Expert Opinion

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The nano spray dryer B-90

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Introduction: Spray drying is an extremely well-established technology for the production of micro-particulate powders suited for a variety of drug delivery applications. In recent years, the rise in nanomedicine has placed increased pressure on the existing systems to produce nanoparticles in good yield and with a narrow size distribution. However, the separation and collection of nanoparticles with conventional spray dryer set ups is extremely challenging due to their typical low collection efficiency for fine particles < 2 μm. Currently, nanoparticles have to be agglomerated into larger microparticles, via a two-step approach, in order to collect them in a sizeable amount. However, this method has to contend with the issue of adequate redispersibility of the primary particles to reap the full benefits of nanosizing.

Areas covered: An overview on the advances in spray drying technology is provided in this review with particular emphasis on the novel Buchi® Nano Spray Dryer B-90. Readers will appreciate the limitations of conventional spray drying technology, understand the mechanisms of the Buchi® Nano Spray Dryer B-90, and also learn about the strengths and shortcomings of the system.

Expert opinion: The Buchi® Nano Spray Dryer B-90 offers a new, simple and alternative approach for the production of nanoparticles suited for a variety of drug delivery applications.

Keywords: drug delivery, electrostatic particle collector, nano spray dryer, nanoparticles and microparticles, powder, spray drying, vibrating mesh spray technology

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1. Introduction

Many existing and new drugs in the pharmaceutical industry fail to be fully commercialized due to their poor solubility in aqueous media, which inadvertently limits bioavailability. These drugs typically fall into Class II of the Biopharmaceutics Classification Scheme: low solubility, high permeability compounds, whereby the dissolution rate is the limiting factor for the drug absorption rate. Nanoparticles, in view of their reduced size and hence larger specific surface areas, are seen as a promising way to enhance the dissolution rates of these poorly water-soluble drugs [1-4].

Spray drying has long been a useful technique to regulate the size and morphology [5-7] of microparticles. However, with the recent emergence of nanotechnology, there is an increased need to extend the capabilities of conventional spray drying into the 'nanometer' regime. Currently, this is achieved via a two-step approach (suspension-based) which involves a previous micro-mixing (e.g., confined liquid impinging jet precipitation [8] or high-gravity precipitation [9]) or wet-milling/homogenization step [10-13]. The direct solution-based approach is not widely applied for nanoparticles using the conventional system due to the inefficiencies at the atomizer and collector. In these existing systems, it is extremely challenging to produce and collect fine particles < 2 μm in large quantities and in a narrowly distributed size range [14].

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Article highlights.

- The Nano Spray Dryer B-90 is the fourth and newest generation of laboratory-scale spray dryers developed by Buchi® and offers a new, simple and alternative approach for the production of nanoparticles suited for a variety of drug delivery applications.
- The novelty of this spray dryer lies in the vibrating mesh spray technology in the spray head, the gentle laminar flow heating system and the highly-efficient electrostatic particle collector.
- As it has been developed specifically to generate particle size ranging from 300 nm to 5 μm for milligram sample quantities at high yields and with minimal activity loss, it is, therefore, suited for the early stages of product development in the pharmaceutical, biotechnology, food, medical, chemicals, materials and nanotechnology industry.
- It is highly appealing to the drug delivery community, as the desired particle size of most drug delivery applications in the oral, intravenous, transdermal and pulmonary fields all fall within the equipment's achievable size range (i.e., 300 nm to 5 μm).
- As preliminary applications of this novel technology have been rather promising, it is anticipated that its momentum of uptake across a variety of fields will only escalate in the near future, spurred partly by the rise of biotechnology and nanotechnology.

This box summarizes key points contained in the article.

The spray drying process generally consists of three major phases: i) atomization/droplet formation, ii) solvent evaporation and iii) particle collection. Briefly, the liquid stream is sheared or atomized into fine droplets via an appropriate device, then subjected to drying in a drying chamber to yield the solid particles and, finally, separated and collected via a suitable dry powder collector. A comprehensive discussion of the general spray drying process is available in the book by Keith Masters [15], and for applications to pharmaceuticals, the reader is advised to refer to the review by Broadhead *et al.* [16].

1.1 Atomization

Atomization is the act of reducing a fluid into a fine spray. The driving force to assist atomization includes pressure, centrifugal, electrostatic and ultrasound, and they are typically installed in the atomizer spray nozzle [6,15]. The size of the droplets is controlled by the atomizer type and the surface tension, viscosity and density of the fluid [6].

Presently, the commercial atomizers are the rotary disk, hydraulic or pressure nozzle, pneumatic or multi-fluid nozzle and the ultrasonic nebulizer [6,17-18]. The electro-hydrodynamic nozzle is currently under development [18-20]. **Table 1** compares the various methods of atomization. Out of the three commercially available atomizers, the ultrasonic nebulizer appears to be the most suitable option for the production of fine, narrowly-distributed droplets.

1.2 Solvent evaporation

Following atomization, the droplet undergoes conversion into the dried particle form while traversing the drying chamber with the carrier gas (e.g., air, inert gases). Electric heaters are commonly used in laboratory spray dryers [18]. In the traditional spray dryer chamber, the dispersed droplets are subjected to different local air temperature and humidity conditions as a result of non-laminar (i.e., turbulent) gas flow through the system [18]. Therefore, this gives rise to differences in drying degree and hence, the potential non-homogeneity in particle size and morphology. In this regard, a spray dryer system that is able to provide gentle and uniform heating via a laminar flow configuration will definitely be of value to academia and industry, especially in the emerging biological era.

1.3 Particle collection

Existing particle collection methods include the bag filter, electrostatic precipitator and the cyclone [6,18]. In bag filtration, the fabric of the filter separates the particles from the exhaust air. The efficiency of the filter increases with a reduction in fabric pore diameter [18]. The cyclone is currently the most commonly applied device for the separation and collection of particles. Separation is brought about via the set up of centrifugal forces arising from the highly rotated air stream, which propels the particles towards the walls of the device [18]. Electrostatic precipitators have not been widely applied due to the high cost [18]. **Table 2** compares the performance of these particle collectors. As the cyclones used in commercial laboratory spray dryers are unable to collect small particles < 2 μm efficiently [14], the only feasible options for nanoparticles are the filter bags and electrostatic precipitators. Electrostatic precipitators, however, have the advantage of collecting particles with lower sizes (i.e., down to 50 nm) (**Table 2**) [21] and the ease of uncontaminated powder recovery.

2. Limitations of existing nanoparticle production technologies

Currently, there are a number of nanoparticle production technologies available ranging from the 'top-down' (e.g., homogenizers and wet-mills [10-13]) to the 'bottoms-up' approaches (e.g., confined liquid impinging jets [8,22] and high-gravity-controlled-precipitation reactors [9]). The former has been plagued by issues of milling media contamination and the pre-requisites of micronized drug particles and suspension formation [23], while the latter requires the application of suitable solvent–antisolvent combinations utilized in large volumes (e.g., solvent:antisolvent ratios of 1:10 or 1:20), and has a higher potential for nanoparticle aggregation [9,24]. An unaggregated spherical particle with a narrow size distribution is the preferred state for most applications, especially in powder flow and in the compacting and sintering of particles [25]. For these existing nanoparticle production technologies, the final product is still in the suspension form and will require an

Table 1. Types of atomizers.

Atomizer	Droplet size (μm)	Strengths	Weaknesses	Ref.
Rotary disk	200	Most effective means of atomization Effective control of particle size Low rate of clogging	Wall deposits High price Requires wide chambers	[6,18]
Hydraulic nozzle	100 – 400	Low price Low energy consumption Simple construction	Nozzles show quick wear Unsuitable for highly viscous feeds High rate of clogging Not recommended for pharmaceutical applications due to viscosity limitations Limited control of particle properties	[18,59]
Multi-fluid nozzle	10 – 1000	Suitable for a wide range of typical liquid viscosities Robust efficiency Homogeneous dispersion Effective control of particle size	Requires large amounts of compressed gas to facilitate atomization Unsuitable for extremely viscous liquids	[6,18,60]
Ultrasonic nebulizer	1 – 10	Narrow size distribution Suitable for thermolabile particles Ideal for drug delivery applications	Cost Laboratory-scale Possible clogging of nozzles for suspensions	[6,18,44,45]
Electro-hydrodynamic nozzle	< 5	Suitable for thermolabile particles Narrow size distribution	Low yield (i.e., 20%) Hard to scale-up Undergoing testing, not commercialized yet	[18,19,61]

Table 2. Types of particle collectors.

Collector	Collection efficiency	Effective collection size range (μm)	Strengths/weaknesses	Ref.
Filtration (filter bag)	Up to 90 – 99%	0.1 – 20	Medium to high equipment cost Medium to high operating cost Possible contamination of particles with fiber during recovery	[6,18,21]
Cyclone	Up to 60 – 70%	2 – 100	Medium equipment cost Medium operating cost Pure, free-flowing powder	[6,14,18,21,60,62]
Electrostatic precipitator	Up to 90 – 99%	0.05 – 10	High equipment cost Small to medium operating cost Pure, caked powder	[6,18,21]

additional drying step (e.g., spray drying or freeze drying) to convert the nanoparticles into fine dry powder.

Spray drying has been known to be a convenient and useful technology to regulate the size [26], polydispersity [27] and morphology [5,7,28] of particles. The beauty of this technology lies in the elegant combination of particle engineering and drying in a single step. Furthermore, the particles obtained are usually discrete and non-aggregated due to the rapid drying environment in the spray dryer system [29].

Limitations associated with the production of fine droplets and the effective collection of nanoparticles under the conventional systems have been resolved with the advent of the Nano Spray Dryer B-90's vibrating mesh spray technology and electrostatic particle collector.

3. Nano spray drying

3.1 Overview

The Nano Spray Dryer B-90 is the fourth and newest generation of laboratory-scale spray dryers developed by Buchi®, following on the success of the previous three generations (i.e., Mini Spray Dryers B-190, B-191 and B-290) since the

1970s [30]. This new system has been developed specifically to generate particle size ranging from 300 nm to 5 µm for milligram sample quantities at high yields, and is especially suited for the early stages of product development in the pharmaceutical, biotechnology, food, medical, chemicals, materials and nanotechnology industry [30,31]. In particular, it is highly appealing to the drug delivery community, as the desired particle size of most drug delivery applications in the oral, intravenous, transdermal and pulmonary fields all fall within this size range [8,29,32-34]. The novelty of this spray dryer lies in the spray head, heating system and particle collector, and these aspects are discussed in detail in the following sections.

3.2 Spray head: vibrating mesh spray technology

The design of the spray head is essentially modeled after the traditional nebulizer used typically in the treatment of asthma. As such, due to its 'aerosol origins', the system is expected to be highly applicable for dry powder inhaler (DPI) aerosol formulations. The nebulizer converts liquids into aerosol droplets for respiratory lung delivery and is generally available in two different modes: ultrasonic [35-37] and pneumatic or air-jet [35,38]. Ultrasonic nebulizers use electricity to vibrate a piezoelectric crystal at moderate-to-high frequencies to generate acoustic waves used in the break-up of a liquid source into aerosol droplets, whereas air-jet nebulizers use compressed gas flow to aerosolize a liquid through a narrow 'venturi' nozzle [36,37,39-40]. Air-jet nebulizers have been known to be inefficient due to the high drug loss at the baffles and in the residual volume [39,41-42].

The vibrating-mesh nebulizer is a variant of the ultrasonic nebulizer that utilizes a vibrating mesh or plate with multiple apertures to generate a fine aerosol at low velocity [37,40,43]. Commercially available from Aerogen®, Omron®, ODEM®, Nektar®, Pari® and Respironics®, it is able to generate aerosols at a faster rate, with a higher fine particle fraction and also with a higher deposition efficiency than the jet or conventional ultrasonic nebulizers [37,43]. As the energy source for nebulization is not applied directly to the fluid, but to the vibrational element, temperature increases to the fluid can be minimized. Therefore, this nebulizer is especially suited for proteins, peptides and antibiotics, as any denaturation or activity loss could be kept to a minimum level [37,40,43].

In the Buchi® Nano Spray Dryer B-90, the piezoelectric crystal driven spray head consists of a small spray cap that has a thin perforated membrane (spray mesh) in its internals. This membrane has an array of precisely fabricated holes of diameters 4, 5.5 or 7 µm. When the piezoelectric actuator is driven at an ultrasonic frequency (i.e., 60 kHz), vibration (i.e., upwards and downwards) in the mesh is initiated. This has the effect of ejecting millions of precisely sized droplets from the holes to generate the aerosols [29]. Droplet sizes of ~ 4.8, 6 and 7.2 µm could be obtained from the 4, 5.5 and 7 µm spray meshes, respectively, when water was applied [29,44]. The vibrating mesh is capable of handling liquid viscosities of up to 10 cps [45]. **Figure 1** illustrates the functional principle of mesh vibration occurring at the piezoelectric driven spray head of the Nano Spray Dryer B-90.

The coupling of ultrasound to spray drying is not unique and had previously been applied in an external configuration (i.e., prior ultrasound-mediated precipitation process followed by spray drying) for the production of inhalable sodium chloride particles [46], and in an internal configuration (i.e., ultrasonic atomization in a laboratory spray dryer) for the production of protein loaded microspheres from poly(lactide-co-glycolide) [47].

3.3 Heating system and architecture

Although the turbulent flow in a conventional spray dryer facilitates a more efficient drying as a result of higher heat transfer efficiency, exposure of the particles to elevated temperatures can sometimes result in denaturation of heat-sensitive materials such as proteins and peptides. In contrast, the heating system of the Nano Spray Dryer B-90 operates on a laminar flow principle, whereby the laminar flow is generated by air passing through a compact porous metal foam that is conducive for optimal energy input and has short heating-up rates. As gentle heating is achievable with laminar flow, this thus makes the system extremely ideal for heat-sensitive biopharmaceutical products [29,30].

The modular glass assembly of the spray cylinder in a vertical configuration (i.e., tall or short set ups) also confers different drying degrees to the droplet/particle. Short instrument set ups are ideal for fine droplets, while the taller set ups are recommended for larger droplets and water-based samples, as there would be a longer residence time in the system [30]. The vertical configuration also facilitates direct and straight-down collection of the particles into the collector, which helps to minimize particle adherence to the side walls of the glass chamber, hence allowing for much higher collection yields [29].

3.4 Electrostatic particle collector

Particle collection in the Nano Spray Dryer B-90 is effected by the electrostatic precipitator, whereby the collection mechanism is independent of particle mass. High efficiency collection of fine particles is achievable in this system, which consists of a grounded star electrode (cathode) and a cylindrical particle collecting electrode (anode). During spray drying, the high voltage applied between the electrodes sets up an electrostatic field that accelerates the deposition of negatively charged particles onto the inner wall of the cylindrical particle collecting electrode. This is followed by a discharging process. The fine powder is then collected from the internals of the cylinder via the use of a particle scrapper [29,44]. **Figure 2** illustrates the functional principle of an electrostatic particle collector in the Nano Spray Dryer B-90. This method of particle separation has the advantage of collecting micron to sub-micron sized particles effectively at high yields even at small samples quantities in the milligram or milliliter range [29,30,44,48]. For more details on the basic and theoretical operation of electrostatic precipitators, the reader is advised to

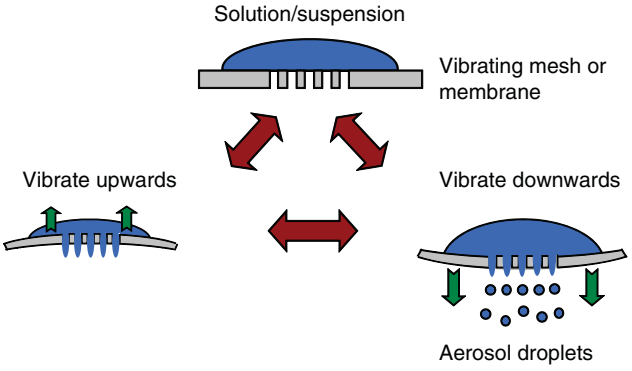

Figure 1. The functional principle of mesh vibration occurring at the piezoelectric driven spray head of the Nano Spray Dryer B-90.
Adapted with permission from BÜCHI Labortechnik AG (2009), Flawil, Switzerland [30].

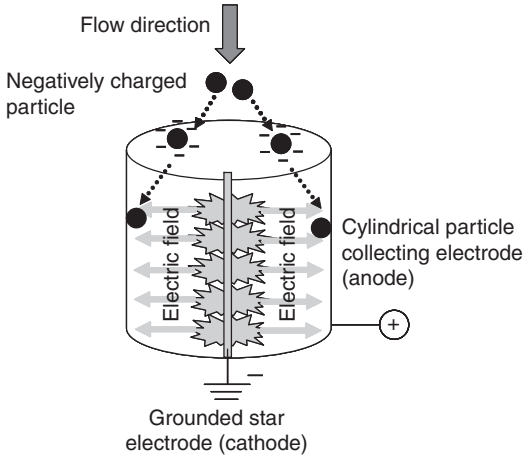

Figure 2. The functional principle of an electrostatic particle collector in the Nano Spray Dryer B-90.
Adapted from [29] by permission from the publisher.

refer to the book chapter by Riehle [48]. **Figure 3** shows the schematic diagram of the Nano Spray Dryer B-90.

4. Relevance to drug delivery

This technology is highly suited for a variety of drug delivery applications (e.g., oral, intravenous, transdermal and pulmonary) as nanoparticles are useful for the enhancement of absorption rates and bioavailabilities, targeted delivery in cancer therapy and in the modification of agglomerate surface architecture [4,8,32-34,49-50].

In inhalation aerosol drug delivery, the current modes of delivery are via the pressurized metered-dose inhaler, DPI and the nebulizer. DPIs are highly favored as they offer several advantages (e.g., small size and portability, drug stability, propellant-free design and ease of coordination by patients) over the other existing platforms [51]. As a result, the DPI is emerging as an important non-invasive delivery technology. DPIs are made up of a dry powder formulation incorporated into an inhaler device. As the drugs marketed for DPI use are usually prepared as micronized particles under 5 µm [50,52-54], the suitability of the Nano Spray Dryer B-90 in this regard cannot be overemphasized. This spray dryer is able to produce narrowly-distributed particles in the range of 300 nm – 5 µm. A narrow size distribution will not only increase the efficiency of delivery to specific regions of the lung, but will also minimize oral deposition [19,27].

The low outlet temperatures achievable in the system are highly favorable for biologicals. In a model protein scenario, Lee *et al.* [29] had demonstrated that at inlet temperatures of 80°, 100° and 120°C, the range of outlet temperatures observed were in the range of 36 – 40°C, 42 – 45°C and 51 – 55°C, respectively. Clearly, these low outlet temperatures are highly favorable for the spray drying of temperature-sensitive biologicals [55,56]. Increased outlet temperatures and the use of small-dimensioned cyclones have more recently been shown to result in a loss of enzymatic activity for spray-dried lysozyme particles [55]. To date, the technology has been successfully demonstrated for excipients [44,57], model drugs [44] and proteins [29,58].

While Schmid *et al.* [44] had produced mannitol and trehalose submicron particles (i.e., 500 – 800 nm) at reasonably high yields (i.e., 50 – 78%), Li *et al.* [57] had explored its suitability for the production of polymeric wall materials (i.e., Arabic gum, whey protein, polyvinyl alcohol, modified starch and maltodextrin) and its subsequent application in the encapsulation of nano-emulsions. For the latter, submicron particles as low as 350 nm were obtained at much higher yields of 70 – 90%. In response to the growing developments in biotechnology (e.g., peptides and proteins), Lee *et al.* [29] had utilized an experimental design to study and optimize the impact of spray mesh size, protein solution concentration, surfactant concentration, drying air flow rate and inlet temperature on the size and morphology of a model protein (i.e., bovine serum albumin). The size of the particles produced ranged from 460 to 2609 nm, predominantly influenced by the spray mesh aperture, while the morphology was affected by the presence of surfactant. Optimized production of smooth spherical protein nanoparticles (i.e., 460 nm) were obtained at high yield (i.e., > 70%) with the smallest spray mesh size (i.e., 4µm) and the inclusion of a small amount of surfactant (i.e., 0.05% w/v) into the solution. Subsequent work by Burki *et al.* [58], also via an experimental design, involved a study of the effect of inlet temperature, spray mesh size and ethanol concentration in the spray solution on the activity, size, span, yield and shelf life of a model protein microparticle (i.e., β-galactosidase) with trehalose as a stabilizer. Protein activity loss was minimized when larger spray mesh sizes and pure aqueous solutions were applied. Smaller spray mesh sizes required lower inlet temperatures to avoid protein degradation. Optimized production of protein microparticles (i.e., 1.93 µm) with full activity and

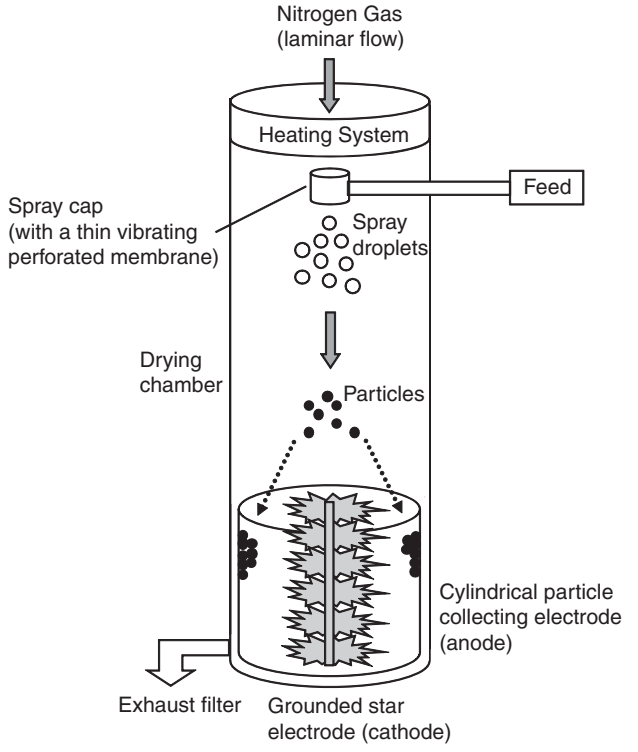

Figure 3. Schematic diagram of the laboratory-scale Nano Spray Dryer B-90.
Adapted from [29] by permission from the publisher.

high yield (i.e., ~ 90%) were achieved with the smallest spray mesh size (i.e., 4 μm), a low inlet temperature of 80°C and a pure aqueous spray solution.

5. Conclusion

The Buchi® Nano Spray Dryer B-90's simplicity and ability to handle biologically-active materials could make it an important tool for novel developments in the biopharmaceutical industry. Nanoparticles or microparticles in the range of 300 nm – 5 μm could be obtained directly from solution at high yields and with minimal activity loss for a variety of drug delivery applications. As preliminary applications of this novel technology have been rather promising, it is anticipated that its momentum of uptake across a variety of fields will only escalate in the near future.

6. Expert opinion

The advent of the Nano Spray Dryer B-90 has indeed made 'nano' spray drying a reality. Compared to traditional methods of obtaining nanoparticles, this method offers a simple and one-step approach to obtaining these particles in the dried form and in a narrowly distributed size range, directly from solution at high yields (70 – 90%). The achievable size range is from 300 nm to 5 μm which makes it highly desirable for drug delivery applications across the oral, transdermal and inhalation fields.

The spray drying system consists of spray meshes of size 4, 5.5 and 7 μm. As the spray mesh size was previously demonstrated by Lee *et al.* [29] to be the main parameter controlling the particle size, it would indeed be highly beneficial if they were commercially available in a much wider size range (i.e., < 4 and > 7 μm) to extend the capabilities of the system. This was similarly echoed by Schmid *et al.* [44] who had suggested a higher size range. A lower range could be beneficial in forming much smaller nanoparticles while a higher range might be useful in the formation of large porous particles/nanoparticle agglomerates. Although these spray mesh nozzles have revolutionized spray drying, it is worth pointing out that there is a risk of aperture blockage with the drug particles, especially when suspensions are applied. The particles in suspensions thus have to be fine enough to pass through the minute apertures without clogging the pores. Hence, it is imperative for the operator to adopt adequate cleaning procedures to extend the lifespan of the nozzles.

One of the major strengths of this spray dryer over the existing laboratory units is the modular glass assembly of the spray cylinder, which allows for a more simplified set up in spray drying and cleaning. Existing operators have appreciated the convenience and the appeal will no doubt be extended to future operators as well.

Dry powder deposited on the cylindrical particle collecting electrode has to be scrapped off using a rubber spatula. The nature of the powder collected is somewhat similar to a filter cake on a filter paper and is definitely not free-flowing. Therefore, there is a need to explore suitable 'de-caking' or 'loosening' methods (e.g., sieving) to further process and optimize the delivery of these powders (i.e., downstream processing) for certain drug delivery applications. The ability to generate free-flowing and aerodynamic powders is of significant importance to inhalation aerosol drug delivery.

As this spray dryer has been designed initially for the early stages of product development, the technology is thus not expected to be widely adopted for large-scale industrial applications as yet [31]. It is currently limited by a low throughput and a long process time. However, the potential is still there. Increased consumer demand on the laboratory model coupled with promising applications will eventually encourage and stimulate the development of more industrial-relevant models. However, a potential drawback of such systems might be the high cost, which might encourage industry to utilize this technology only for the high-end pharmaceuticals. Nevertheless, this cost might decline over time with increased demand, as in the case for electronics. Possible scale-up solutions in future could be via the use of multiple nozzles or a larger nozzle in a unit coupled with improvements to the engineering and design of the existing system.

The emergence of biotechnology will no doubt contribute to the next wave of development for pharmaceuticals. In particular, there will be an increased demand for biologics to

be formulated in the dry powdered form for added stability and ease-of-storage. The arrival of the Nano Spray Dryer B-90 has indeed been timely. Its ability to formulate temperature-sensitive compounds effectively will make it an 'indispensable partner' to the formulation scientist in the new decade and beyond.

Declaration of interest

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