray drying as an advantageous strategy for enhancing pharmaceuticals bioavailability

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Published online: 29 May 2019

Abstract

Spray drying is an efficient technique that is used not only for rapid evaporation of the solvent from different systems but also for designing ultra-fine particles with various desirable characteristics. The obtained powders demonstrate reasonably narrow size distribution with a submicron-to-micron size range. It is one of the recent techniques applied to present acceptable solutions to enhance the absorption and bioavailability of some challenging drugs. In view of that, the purpose of this review is to shed some light on the wide variety of the recently developed fine particulate products that can be produced from spray-drying technique. This article reports the most outstanding advantages and challenges that could be overcome by exploiting the spray-drying technique for the production of different pharmaceuticals, including pure drug particles and drug-loaded polymeric carriers. The potential of this technique, whether used alone or in combination with other methods, in order to develop reproducible and scalable procedures for the best translation of bench-to-bedside innovation of pharmaceutical products is hereby discussed.

Keywords Spray dryer · Pharmaceutical carriers · Drug bioavailability

Introduction

Among the recent techniques adopted for producing dry ultra-fine powders, spray drying is the most important reproducible, affordable, time-saving, continuous, and scalable process [1, 2]. The idea behind this process depends mainly on producing dry product from a liquefied system through spraying in the presence of hot air (sometimes nitrogen); the solvent is evaporated, while the produced ultra-fine powder is collected. Although spray drying was previously considered primarily as a dehydration process, recent trends apply this technique nowadays as a means for designing various pharmaceutical carriers encapsulating hydrophilic and hydrophobic active compounds. Interestingly, thermal degradation is not expected, even for thermolabile molecules, owing to the short time of heat exposure (seconds or milliseconds) and the fast drying process. Examples of the produced pharmaceutical carriers are amorphous solid dispersions, micro- and/or nano-particles, and self-emulsifying drug delivery systems. The obtained products display a homogenously distributed, submicron-to-micron particle size [2].

The first application of spray-drying technique in the field of pharmaceutical technology was to dry the naturally obtained medicated extracts. The popularity of using spray-drying technique in this field refers mainly to its ability to dry even the highly risked thermo-sensitive extracts avoiding the risk of decomposition of their components. Thus, dry extracts are exclusively industrially produced by spray-drying technique, as it yields homogenous powders with better properties when compared to other drying techniques [3]. Evaporation of the solvent usually causes a cooling effect, which, thus, keeps the droplet temperature relatively low [4].

Drying of various ingredients (pharmaceuticals or others) can be performed using different types of dryers, depending on the nature of the ingredients, as well as the desired product characteristics. For example, lyophilization (freeze-drying) is a widely used technique in the industry that is based on the sublimation principle. During lyophilization, substances are protected from high-temperature degrees and have a good chance to preserve their initial desirable characteristics [5]. Alternatively, spray-drying technique involves maximizing

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heat transfer and can be used for any material having a liquid-like behavior. Its versatility and speed render it the mostly used drying technique for various materials, even for the heat-sensitive ones. The excellent product quality along with maintained texture and quick rehydration gives spray drying more advantageous characteristics over other dehydrating techniques [3].

A previous study compared spray and freeze drying to obtain powdered *Rubrivivax gelatinosus* biomass. The terms of comparison were yield, productivity, and product recovery, as well as product characteristics involving color, proximate composition, and oxycarotenoids (representing pigment content). The study revealed lack of difference in the yield between the two applied techniques. However, higher productivity was obtained with using spray drying. No difference in oxycarotenoid content was observed between the biomasses. Spray drying was more productive, faster, giving similar yields as freeze-drying, although lower recovery rate was noticed. Spray dryer was selected as the method of choice for obtaining *Rubrivivax gelatinosus* biomass in that study [5].

The applications of spray drying extend beyond being a mere drying instrument. Other aspects of utilizing the spray-drying technique in pharmaceutical technology field include the following: controlling the particle size, solid-state form (amorphous/crystalline), porosity, and morphology; direct conversion of various fluids into dry powders in a one-step process; designing controlled drug-release particles; enhancing the entrapment efficiency; extending the shelf lives of active ingredients; and formulating nanocapsules with numerous encapsulating excipients [6, 7].

This review presents a recapitulation of the notable developments of spray-dryer devices, demonstrating the advantages and drawbacks of each generation. Concomitant with the growing need of developing new designs for pharmaceuticals for enhanced biological availabilities, a brief presentation of recent research articles applying the spray-drying technique is also demonstrated in this review. Thus, the reader is provided with the most suitable elucidation of the appropriate application of the spray-drying technique used for developing potential pharmaceuticals.

Precedence of spray-drying technique

Spray-drying technique has also been exploited in fields other than pharmaceutical industry. Other applications include chemical materials, cosmetics, and food and flavor industries [8–11]. The technique demonstrates advantageous merits, such as being rapid, continuous, and reproducible. Thus, it is successfully applied at both laboratory and industrial scales. Furthermore, it has the ability of producing particles at a single-step process, whereas other commonly used techniques, such as the "emulsion/solvent evaporation," involve multi-step techniques that can affect the results' reproducibility [12–14]. The successful translation of "bench-to-bedside" expression, comprising two important criteria, scalability and cost-effectiveness, is highly complied in the spray-drying process [15, 16]. It gained much interest when compared to other commonly used drying techniques, such as lyophilization, as it is cheaper, less time-consuming, and does not involve freezing, which consumes high energy [10, 17, 18]. Therefore, it has been recommended by some researchers as an alternative method to lyophilization [19–21]. Other advantages include being a simple process that is easily operated at low costs and energy-saving process that is easily scaled-up. Additionally, it has the ability to operate with either aqueous or organic solvent, using open or closed cycle design for spray-drying technique [6, 7].

The ability of the spray dryer to produce ultra-fine dry powder forms for a wide range of materials, including heat-sensitive ones, without high damaging effects can be considered a remarkable advantage. The rapid solvent evaporation occurring during the spray-drying technique results from the atomization of the fluid into tiny droplets with great ratio of surface area-to-volume [22]. Although one could expect that the droplets could be subjected to high temperature during the drying process, this drying time is very short (seconds or even milliseconds). Thus, drug decomposition does not occur under these conditions [23].

As other dehydrating techniques, spray-drying process is applied to prolong the products' lifespan. Also, it has been used as a procedure with high inherent potential to yield pure drug compounds [16]. Meanwhile, it was extensively investigated by researchers to entrap drugs, aromatic oil extracts, flavors, and pigments, within a various range of pharmaceutical carriers, such as polymeric nano-/microparticles [17, 18, 24].

Among the remarkable characteristics of the spray-dried powders are their enhanced flow properties. A previous study by Anish et al. compared the angle of repose of poly(D,L-lactide) microparticles produced by spray drying with that produced by a conventional double emulsion/solvent evaporation method, and an outstanding powder-flow property was achieved by the spray-drying process [25].

A spray-dried powder is characterized by greater stability against different environmental conditions (e.g., light, oxidation, and temperature) and by being easily handled and stored with high redispersing ability in aqueous solutions [26, 27]. The long shelf-life stability is largely attributed to the low moisture content of the spray-dried powders [28]. Moreover, they can be utilized as precursors for producing suitable dosage forms [19, 29, 30].

A very famous industrial and commercial application of spray-drying process is the production of powdered milk. It turned out to be prevalent in the 1960s, and, since then, the

manufacturing of powdered milk became a huge business in the twenty-first century. Likewise, in the pharmaceutical industry field, the pharmaceutical companies Pfizer and MannKind developed inhalable insulin powder under the trade names of Exubera® and Afrezza®, respectively. Moreover, several excipients are produced in the market for direct compression purposes, such as F-Melt® (fast-dissolving dosage forms excipient composed of a mixture of mannitol, xylitol, inorganic excipient, and disintegrating agent), Starlac® (maize starch in combination with lactose monohydrate), Microcelac® (a mixture of microcrystalline cellulose and lactose monohydrate), Cellactose® (lactose monohydrate mixed with powdered cellulose), and Prosolv® (silicon dioxide and microcrystalline cellulose).

A noteworthy remark about conventional spray dryers is that its process yield is highly dependent on the scale of work. Meaningfully, high yields are obtained in larger scale operations as the lost portions are significantly lower relative to the total production volume [31]. Conversely, at the laboratory scale, the yield can range from 20 to 70% [32, 33]. This can be attributed to the loss of significant portion of the product upon sticking to the drying chamber inner walls; thus, the amount is relatively constant for large scale production. Furthermore, fine powders of less than 2 μm in size could escape into the exhaust air if wrong cyclone size is used [34–36]. However, this could be overcome if the right size cyclone was used and if some filter system separators are used [34].

Factors influencing properties of spray-dried powders

Characteristics of the spray-dried powder can be greatly affected and tuned by the following: (a) the equipment design, (b) the process parameters, and (c) fluid feed properties. Equipment design comprises concurrent flow and counter-current, in addition to the mixed flow system. Two possibilities exist concerning the directions of the flow of the drying gas and liquid atomization—concurrent flow (similar direction) and counter-current flow (different direction). In concurrent flow, the final product exists in the area of lowest temperature, making it the preferable choice for drying heat-sensitive substances [20]. In counter-current flow, however, the dry product contacts hottest air allowing higher thermal efficiency [2]. The atomizer geometry also can affect particle size of the product. For example, large-nozzle diameter favors formation of large particle size product and vice versa.

The spray-drying operation patterns can be either open- or closed-loop. The open-loop uses air as the drying medium which is not re-circulated. It is preferable in most cases as it is cheaper and more stable [37, 38]. In the other pattern, however, nitrogen (as an inert gas) is used and re-cycled in the drying chamber during the whole process preventing mixing of gases [39] and permitting better management of oxidation-sensitive substances [40].

The characteristics of the product can be also varied largely according to the fluid feed properties (concentration, viscosity, density, surface tension, and solvent boiling point); e.g., concentrated formulations favor larger particle formations and fluids with low surface tension yield smaller particle size. Additionally, fluids with low boiling points usually produce particles with porous surface [25, 41–45]. Thus, fine tuning of the process parameters can largely affect the obtained product and various possibilities of the formed product can be produced using the same device and fluid feed. Figure 1 summarizes the process parameter effects on the spray-dried product. For example, increasing feed viscosity causes moderate increase in the outlet temperature of the product, a minor increase in the yield, high increase in particle size, and a minor decrease in product humidity [34, 46].

The evolution of the nano spray-dryer technique

In an attempt to improve traditional spray-dryer models and extending its application to the production of more developed product, a new generation of laboratory-scale devices named “nano spray-dryer” was produced. Fine powders with particle sizes ranging from 300 nm to 5 μm with optimum yield can be produced from this generation even if small sample sizes is used [47]. Such advantage is very useful when a new, expensive material is being developed in its early stages [48]. Also, its ability to produce particles within the nano range is of extreme importance for drug delivery purposes as it enhances the bioavailability and release of the loaded biologically active agents. Drug-loaded nanoparticles have innumerable advantages, such as higher surface area-to-volume ratio, enhanced cell penetration rate, and improved stability [4].

The nano spray dryer was invented with the aim of modifying submicron-particle production using conventional spray dryers. The incomplete separation and collection of nanoscaled particles comprises a significant constraint of traditional cyclone separators [4]. Particles with sizes less than 2 μm could hardly be collected with typical cyclones even with the use of high-performance ones [49–53]. Thus, electrostatic particle collectors were utilized to collect nanoscale particles in a feasible way [47, 54–56].

Moreover, the inefficient production of very fine droplets by the traditional atomizers was improved through the development of spray cap based on vibrating mesh technology; hence, submicron powders can be produced. The vibrating mesh technique has been inspired by the nebulizers used in aerosol manufacturing [57–59]. The spray cap consists of a vibrating mesh controlled by a piezoelectric actuator with a pre-determined ultrasonic frequency generating ultra-fine droplets. The vibrating mesh is

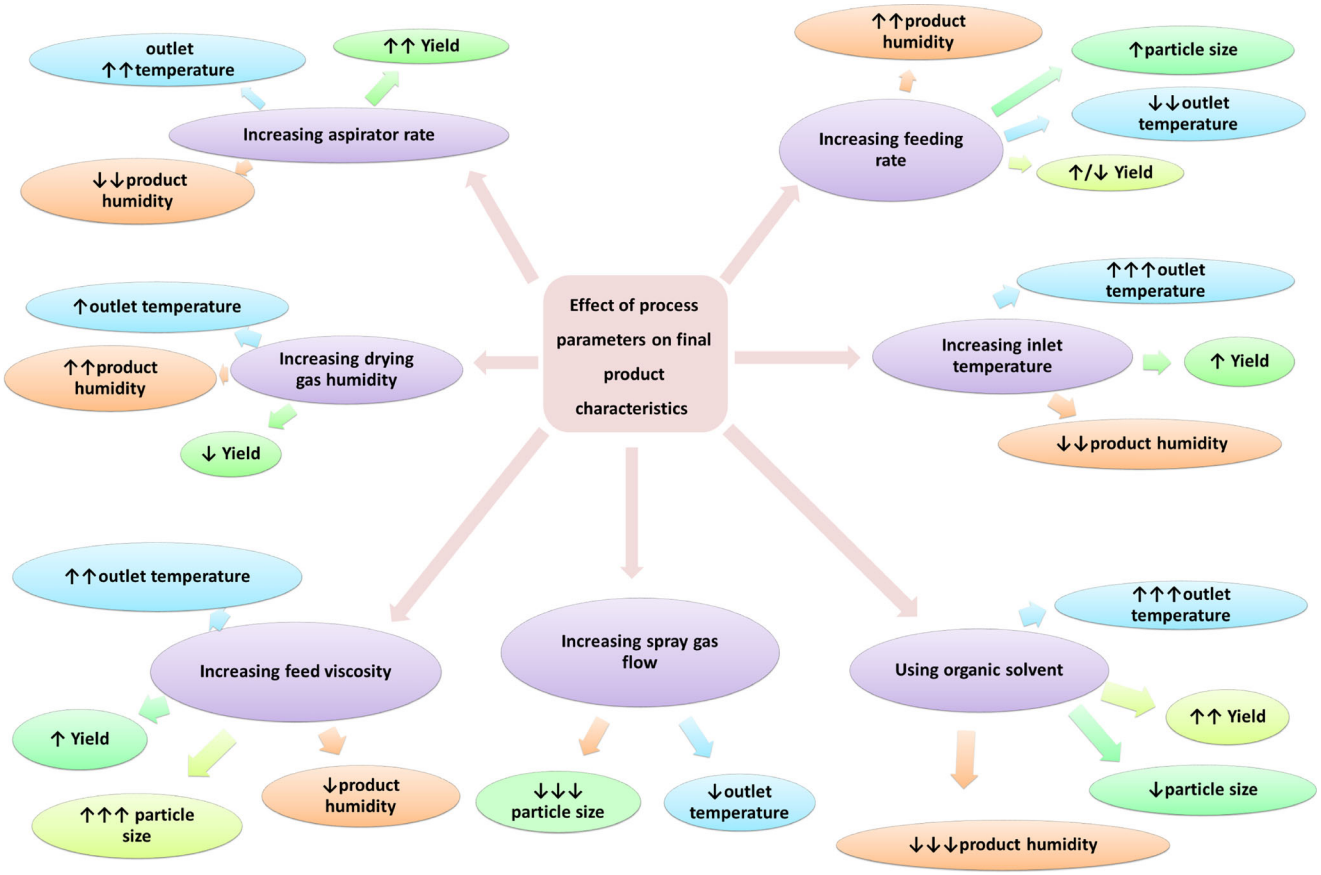

Fig. 1 Effect of process parameters on the final product characteristics (www.buchi.com). ↑↑↑, high increasing influence; ↑↑, moderate increasing influence; ↑, minor increasing influence; ↓↓↓, high decreasing influence; ↓↓, moderate decreasing influence; ↓, minor decreasing influence

a thin metal plate with tiny laser-drilled holes. The piezoelectric vibration causes rapid repetitive movement of the spray mesh in the upward and downward directions, leading to ejection of millions of accurately sized droplets into the drying chamber. Spray meshes are supplied with various hole diameters, thus, producing a large variety for controlling droplet size according to the physical and chemical properties of the fluid (e.g., viscosity and surface tension). These droplets can be transferred upon drying into dry powder with narrow and reproducible particle size distribution [6, 47, 60].

The generated submicron particles are driven by the concurrent drying gas flow to the electrostatic particle collector and attracted to it. Simultaneously, adhesion of the particles to the drying chamber's inner walls is greatly diminished; therefore, high-collection efficiency for the particle is attained [32, 61]. The laminar flow of the drying gas contributes to the suitability of the system to dry thermo-sensitive products, decreasing the probability of degradation and loss of activity. In addition, it provides mild, uniform, and instant heating [32, 39, 47, 62]. The drying air leaves the instrument in a powder-free form [4]. The high voltage at the collecting electrode permits efficient recovery and separation of submicron particles that can reach approximately 100% even for small solid batches [32, 33, 56, 63]. The electrostatic particle collector has the ability to reserve thin-walled particles without any damage [64, 65]. The produced particles can be gently scraped from the walls of the collecting electrode.

A critical remark that a spray dryer operator must take care about is that the much smaller vibrating mesh orifices' diameter may result in longer processing times and limits drying of highly viscous polymeric solutions [66]. A small incidence of product deposition on the vibrating mesh may occur which can lead to reduction of the yield and might mix the collected fine particles with coarse particles generated from the eruption of the crust [47]. Some researchers reported the limitation of nano spray dryer with shear-sensitive substances because of the mechanical shear of the vibration [67].

Applications of spray-drying technique for preparing pharmaceutical technology products

Table 1 summarizes the recently published pharmaceutical applications of spray dryer.

Table 1 Recently published pharmaceutical technology applications of spray-drying technique

Pharmaceutical application	Drug	Aim
Nanostructured systems	Bovine serum albumin	Offering a novel approach for protein nanoparticle development [32]
	Naproxen	Fabrication of fast-dissolving naproxen formulation to be compressed as tablets [68]
	Phenytoin	Improving the anti-convulsant activity of phenytoin through developing reconstitutable spray-dried nanocapsules [69]
	Itraconazole	Enhancing the dissolution of itraconazole through nanocomposite formation [70]
	Simvastatin	Enhancing the dissolution rate and bioavailability of simvastatin via solid SNDDS [71]
Microparticles	Insulin	Studying the potential of spray-drying process to formulate solid lipid microparticles encapsulating protein drugs [72]
	FITC-dextran 150	Delivering high-molecular weight biopharmaceuticals in a sustained-release pattern using the sol–gel technology [73]
	Rifampicin and kanamycin	A combination therapy for treatment of respiratory tract infections [74]
	Isoniazid and rifabutin	Inhalable tuberculosis therapy [75]
	Galactosidase	A model protein drug [56]
	Polio vaccine	Minimizing the loss of activity during drying and storage [76]
Amorphous solid dispersions	Darunavir	Improving drug solubility [77]
	Felodipine	Increasing drug solubility [78]
Co-crystals	Ibuprofen and isonicotinamide	Enhancing the rate of dissolution, solubility, stability, and ability to be compressed in a tablet form [79]
	Sulfadimidine and 4-aminosalicylic acid	Investigating the effect of feeding a three-component solution to be feed during the spray-drying process to form a co-crystal [80]
Nanosuspensions	Econazole nitrate	Improving its aqueous solubility and ocular bioavailability [81].
	Risperidone	Designing an effective formulation with intended criteria of low particle size, high yield, and considerable compressibility [82]
Spray-dried emulsions	Atorvastatin calcium	Enhancing the anti-hyperlipidemic activity [83].
Natural extracts	Liquid extract of sisal	Production of a low moisture content, a good solubility, and optimum hecogenin content [84].

Nanostructured systems

Despite the increasing demands for developing nano-therapeutics containing proteins for treating cancer, diabetes, and asthma and the emerging of spray drying to obtain these structures, a challenge exists in separating and collecting the protein-loaded nanoparticles using old-fashioned spray dryers. The limited yield percentages and difficulty in obtaining a submicron-particle size encouraged a research team to utilize the nano spray-dryer B-90 for formulating bovine serum albumin (BSA) in nanoparticulate form [32]. A Taguchi statistical experimental design method (with five variables in three levels) was employed to study the effect of independent variables and adjust the experimental conditions for the accurate selection of the best formulation. The independent variables were spray cap mesh size, concentration of BSA solution and surfactant, drying air flow rate, as well as the inlet temperature. The dependent variables were the size and morphology (axial ratio) of the fabricated nanoparticles. Analysis of the results revealed that morphology and particle size were principally affected by the concentration of surfactant and spray cap mesh size, respectively; whereas, the inlet temperature and drying air flow rate displayed a minimal effect. Finally, an optimized spherical nanoparticle formulation with smooth surfaces was produced with a size of 460 ± 10 nm and a production yield of 72 ± 4% through the utilization of 4 μm spray mesh size with a BSA and surfactant concentrations of 0.1% and 0.05% *w*/*v*, respectively, and the drying air flow rate was 150 L/min with an inlet temperature of 120 °C. These results demonstrate the ability of the nano spray-dryer B-90 as a simple and alternative technology for protein nanoparticle production for a wide range of drug delivery applications.

Braig et al. succeeded to fabricate fast-dissolving crystalline nanoparticles containing naproxen. The rates of dissolution of the pure crystalline drug nanodispersion, pure drug

microsuspension, and spray-dried granules were compared with those of the compressed tablets (containing the spray-dried granules in addition to a bulking agent as well as a disintegrant). With frequent sampling during the first 120 s under both sink and non-sink conditions, nanodispersion showed complete dissolution after 60 s. Spray-dried formulation prepared with mannitol showed slightly delayed dissolution [68].

A recent study developed reconstitutable spray-dried nanocapsules containing the anti-convulsant drug, phenytoin, within a lipid core [69]. Chitosan-coated lipid core nanocapsules were formed from a lipid core (composed of a surfactant and medium-chain triglycerides) coated with a polymeric membrane of poly(ε-caprolactone) with the addition of maltodextrin as an adjuvant in the process of spray drying. Transmission electron microscopy images showed the spherical-shaped nanosized particles for both uncoated and chitosan-coated phenytoin-loaded nanocapsules. The investigated powders demonstrated good physical and chemical properties as well as gastrointestinal stability after being reconstituted in water. The reconstituted powder improved the anti-convulsant activity of phenytoin against pilocarpine-induced seizures in mice, in comparison with the pure drug.

In an attempt to enhance the dissolution of one of the hydrophobic drugs, Li et al. combined the wet-milling and spray-drying techniques to form nanocomposites [70]. The impact of several dispersants on itraconazole dissolution rate from the produced nanosuspensions was studied. Either hydroxypropyl cellulose or sodium dodecyl sulfate and their combination were considered as baseline dispersant system. Different formulations were prepared using different classes of dispersants. Two model hydrophilic dispersants (mannitol and sucrose) were added with hydroxypropyl cellulose to the wet-milled itaconazole nanosuspensions. Additives were wet-co-milled with the itaconazole–hydroxypropyl cellulose system as they are considered swellable super-disintegrants. Nanocomposites were then formed by drying the wet-milled suspensions. Characterization of the produced powder revealed that a median drug size of less than 0.20 μm was recorded for formulations fabricated with hydroxypropyl cellulose–sodium dodecyl sulfate and hydroxypropyl cellulose with concentrations of 4.5% and more as measured by laser diffraction analysis. Dissolution studies demonstrated a fast itraconazole release that reached 80% within 20 min. The addition of the selected dispersants resulted in higher drug dissolution rates, owing to the faster erosion of the nanocomposite matrix with significant superiority to the superdisintegrants. The dissolution impact was absolutely correlated with the swelling capacity of disintegrants ensuring a swelling/erosion-based mechanism [70].

Meanwhile, the impact of carrier type and spray-drying conditions was thoroughly investigated by Sharma et al. [71] who developed a solid self-nanoemulsifying drug delivery system (S-SNEDDS) to investigate their effects on dissolution rate and bioavailability of an anti-hyperlipidemic drug, simvastatin. Different formulations were prepared using the examined carriers to enhance the dissolution rate and bioavailability of simvastatin. Firstly, liquid-SNEDDS composed of Labrafil M 1944 CS/Tween-80/Ethanol containing simvastatin were prepared and recorded a droplet size of 40.69 nm. Then, the carrier was added and subjected to spray-drying process. The spray-dried formulation, containing the hydrophilic Aerosil 200, produced nanoemulsions with unaffected droplet size and drug release patterns upon subjection to different stress conditions (such as thermodynamic stress and freeze–thaw cycles).

Furthermore, a remarkable superiority of the formulation prepared with Aerosil 200 (either in its liquid or solid form) was proven in the in vitro simvastatin dissolution studies over the pure and marketed simvastatin. DSC and powder-XRD characterization revealed presence of simvastatin in an amorphous state in Aerosil 200-based SNEDDS formulation. Transmission electron micrograph for the solid SNEDDS demonstrated non-agglomerated, distinct spherical droplets with size less than 100 nm. Upon carrying out in vivo study using rats and performing the pharmacokinetic study, a proven superiority of the developed solid SNEDDS over the market product was recorded with an increase in C_{max}, mean residence time, and $AUC_{0\text{-}\infty}$ values, as well as superior bioavailability [71].

Microparticles

Wu et al. investigated the potential of spray-drying process to formulate solid lipid microparticles encapsulating protein drugs [72]. Firstly, insulin, as a model protein, was transformed into insulin–phospholipid complex, by dissolving with lipid excipients in an organic solvent. Then, the system was spray-dried to fabricate solid lipid microparticles. A similar method was adopted to formulate polymeric microparticles using D,L-lactic-co-glycolic acid (PLGA). As viewed by scanning electron microscope, spray-dried solid lipid microparticles and PLGA microparticles had smooth surface and spherical particles. Spray drying of insulin caused minor alteration in its secondary structure. Sustained release of insulin was achieved from the solid lipid microparticles with a significantly lower burst release compared to insulin-loaded PLGA microparticles. This can indicate the potentiality of spray drying to develop sustained-release protein-encapsulated solid lipid microparticles.

The sol–gel technology is currently thought to be one of the most favorable approaches for achieving controlled drug release. The drug is entrapped within a porous mesh without the need of covalent linkage formation. Furthermore, the sustained thermal stability of drugs can be supported when entrapped with a micro-/nano-structured amorphous glass matrix [85]. The sol–gel technique involves the use of a metal or silicon alkoxide as a precursor. A recent precursor, tetrakis (2-methoxyethyl)

orthosilicate, was utilized in a study by Wang and Friess [73] to develop sustained-release microparticles for delivery of bioactive agents by spray drying. The spray-dried silica particles encapsulating FITC-dextran 150 (as a model compound of high molecular weight) were produced by nano spray-dryer Büchi-90. The formulation parameters affected and controlled the encapsulated drug release profile. Particles with spherical shapes and smooth surfaces were formed. The adjustment of the pH of the precursor solution had an impact on the internal microstructures. In conclusion, the spray-drying process was capable of forming a promising alternative sol–gel technology based on drug delivery system with the use of the new precursor, tetrakis (2-methoxyethyl) orthosilicate, exhibiting the ability of delivering high-molecular weight biopharmaceuticals in a sustained-release pattern.

Momin et al. recorded the improvement of co-spray drying of the hygroscopic kanamycin with the hydrophobic drug rifampicin aiming at producing an inhalable powder for enhancing the treatment of respiratory tract infections [74]. In this study, direct delivery of a combination therapy was inhaled in high dose to eliminate local respiratory infections. Thus, a mixture of both drugs was co-spray-dried and inhalable particles with rifampicin-enriched surfaces were produced. The produced powders were inhalable, amorphous, and having a particle size range of 1.1–5.9 μm. Analysis of particles' surfaces with X-ray photoelectron spectroscopy and time-of-flight secondary ion mass spectrometry proved rifampicin-enriched surfaces. As appeared by scanning electron microscopy, the produced formulation was flake-shaped. The combination powder showed good stability profile when stored for 30 days in an open Petri dish at 15 and 53% RH and 25 ± 2 °C. Upon examining its safety to human, cytotoxic study was performed using A549 alveolar basal epithelial cell line and Calu-3 bronchial epithelial cell line. The combination powder was non-toxic. This proves the success of spray-drying technique in producing surface-enriched rifampicin–kanamycin particles as combination therapy for combating dangerous local respiratory infections by delivering high-dose medication to the lungs.

Spray-dried Konjac glucomannan microparticles (KGM) encapsulating isoniazid and rifabutin were produced to be administered as an inhalable tuberculosis therapy. KGM, a naturally occurring compound used as a drug-delivery matrix, was utilized for microparticle fabrication in this study in the presence of excipients. Isoniazid and rifabutin were entrapped efficiently within the microparticles. Presence of excipients further promoted drug release. Furthermore, no toxicity was observed when microparticles were tested on Calu-3 and A549 cells (cell viabilities were higher than 70%) [77]. As shown in the scanning electron micrograph, KGM microparticles demonstrated a convoluted shape with a spherical or approximately spherical shape.

Bürki et al. [56] exploited the nano spray dryer to fabricate respirable protein powder ranging in size from 1 to 5 μm. With the use of galactosidase as a model protein in association with stabilizer (trehalose), respirable powder formulations were prepared. The influence of inlet temperature, pore size of the spray mesh, and amount of ethanol in the formulated solutions were studied and analyzed using a full factorial design. Results showed that spherical particles with smooth surfaces were produced with spray cap size of 4.0 μm, while powders with a mixture of shriveled and smooth spheres were obtained with different spray cap sizes (5.5 and 7.0 μm, respectively). Some of the spheres were hollow from inside. The authors also recorded the effect of process parameters as follows: a significant effect of the inlet temperature and its interaction with spray cap mesh size on the enzyme activity as maintained full activity was recorded with the suggested process. However, higher storage stability of the protein was attained for spray-dried formulations prepared without ethanol and large spray cap size [56].

A stable spray-dried Sabin inactivated polio vaccine (sIPV) formulation was developed by Kanojia et al. [76] with the target of minimizing the loss of activity during drying and storage. The influence of atomization during the spray-drying process was investigated, and the excipients were screened. Tailoring of excipient combinations and their concentrations was extensively studied in order to maximize the activity of sIPV after spray drying and storage. It was recommended to separately spray dry the different serotypes and then mixing them to obtain the trivalent vaccine.

Amorphous solid dispersions

Amorphization is an approach to change the solid drug state from a crystalline to an amorphous form. The amorphous form displays higher solubility relative to the crystalline form because no energy requirement is needed to disrupt the crystal lattice structure of the drug molecule, promoting better interaction chances with solvent molecules through intermolecular interactions, and, hence, solubilization occurs [86, 87]. However, the excess thermodynamic properties of the amorphous forms can lead to a tendency to crystallization resulting in negating the solubility advantage. A potential solution is the development of amorphous solid dispersion idea. Amorphous solid dispersion comprises drug molecules entrapped within an amorphous polymeric carrier. Several factors, namely, the anti-plasticizing effect of the polymer, intermolecular interactions, and physical inhibition of crystallizing along with reducing the drug chemical potential, result in a greater drug solubility [87]. Additionally, the polymeric carrier role extends to improve dissolution rate and absorption [88].

Amorphous solid dispersions of darunavir and hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, or polyvinylpyrrolidone K-30 were prepared by both spray-drying and electrospraying techniques. Both techniques were successful in producing amorphous preparations with similar characteristics regarding the residual solvent and

drug release. Differences were recorded in the morphology and the particle size distribution; however, this did not affect the formulations' pharmaceutical performance [77].

The Flory–Huggins theory was utilized to predict both drug solubility and miscibility in polymers during formulation of amorphous solid dispersion with the comparison of two process techniques, melt extrusion and spray drying. The research team of Tian and co-authors [78] prepared solid-dispersion formulations of felodipine with a carrier polymer (PVPK15, Soluplus, HPMCAS) fabricated by hot-melt extrusion and spray-drying techniques and characterized the formulae using thermogravimetric analysis, DSC, FTIR, and XRD methods. Results showed that the spray-drying technique generated amorphous solid dispersions with higher drug loading than the hot melt extrusion. FTIR analysis confirmed that all spray-dried formulae were not crystalline with the existence of integrated amorphous drug moieties, even with samples containing high drug concentrations.

Co-crystals

Co-crystallization is a promising evolving method to enhance the physicochemical properties of solid-state of active pharmaceutical ingredients, namely, rate of dissolution, solubility, stability, and ability to be compressed in a tablet form. Co-crystals provide a distinctive chance for developing drug molecules with relatively low risk and high investment return [89]. Various methods have been reported for co-crystal manufacturing, such as solution-based crystallization method, solid-based crystallization method, and spray drying.

Spray-drying technique showed superiority over other methods upon formulation of co-crystals within a carrier polymer according to Walsh et al. [79], where a model co-crystal containing a combination of 1:1 mixture of ibuprofen and isonicotinamide was designed. The authors examined the effect of the polymeric carrier type (mannitol, Soluplus, xylitol, and polyvinylpyrrolidone K15) as well as the ratio of co-crystal components to carrier for both adopted techniques. The prediction of co-crystal formation was carried out by analyzing Hansen Solubility Parameter (HSP) for the co-crystal and carrier. During the spray-drying process, large difference in HSP between the co-crystal and the excipients allowed the incorporation of high amounts of excipients without altering the co-crystal integrity (e.g., ΔHSP of 18.3 $MPa^{0.5}$ in the case of mannitol). In contrast, the small ΔHSP between two other excipients (Soluplus and PVP K15) limited the ratio of forming co-crystals at a very low value of excipients. On comparing the obtained results from the two techniques, ibuprofen:isonicotinamide co-crystal spray drying suggested greater feasibility over hot melt extrusion as a procedure for co-crystal formation within a carrier excipient, with a significant reduction of the unit operation number needed to develop the intended final pharmaceutical product.

Another study by Walsh et al. [80] investigated the effect of feeding a three-component solution during the spray-drying procedure. The aim behind this research was to reduce the trials needed to develop a final pharmaceutical product to a one-step process (like eliminating blending with excipient). Herein, the hydrophobic drug, sulfadimidine, and the hydrophilic 4-aminosalicylic acid were considered as the co-former model drug and intended to form a co-crystal with a third component (an excipient) by spray drying. Thermal analysis approach was utilized to assess the co-crystal solubility in the excipient. By altering the ratio of co-crystal components to excipient, different formulations were prepared. For immiscible systems (difference in HSP was larger than 9.6 $MPa^{0.5}$), formation of co-crystals occurred with a preserved integrity even with high excipient proportion (90% *w*/*w*). However, when using an excipient that was miscible with the co-crystal components, an amorphous dispersion was formed even with low proportion of excipient. Co-spray drying of the excipient (of either nature; crystalline or amorphous) with the co-crystal components would lead to a co-crystal formation.

Nanosuspensions

The utilization of the nano spray-drying technique to produce a nanosuspension formulation for econazole nitrate was explored by Maged et al. [81]. The effects of the used carriers (methyl-β-cyclodextrin and hydroxylpropyl-β-cyclodextrin) and stabilizers (polyvinylpyrrolidone k30, polyethylene oxide, poloxamer 407, Cremophor EL, and Tween 80) were investigated. The nano spray-dried formulations displayed nearly spherical particles with smooth surface, and with no observed drug crystals, that ranged in size from 121 to 1565 nm. High-yield values were obtained (≈ 80%). The significantly improved drug release from the prepared nanosuspension formula (prepared with hydroxypropyl-β cyclodextrin and Tween 80) was a result of the presence of the drug in amorphous form. The selected formula succeeded to preserve the econazole nanosuspension from aggregation during a one year of storage at room temperature. Moreover, a distinct superior bioavailability was demonstrated when the selected formulation was tested on albino rabbit's eyes in comparison with the crude drug suspension. Thus, nano spray dryer proved to act as a one-step technique in producing effective and stable nanosuspensions.

Risperidone nanosuspension was prepared by optimizing the spray-drying conditions to achieve an effective formulation with the intended criteria of low particle size, high yield, and optimum compressibility applying the Quality by Design approach [82]. Nanosuspension was prepared by the anti-solvent precipitation method using stabilizers namely, Poloxamer 68 and Poloxamer 127. A factorial design was used with two independent factors (inlet temperature and feed

pump speed), while the dependent variables were size and entrapment efficiency.

The spray-dried powders were compressed in an orally dispersible tablet form and were characterized by their wetting time, hardness, disintegration time, weight variation, friability, and dissolution. Nanosuspension displayed particle size of 200.00 ± 0.40 nm and a PDI value of 0.210 ± 0.03. Spray-dried risperidone suspension displayed rounded-edge particles when viewed by the scanning electron microscope. Loss of risperidone crystallinity occurred during the spray-drying process as proved by the AFM, DSC, FTIR, and XRD. The orodispersible tablets prepared using the optimum spray-dried nanosuspension displayed better dissolution compared to its marketed analog [82].

Spray-dried emulsions

Ultra-fine powder, containing atorvastatin calcium, was developed using the spray-drying technique by Basha et al. [83]. Atorvastatin calcium was solubilized in an emulsion form, and hydrophilic carriers (sodium alginate, pectin, hydroxypropylmethyl cellulose, and chitosan HCl) were added in two different concentrations. Then, these formulations were spray-dried and thoroughly investigated for their powder-related characteristics, as well as their dissolution profiles. An optimum formulation prepared using pectin demonstrated a superior dissolution rate compared to other formulations. Upon performing the in vivo studies using hyperlipidemic rats, normal lipid profile was attained by the optimum formulation compared to atorvastatin calcium-marketed tablets. This was confirmed histopathologically, revealing normal liver sections. The superior anti-hyperlipidemic activity of the suggested formula was mainly due to the enhanced dissolution of the drug.

Natural extracts

A spray-dried powder product (hecogenin) was obtained by drying the liquid extract of sisal (*Furcraea* spp.) [84]. Optimization of the process was carried out based on adjusting the spray-dryer operating conditions and monitoring the final product quality properties. The best conditions that achieved reasonable results were inlet and outlet temperatures of 160 and 82.6 °C, respectively, with an atomizer speed of 26,800 rpm. As a result of these conditions, a powder was obtained with yield and stickiness values of 62.2 and 14%, respectively. It also displayed low moisture content, good solubility, and optimum hecogenin content.

Another research, performed to enhance the operation conditions for spray drying of the leaf extract of *Murraya koenigii* (Linn), was carried out by Sablania et al. [90] using response surface methodology. The independent variables were adjusted as follows: an inlet temperature of 140–180 °C, maltodextrin concentration of 10–30%, and concentration of gum acacia of 2–10%. The dependent responses were the product yield along with its solubility, the total phenolic content, and the moisture content. The optimized conditions for the parameters confirmed a quadratic model, and the optimum spray-drying conditions of *Murraya koenigii* leaf extract were suggested to be an inlet temperature of 165 °C, maltodextrin concentration of 30%, and 10% gum acacia. Thus, a product was obtained with high desirability level of 0.918.

Conclusion

The current review presents an insight on the spray-drying technique for drying substances and developing various drug delivery systems. A wide range of particle sizes can be produced, paving the way for various pharmaceutical technology applications at both the laboratory and industrial scales. The continuous production of new spray-dryer generations, along with the increasing number of annually published articles applying this technique, comprises a prosperous future of developing pharmaceuticals with enhanced biological performances. This review displays with case presentations the different pharmaceutical technology products that can be obtained by this technique (nano- or micro-particles, amorphous solid dispersion systems, co-crystals, formulation of spray-dried emulsions, as well as natural extracts). In addition, parameters, characterization, physicochemical stability, and regulatory consideration are highlighted in-depth. Finally, the perspective of this article is to inspire further researches to apply the addressed technique to develop more advanced drug delivery technologies.

Compliance with ethical standards

Conflict of interest The author confirms that this article content has no conflict of interest.

References

1. Rattes ALR, Oliveira WP. Spray drying conditions and encapsulating composition effects on formation and properties of sodium diclofenac microparticles. Powder Technol. 2007;171(1):7–14.
2. Sosnik A, Seremeta KP. Advantages and challenges of the spray-drying technology for the production of pure drug particles and drug-loaded polymeric carriers. Adv Colloid Interf Sci. 2015;223:40–54.
3. Sollohub K, Cal K. Spray drying technique: II. Current applications in pharmaceutical technology. J Pharm Sci. 2010;99(2):587–97. https://doi.org/10.1002/jps.21963.
4. Arpagaus C, Collenberg A, Rutti D, Assadpour E, Jafari SM. Nano spray drying for encapsulation of pharmaceuticals. Int J Pharm. 2018;546(1–2):194–214. https://doi.org/10.1016/j.ijpharm.2018.05.037.
5. Santo EFE, LKFd L, Torres APC, Oliveira G, Ponsano EHG. Comparison between freeze and spray drying to obtain powder

Rubrivivax gelatinosus biomass. Food Science and Technology. 2013;33(1):47–51.
6. Arpagaus C, John P, Collenberg A, Rütti D. Chapter 10: nanocapsules formation by nano spray drying. In: Jafari SM, editor. Nanoencapsulation technologies for the food and nutraceutical industries: Elsevier Inc.; 2017:346–401.
7. Wong TW, John P. Advances in spray drying technology for nanoparticle formation. In: Aliofkhazraei M, editor. Handbook of nanoparticles: Springer International Publishing; 2016:329-46.
8. Fu YJ, Shyu SS, Su FH, Yu PC. Development of biodegradable copoly(D, L-lactic/glycolic acid) microspheres for the controlled release of 5-FU by the spray drying method. Colloids Surf B: Biointerfaces. 2002;25:269–79.
9. Sen D, Khan A, Bahadur J, Mazumder S, Sapra B. Use of small-angle neutron scattering to investigate modifications of internal structure in self-assembled grains of nanoparticles synthesized by spray drying. J Colloid Interface Sci. 2010;347(1):25–30.
10. Gong P, Zhang L, Han X, Shigwedha N, Song W, Yi H, et al. Injury mechanisms of lactic acid bacteria starter cultures during spray drying: a review. Dry Technol. 2014;32(7):793–800.
11. Patel BB, Patel JK, Chakraborty S. Review of patents and application of spray drying in pharmaceutical, food and flavor industry. Recent Pat Drug Deliv Formul. 2014;8(1):63–78.
12. Gula A, Ren L, Zhou Z, Lu D, Wang S. Design and evaluation of biodegradable enteric microcapsules of amifostine for oral delivery. Int J Pharm. 2013;453(2):441–7.
13. Bowey K, Swift BE, Flynn LE, Neufeld RJ. Characterization of biologically active insulin-loaded alginate microparticles prepared by spray drying. Drug Dev Ind Pharm. 2013;39(3):457–65.
14. Baras B, Benoit M-A, Gillard J. Parameters influencing the antigen release from spray-dried poly (DL-lactide) microparticles. Int J Pharm. 2000;200(1):133–45.
15. Bhowmik T, D'Souza B, Shashidharamurthy R, Oettinger C, Selvaraj P, D'Souza M. A novel microparticulate vaccine for melanoma cancer using transdermal delivery. J Microencapsul. 2011;28(4):294–300.
16. Tshweu L, Katata L, Kalombo L, Chiappetta DA, Hocht C, Sosnik A, et al. Enhanced oral bioavailability of the antiretroviral efavirenz encapsulated in poly (epsilon-caprolactone) nanoparticles by a spray-drying method. Nanomedicine. 2014;9(12):1821–33.
17. Gharsallaoui A, Roudaut G, Chambin O, Voilley A, Saurel R. Applications of spray-drying in microencapsulation of food ingredients: an overview. Food Res Int. 2007;40(9):1107–21.
18. Mahdavi SA, Jafari SM, Ghorbani M, Assadpoor E. Spray-drying microencapsulation of anthocyanins by natural biopolymers: a review. Dry Technol. 2014;32(5):509–18.
19. Takashima Y, Saito R, Nakajima A, Oda M, Kimura A, Kanazawa T, et al. Spray-drying preparation of microparticles containing cationic PLGA nanospheres as gene carriers for avoiding aggregation of nanospheres. Int J Pharm. 2007;343(1–2):262–9.
20. Freitas C, Mullera RH. Spray-drying of solid lipid nanoparticles (SLN TM). Eur J Pharm Biopharm. 1998;46(2):145–51.
21. Lane ME, Brennan FS, Corrigan OI. Comparison of post-emulsification freeze drying or spray drying processes for the microencapsulation of plasmid DNA. J Pharm Pharmacol. 2005;57(7):831–8. https://doi.org/10.1211/0022357056406.
22. Fatnassi M, Tourné-Péteilh C, Peralta P, Cacciaguerra T, Dieudonné P, Devoisselle J-M, et al. Encapsulation of complementary model drugs in spray-dried nanostructured materials. JSST. 2013;68(2):307–16.
23. Seremeta KP, Tur MI, Perez SM, Hocht C, Taira C, Lopez Hernandez OD, et al. Spray-dried didanosine-loaded polymeric particles for enhanced oral bioavailability. Colloids Surf B: Biointerfaces. 2014;123:515–23. https://doi.org/10.1016/j.colsurfb.2014.09.055.
24. Tewa-Tagne P, Briancon S, Fessi H. Preparation of redispersible dry nanocapsules by means of spray-drying: development and characterisation. Eur J Pharm Sci. 2007;30(2):124–35. https://doi.org/10.1016/j.ejps.2006.10.006.
25. Anish C, Upadhyay AK, Sehgal D, Panda AK. Influences of process and formulation parameters on powder flow properties and immunogenicity of spray dried polymer particles entrapping recombinant pneumococcal surface protein A. Int J Pharm. 2014;466(1–2):198–210.
26. Murugesan R, Orsat V. Spray drying for the production of nutraceutical ingredients—a review. Food Bioprocess Technol. 2012;5:3–14.
27. Okuyama K, Abdullah M, Lenggoro IW, Iskandar F. Preparation of functional nanostructured particles by spray drying. Adv Powder Technol. 2006;17:587–611.
28. Anandharamakrishnan C, Ishwarya PS. Chapter 8: spray drying for nanoencapsulation of food components. In: Spray drying techniques for food ingredient encapsulation. Chichester: Wiley; 2015. p. 180–97.
29. Berggren J, Frenning G, Alderborn G. Compression behaviour and tablet-forming ability of spray-dried amorphous composite particles. Eur J Pharm Sci. 2004;22(2–3):191–200. https://doi.org/10.1016/j.ejps.2004.03.008.
30. Mu L, Teo MM, Ning HZ, Tan CS, Feng SS. Novel powder formulations for controlled delivery of poorly soluble anticancer drug: application and investigation of TPGS and PEG in spray-dried particulate system. J Control Release. 2005;103(3):565–75. https://doi.org/10.1016/j.jconrel.2004.12.023.
31. Zhu C, Shoji Y, McCray S, Burke M, Hartman CE, Chichester JA, et al. Stabilization of HAC1 influenza vaccine by spray drying: formulation development and process scale-up. Pharm Res. 2014;31(11):3006–18. https://doi.org/10.1007/s11095-014-1394-3.
32. Lee SH, Heng D, Ng WK, Chan HK, Tan RB. Nano spray drying: a novel method for preparing protein nanoparticles for protein therapy. Int J Pharm. 2011;403(1–2):192–200. https://doi.org/10.1016/j.ijpharm.2010.10.012.
33. Li X, Anton N, Arpagaus C, Belleteix F, Vandamme TF. Nanoparticles by spray drying using innovative new technology: the Büchi Nano spray dryer B-90. J Control Release. 2010;147(2):304–10.
34. Stahl K, Claesson M, Lilliehorn P, Linden H, Backstrom K. The effect of process variables on the degradation and physical properties of spray dried insulin intended for inhalation. Int J Pharm. 2002;233(1–2):227–37.
35. Bittner B, Morlock M, Koll H, Winter G, Kissel T. Recombinant human erythropoietin (rhEPO) loaded poly(lactide-co-glycolide) microspheres: influence of the encapsulation technique and polymer purity on microsphere characteristics. Eur J Pharm Biopharm. 1998;45(3):295–305.
36. Maury M, Murphy K, Kumar S, Shi L, Lee G. Effects of process variables on the powder yield of spray-dried trehalose on a laboratory spray-dryer. Eur J Pharm Biopharm. 2005;59(3):565–73. https://doi.org/10.1016/j.ejpb.2004.10.002.
37. Cheow WS, Li S, Hadinoto K. Spray drying formulation of hollow spherical aggregates of silica nanoparticles by experimental design. Chem Eng Res Des. 2010;88(5–6):673–85.
38. NíÓgáin O, Tajber L, Corrigan OI, Healy AM. Spray drying from organic solvents to prepare nanoporous/nanoparticulate microparticles of protein: excipient composites designed for oral inhalation. J Pharm Pharmacol. 2012;64(9):1275–90.
39. Schafroth N, Arpagaus C, Jadhav UY, Makne S, Douroumis D. Nano and microparticle engineering of water insoluble drugs using a novel spray-drying process. Colloids Surf B: Biointerfaces. 2012;90:8–15.
40. Mujumdar AS. Handbook of industrial drying. Third ed. US: Taylor & Francis Group, CRC Press; 2006.

41. Elversson J, Millqvist-Fureby A, Alderborn G, Elofsson U. Droplet and particle size relationship and shell thickness of inhalable lactose particles during spray drying. J Pharm Sci. 2003;92(4):900–10. https://doi.org/10.1002/jps.10352.
42. Schoubben A, Blasi P, Giovagnoli S, Rossi C, Ricci M. Development of a scalable procedure for fine calcium alginate particle preparation. Chem Eng News. 2010;160(1):363–9.
43. Beck-Broichsitter M, Schweiger C, Schmehl T, Gessler T, Seeger W, Kissel T. Characterization of novel spray-dried polymeric particles for controlled pulmonary drug delivery. J Control Release. 2012;158(2):329–35.
44. Park C-W, Li X, Vogt FG, Hayes D Jr, Zwischenberger JB, Park E-S, et al. Advanced spray-dried design, physicochemical characterization, and aerosol dispersion performance of vancomycin and clarithromycin multifunctional controlled release particles for targeted respiratory delivery as dry powder inhalation aerosols. Int J Pharm. 2013;455(1–2):374–92.
45. Wan F, Bohr A, Maltesen MJ, Bjerregaard S, Foged C, Rantanen J, et al. Critical solvent properties affecting the particle formation process and characteristics of celecoxib-loaded PLGA microparticles via spray-drying. Pharm Res. 2013;30(4):1065–76.
46. Nandiyanto ABD, Okuyama K. Progress in developing spray-drying methods for the production of controlled morphology particles: from the nanometer to submicrometer size ranges. Adv Powder Technol. 2011;22(1):1–19.
47. Schmid K, Arpagaus C, Friess W. Evaluation of the nano spray dryer B-90 for pharmaceutical applications. Pharm Dev Technol. 2011;16(4):287–94.
48. Schoubben A, Giovagnoli S, Tiralti MC, Blasi P, Ricci M. Capreomycin inhalable powders prepared with an innovative spray-drying technique. Int J Pharm. 2014;469(1):132–9. https://doi.org/10.1016/j.ijpharm.2014.04.042.
49. Bowen M, Turok R, Maa Y-F. Spray drying of monoclonal antibodies: investigating powder-based biologic drug substance bulk storage. Dry Technol. 2013;31:1441–50.
50. Chan H-K, Kwok PCL. Production methods for nanodrug particles using the bottom-up approach. Adv Drug Deliv Rev. 2011;63:406–16.
51. Heng D, Lee SH, Ng WK, Tan RBH. The nano spray dryer B-90. Expert Opin Drug Deliv. 2011;8:965–72.
52. Maltesen MJ, Bjerregaard S, Hovgaard L, Havelund S, van de Weert M. Quality by design—spray drying of insulin intended for inhalation. Eur J Pharm Biopharm. 2008;70:828–38.
53. Brandenberger H. Development of a novel high-performance cyclone to increase the yield in a mini spray dryer. best@buchi Information Bulletin. 2003;Number 27/2003.
54. Arpagaus C. Nano spray dryer B-90: literature review and applications. best@buchi Information Bulletin. 2011;Number 63/2011.
55. Arpagaus C. Spray drying R&D solutions—BÜCHI's nano spray dryer: a world novelty in laboratory scale. ONdrugDelivery. 2010; March 2010 (page 30).
56. Bürki K, Jeon I, Arpagaus C, Betz G. New insights into respirable protein powder preparation using a nano spray dryer. Int J Pharm. 2011;408(1–2):248–56.
57. Lass JS, Sant A, Knoch M. New advances in aerosolised drug delivery: vibrating membrane nebuliser technology. Expert Opin Drug Deliv. 2006;3:693–702.
58. Vecellio L. The mesh nebulizer: a recent technical innovation for aerosol delivery. Breathe. 2006;2:252–60.
59. Knoch M, Keller M. The customised electronic nebuliser: a new category of liquid aerosol drug delivery systems. Expert Opin Drug Deliv. 2005;2:377–90.
60. Baba K, Nishida K. Calpain inhibitor nanocrystals prepared using nano spray dryer B-90. Nanoscale Res Lett. 2012;7:436.
61. Arpagaus C. A novel laboratory-scale spray dryer to produce nanoparticles. Dry Technol. 2012;30:1113–21.
62. Beck-Broichsitter M, Schweiger C, Schmehl T, Gessler T, Seeger W, Kissel T. Characterization of novel spray-dried polymeric particles for controlled pulmonary drug delivery. J Control Release. 2012;158(2):329–35. https://doi.org/10.1016/j.jconrel.2011.10.030.
63. Arpagaus C, Meuri M. Laboratory scale spray drying of inhalable particles: a review. Respir Drug Deliv. 2010:469–76.
64. Feng AL, Boraey MA, Gwin MA, Finlay PR, Kuehl PJ, Vehring R. Mechanistic models facilitate efficient development of leucine containing microparticles for pulmonary drug delivery. Int J Pharm. 2011;409:156–63.
65. Sun Y, Song X, Wang J, Yu J. Preparation of lithium carbonate hollow spheres by spray pyrolysis. Cryst Res Technol. 2011;46:173–7.
66. Oliveira AM, Guimarães KL, Cerize NN, Tunussi AS, Poço JG. Nano spray drying as an innovative technology for encapsulating hydrophilic active pharmaceutical ingredients (API). J Nanomed Nanotechnol. 2013;4:6.
67. Brinkmann-Trettenes U, Barnert S, Bauer-Brandl A. Single step bottom-up process to generate solid phospholipid nano-particles. Pharm Dev Technol. 2014;19:326–32.
68. Braig V, Konnerth C, Peukert W, Lee G. Enhanced dissolution of naproxen from pure-drug, crystalline nanoparticles: a case study formulated into spray-dried granules and compressed tablets. Int J Pharm. 2018;554:54–60. https://doi.org/10.1016/j.ijpharm.2018.09.069.
69. de Oliveira EG, Cardoso AM, Paese K, Coradini K, de Oliveira CV, Pohlmann AR, et al. Reconstituted spray-dried phenytoin-loaded nanocapsules improve the in vivo phenytoin anticonvulsant effect and the survival time in mice. Int J Pharm. 2018;551(1–2):121–32. https://doi.org/10.1016/j.ijpharm.2018.09.023.
70. Li M, Suriel I, Vekaria J, Proske J, Orbe P, Armani M, et al. Impact of dispersants on dissolution of itraconazole from drug-loaded, surfactant-free, spray-dried nanocomposites. Powder Technol. 2018;339:281–95.
71. Sharma P, Singh SK, Pandey NK, Rajesh SY, Bawa P, Kumar B, et al. Impact of solid carriers and spray drying on pre/post-compression properties, dissolution rate and bioavailability of solid self-nanoemulsifying drug delivery system loaded with simvastatin. Powder Technol. 2018;338:836–46.
72. Wu C, van de Weert M, Baldursdottir SG, Yang M, Mu H. Effect of excipients on encapsulation and release of insulin from spray-dried solid lipid microparticles. Int J Pharm. 2018;550(1–2):439–46. https://doi.org/10.1016/j.ijpharm.2018.09.007.
73. Wang B, Friess W. Spray drying of silica microparticles for sustained release application with a new sol-gel precursor. Int J Pharm. 2017;532(1):281–8. https://doi.org/10.1016/j.ijpharm.2017.09.016.
74. Momin MAM, Tucker IG, Doyle CS, Denman JA, Sinha S, Das SC. Co-spray drying of hygroscopic kanamycin with the hydrophobic drug rifampicin to improve the aerosolization of kanamycin powder for treating respiratory infections. Int J Pharm. 2018;541(1–2):26–36. https://doi.org/10.1016/j.ijpharm.2018.02.026.
75. Guerreiro F, Pontes JF, da Costa AMR, Grenha A. Spray-drying of konjac glucomannan to produce microparticles for an application as antitubercular drug carriers. Powder Technol. 2019;342:246–52.
76. Kanojia G, Ten Have R, Brugmans D, Soema PC, Frijlink HW, Amorij JP, et al. The effect of formulation on spray dried Sabin inactivated polio vaccine. Eur J Pharm Biopharm. 2018;129:21–9. https://doi.org/10.1016/j.ejpb.2018.05.021.
77. Smeets A, Koekoekx R, Clasen C, Van den Mooter G. Amorphous solid dispersions of darunavir: comparison between spray drying and electrospraying. Eur J Pharm Biopharm. 2018;130:96–107.
78. Tian Y, Caron V, Jones DS, Healy AM, Andrews GP. Using Flory-Huggins phase diagrams as a pre-formulation tool for the

production of amorphous solid dispersions: a comparison between hot-melt extrusion and spray drying. J Pharm Pharmacol. 2014;66(2):256–74. https://doi.org/10.1111/jphp.12141.
79. Walsh D, Serrano DR, Worku ZA, Madi AM, O'Connell P, Twamley B, et al. Engineering of pharmaceutical cocrystals in an excipient matrix: spray drying versus hot melt extrusion. Int J Pharm. 2018;551(1–2):241–56. https://doi.org/10.1016/j.ijpharm.2018.09.029.
80. Walsh D, Serrano DR, Worku ZA, Norris BA, Healy AM. Production of cocrystals in an excipient matrix by spray drying. Int J Pharm. 2018;536(1):467–77. https://doi.org/10.1016/j.ijpharm.2017.12.020.
81. Maged A, Mahmoud AA, Ghorab MM. Nano spray drying technique as a novel approach to formulate stable econazole nitrate nanosuspension formulations for ocular use. Mol Pharm. 2016;13(9):2951–65.
82. Nair A, Khunt D, Misra M. Application of quality by design for optimization of spray drying process used in drying of risperidone nanosuspension. Powder Technol. 2019;342:156–65.
83. Basha M, Salama AH, El Awdan S. Reconstitutable spray dried ultra-fine dispersion as a robust platform for effective oral delivery of an antihyperlipidemic drug. Int J Pharm. 2017;532(1):478–90. https://doi.org/10.1016/j.ijpharm.2017.09.033.
84. Salas MCR, Velásquez HJC, Gonzalez JHG. Spray drying of sisal liquids extracts (Furcraea spp.): overall performance of the drying process. Powder Technol. 2017;321:163–72.
85. Avnir D, Coradin T, Lev O, Livage J. Recent bio-applications of sol-gel materials. J Mater Chem. 2006;16:1013–30.
86. Hancock BC, Parks M. What is the true solubility advantage for amorphous pharmaceuticals? Pharm Res. 2000;17:397–404.
87. Surikutchi BT, Patil SP, Shete G, Patel S, Bansal AK. Drug-excipient behavior in polymeric amorphous solid dispersions. J Excip Food Chem. 2013;4:70–94.
88. Singh A, Van den Mooter G. Spray drying formulation of amorphous solid dispersions. Adv Drug Deliv Rev. 2016;100:27–50. https://doi.org/10.1016/j.addr.2015.12.010.
89. Shaikh R, Singh R, Walker GM, Croker DM. Pharmaceutical cocrystal drug products: an outlook on product development. Trends Pharmacol Sci. 2018;39:1033–48.
90. Sablania V, Bosco SJD. Optimization of spray drying parameters for Murraya koenigii (Linn) leaves extract using response surface methodology. Powder Technol. 2018;335:35–41.