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Electrospraying, spray drying and related techniques for production and formulation of drug nanoparticles

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Importance of the field: Spray drying and electrospraying are two widely used liquid atomization-based techniques for production and formulation of drug nanoparticles. The importance of spray drying in particular has increased lately in the production of nanostructured microparticles. The value of the particles is that they maintain the properties of individual nanoparticles but they are micrometer sized.

Areas covered in this review: In this review the most important liquid atomization techniques, spray drying and electrospraying, are presented in detail, and a short introduction is presented for other methods, including the aerosol flow reactor method and spray congealing.

What the reader will gain: A description of the possible tailoring processes depending on the technique and process parameters. Different product properties can be achieved; for example, nanosuspensions or dry powder formulations may be produced.

Take home message: The most important advantage of these techniques as compared with many other particle formation techniques is that the production of dried powders is possible without any extra drying step.

Keywords: drug nanoparticles, electrospraying, liquid atomization, nanostructured microparticles, spray drying

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1. Introduction

One major problem in drug delivery sciences and therapeutical applications is how to provide an appropriate dosage of the active pharmaceutical ingredient (API) at the right time to the right body location. Size is one determining factor for the successful drug delivery systems [1]. For example, the cell uptake of silver and gold nanoparticles, coated by antibodies, has been found to be size dependent [2]. Different micro- or nanostructured systems show great potential for stabilizing APIs and overcoming transport barriers, and the research in this area has been very intensive during the last few decades [3-6].

Nanometer-sized particles (submicrometer particles) are widely seen as having great potential for bringing benefits to many areas of research and applications owing to their different properties as well as physical behavior compared with the same material at larger size [6]. The reduced particle size and increased surface area of small particles offer, according to the Noyes-Whitney equation, higher dissolution rates and can, hence, improve the bioavailability [7]. Saturation solubility of nanoparticles is related to particle size, and it is increased as the particle size is decreased, as stated by the Ostwald-Freundlich equation. Intracellular drug delivery

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Article highlights.

- Liquid atomization techniques are suitable for making drug-encapsulated nanoparticles and for the production of dry nanoparticle powders.
- Electrospraying is a versatile and inexpensive way to produce nanoparticles and nanosuspensions.
- In spray drying, nanoparticles can be dried as nanostructured microparticles, which are easier to formulate into tablets, for example, and can be redispersed as nanoparticles in water.
- Process parameters such as solid concentration, feed rate, voltage and applied pressure can be used to tailor the particle size and morphology. However, the relations between the parameters are not always straightforward.
- Scale-up of electrospray systems requires new approaches.

This box summarises key points contained in the article.

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may also be possible with the aid of nanoparticles, taste masking becomes feasible, and the variability in drug absorbtion between the physiological fed-fasted states is decreased with the nanosized particles.

Plenty of different techniques for production of nanosized materials exist and new methods are presented constantly [8]. The applied techniques should be able to produce particles with controlled characteristics including size distribution, morphology, purity and composition, as well as be inexpensive, simple and provide large enough throughput during manufacture. Most of the techniques produce nanosuspensions, which are inherently unstable systems [9]. The small size of the nanoparticles causes problems, such as surface and thermal instability, shape preservation, and assembly in drug delivery systems. Therefore, it is not surprising that several attempts have been made to form agglomerates containing nanoparticles with preserved properties of nanoscale materials [10-16]. For further processing, dosage form design and manufacture, nanosuspensions often need to be dried. In that sense, liquid atomization-based techniques have an advantage, as they produce dried products and no further drying steps are needed.

To avoid the problems related to the formulation and stability of the thermodynamically active and electrostatic, prone to aggregation nanosized particles, nanosuspensions may be dried to form nanostructured microparticles, which still possess the unique properties of the original nanoparticles. Further formulation of these nanostructured microparticles, for example to tablets or capsules, is convenient and straightforward. For this reason, the current studies are also focused on the production of optimal nanostructured granulates from the nanoparticle suspensions, which can be processed further into dosage form components with superior properties and, later on, easily redisperse back into the original size for providing an improved therapeutic action [10-16].

The spray drying technique is widely used in the pharmaceutical industry, but mostly for the production of microparticles. Electrospraying is a method that has been presented more recently for the production of pharmaceutical nanoparticles, although it has already been utilized widely, for example for coating purposes. Several other electrostatics and/or atomization-based techniques are also available when producing nanometer- and micrometer-sized particles/crystals and, thereby, drug delivery formulations for therapeutic purposes (**Table 1**). For example, the aerosol flow reactor method [17], electroemulsification [18], electroencapsulation [19], electrospinning of nanofibers [20] and electrostatic assembly (assembly of collagen under a high-voltage electrostatic field) [21] have been utilized in the preparation of nanosystems, whereas, for example, spray cooling (spray congealing) is a widely studied technique to manufacture different types of drug delivery system in the micrometer size range [22]. Electrostatic microencapsulation is another process for pharmaceutical applications based on droplet formation by the electrothermodynamic effect [23]. Microencapsulation of, for example, polyanionic alginate takes place in the electrostatic dripping mode, and when the electrostatic and gravitational forces on the droplet exceed the forces of surface tension, the droplets are detached from the nozzle tip, and the resulting spherical beads are gathered in a collector [23]. Thermal nebulization (thermospray) [24] and particle beam (electron irradiation) [25] techniques have wide applications, especially in analytical systems.

Thus, a wide selection of electrostatics and/or atomization-based techniques is available for nanometer- and micrometer-sized drug delivery purposes. This review concentrates on the liquid atomization techniques, which produce pharmaceutical nanoparticles and/or nanostructured microparticles. The most common and widely used techniques, spray drying and electrospraying, are presented in detail, but also short introductions are presented, for example, for the aerosol flow reactor method and spray congealing.

2. Electrospraying

In electrospray atomization, a high voltage of several kilovolts is applied to a microcapillary nozzle of a spraying system. This is illustrated in **Figure 1**. The high voltage causes the solution interface at the tip to change shape because of the accumulation of electrostatic charge. As the potential is increased the electrostatic forces get stronger and reduce the effect of surface tension on the shape of the interface. When the two forces are equal, the so-called Taylor cone is formed at the capillary interface [26,27]. If the cone is then disturbed by further charge, it will break into small droplets at the tip of the cone. Several aspects, such as conductivity, flow rate, surface tension and viscosity, affect the resulting droplet size [27-30]. In practice, there is always a parameter 'window' in which stable spray can be obtained. For example, flow rate and conductivity should be kept at a certain ratio to each other in order to

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Table 1. Electrostatics/atomization-related techniques to produce nano/micrometer-sized drug delivery systems.

Techniques	Examples of studied APIs	Examples of studied drug delivery systems	Ref.
Electrostatics techniques			
Electrospray	Bovine serum albumin, insulin, paracetamol, budesonide, human antibodies	Inhalation aerosol, emulsion	[18]
Electroencapsulation	Paracetamol, budesonide, paclitaxel, antibodies	Inhalation aerosol, injection	[19,23]
Electrospinning of nanofibers	Antibiotics, anticancer drugs, proteins, DNA	Controlled drug delivery systems	[20]
Others			
Spray drying	Amifostine, calcium fluoride, peptides, hormones	Oral drug delivery, inhalation aerosol	[64]
Aerosol flow reactor method	Ketoprofen, naproxen	Oral drug delivery	[17,105]
Spray cooling (congealing)	Glimepiride, insulin, clarithromycin theophyllin, diclofenac, verapamil, indomethacin	Oral drug delivery	[109,110,112-116]

API: Active pharmaceutical ingredient.

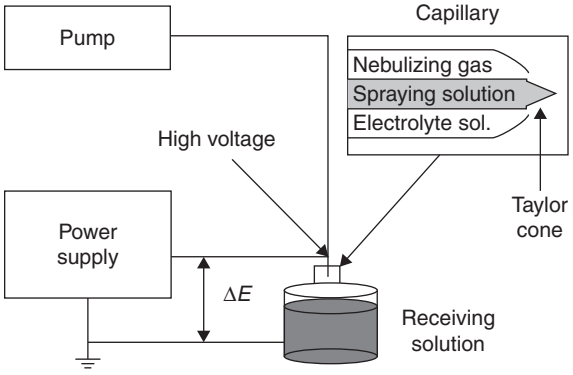

Figure 1. Illustration of a system used for nanoparticle preparation by means of electrospray.

obtain stable spray [28]. Conductivities that are too low or too high are both detrimental for the method.

The highly charged droplets produced in electrospray will travel along the electrical field towards a counter electrode. While the droplets are traveling in the gas phase, they shrink as the solvent evaporates. This can lead to droplet fission if the Rayleigh limit is reached and will result in breaking down of the particles and free ion generation. This mode can be used in mass spectrometry. As the droplet size depends on the flight time and distance, the resulting size is sensitive to the geometry of the spraying system. In a nanoparticle production scheme, the spray is directed towards a receiving solution or surface, which is kept at a fixed distance from the spraying tip and a counter electrode is placed either into the solution or outside the receiving solution vessel. This way, the spray goes towards the receiving solution and the particles are formed at the spray/liquid interface.

When drug nanoparticles are produced, the spraying is done with a drug or drug/polymer solution, with often some amount of electrolyte, and the receiving solution contains extra stabilizers to ensure that the particles do not aggregate after formation. Electrospray has been utilized for the formation of different drug delivery systems and drugs; several articles have been published recently in this field [19,23,30,31].

With the technique, nanoparticles with controlled size and narrow size distribution can be obtained. Although simple to perform, attaining exactly the desired particle size, size distribution and morphology might be challenging with this method. The right parameters have to be found experimentally for each case and instrumentation set-up used (**Table 2**).

Electrospraying is a versatile, inexpensive and simple one-step method for the encapsulation of multiple compounds [18]. Therefore, electrostatic encapsulation of APIs in polymeric nano/microparticles has been one of the most used applications of electrospray. Industrial-scale processing is not reached but encapsulation effectiveness is high compared with conventional techniques [31] such as precipitation [32-34], emulsification and solvent diffusion methods [35,36] or double-emulsion

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Table 2. Correlation and optimization of the first four parameters is required for the formation of stable cone jet mode in the electrospray system*.

Parameter	Primary effects	Product properties affected
Voltage Electrospraying distance Flow rate Solvent conductivity Solvent vapor pressure	Together form a parameter window, in which stable spray can be obtained Evaporation rate of solvent	Monodisperse particles can be produced. Particle size and morphology can be adjusted by changing other properties Particle morphology
Nozzle dimensions (↑)	Droplet size (↑)	Particle size (↑)
Polymer molecular mass (↑)	Viscosity (↑)	Particle size (↑) and morphology
Polymer concentration (↑)	Viscosity (↑)	Particle size (↑) and morphology

*Only in this stable cone jet mode is production of monodisperse particles contrived. Control of the size and morphology of particles can be performed by changing the other parameters.

techniques [37,38]. Owing to the set-up parameters of the process, particle size, morphology and size distribution can be controlled to some extent.

In the electrospray encapsulation process, the polymeric drug nanoparticles are produced by dissolving the polymer and drug into solvent(s). Therefore, forming of a strict core-shell structure is hypothetical and a matrix structure could be more descriptive for these nanoparticles. The concentrations and the characters of the dissolved substances have an influence on the production process. Synthetic polymers, such as polylactic acid (PLA) [39-41], poly(DL-lactide-*co*-glycolic acid) (PLGA) [42-45] and poly(ε-caprolactone) (PCL) [46,47] have been used to entrap drugs to polymer matrix. Recently, natural polymers such as chitosan for ampicillin [48] and elastin-like polypeptides (ELPs) for a cancer chemotherapeutic drug doxorubicin [49] have also been used for the formation of nanoparticles by the electrospray method. Natural polymers may offer new advantages during the electrospray process owing to the more easily controlled composition [50] and molecular mass [51]. In the first place, bioadhesivity of chitosan [48,52,53] and stimuli-responsive character of ELPs [49,54] are fascinating from the drug delivery point of view.

Molecular mass of the polymer used as well as concentration of the solution have significant influence on particle morphology and size owing to viscosity [55]. Wu *et al.* [49] showed that smooth spherical particles could be generated more easily from low-molecular-mass elastin-like polypeptides than higher-molecular-mass elastin-like polypeptides. Meng *et al.* [44] reported that the concentration range of low-molecular-mass PLGA, where it is possible to produce spherical particles, was broader than when high-molecular-mass PLGA was used. In addition to molecular mass, increased polymer concentration in solution was proved to increase the particle size [29,41,56]. Thus, owing to the higher concentration or molecular mass, viscosity of the solution was increased and the formation of tails or fibrous structures was more obvious. However, the porosity of the particles was increased and hollows were formed when the polymer concentration was decreased too much [29,49]. Gomez *et al.* [57] produced relatively monodisperse and biologically active insulin particles ~ 100 nm in diameter by using very low protein concentrations. Also in this case the decreased insulin concentration and/or the decreased flow rate produced smaller particles.

For the production of nanometric and monodisperse polymeric particles, a stable cone jet mode has to be formed in the spraying nozzle. In addition to the polymer-drug solution, the conductivity of the sprayed liquid, diameter of the capillary nozzle, flow rate, operating voltage and the distance between the nozzle and counter electrode have to be optimized [45,58]. Organic solvents such as dicloromethane [39,40,45,47], 1,2-dicloroethane [41], 90% acetic acid [48], acetonitrile [29,45] and trifluoroethanol [49] were evaporated quickly during the fly time towards the receiving surface. As the electrical conductivity of organic solvents is low, organic salts are commonly used to increase the electrical conductivity of the spraying liquid. Correlation between the particle size and liquid conductivity is well known [28,29,45]. Xie *et al.* [29] perceived dramatic changes in the particle size owing to the conductivity variations. Addition of organic salt increased the conductivity from 0.51 to 116.5 μS/cm and the particle size was decreased from 1.2 μm to 355 nm, respectively. However, as stated earlier, the flow rate and conductivity should be correlated to each other. Conductivities that are too low or too high are detrimental to the method. Solvent evaporation rate from the formed particles has an influence on the particles' structures. Production of solid polymer-shell particles requires that the precursor has very good solubility in the solvent used or that the solution evaporation rate is low [40]. However, Ciach [40] showed that fast evaporation of the solvent caused cavities inside the particles and the drug release rate from the hollow particles was unpredicted. Crystallization of the drugs on the particle surfaces can also occur [39,40]. In addition to the solvent properties, the evaporation rate could be controlled by changing the distance between the nozzle and the receiving interface. Despite the simplicity of the electrospraying process, not all variables in the process set-ups can be directly connected with an effect on end products (**Tables 2** and **3**), therefore empirical studies are needed.

Formed nanoparticles can be collected from receiving liquid, such as water without excipients [41], polar solvent with a stabilizer [39], or gelatinizing or polymerizing baths [59,60]. Also, deposition on solid surfaces has been

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Table 3. Examples of compositions, process parameters and product properties for electrosprayed drug nanoparticles.

Matrix material	API	Sprayed liquid, (solvents, excipients)	Collector/particle size	Voltage/flow rate/nozzle	Ref.
–	Insulin (10 mg/cm^3)	89.1 – 9.9 – 1 ethanol–water–4% molar HCl	Solid/88 – 110 nm	5 kV/≤ 0.02 – 0.13 ml/h/ 28-gauge needle	[57]
Polycaprolactone (PCL 65 kDa)	Paclitaxel	Dichloromethane	Solid/1 – 15 μm	8.8 or 14 kV(nozzle), 7.1 or 12 kV (ring)/ 1 ml/h/0.72 mm needle	[47]
Poly-lactic-*co*-glycolic acid (PLGA 50:50 low i.v.) (1 – 16 wt%)	Paclitaxel (0 – 10% w/w)	Acetonitrile (2 – 16%), didodecyldimethylammonium bromide (0 – 2 mM), Pluronic F127 (0 – 16%)	Solid/200 nm ≤	5 – 10 kV nozzle, 0 – 10 kV ring/0.1 – 0.2 ml/h/29-gauge needle	[29]
Polylactic acid (PLA 100 kDa) (5% w/v)	4-Acetamido phenol, budesonide, paclitaxel	Dicloromethane + 20% cyclohexanone, isopropyl alcohol, polyethylene glycol (10,000)	Membrane filter/≥1 μm	5 – 15 kV nozzle, 3 – 10 kV ring/0.5 – 5 ml/h/4 mm	[40]
Polylactic acid (PLA 175 kDa) (3% w/v)	Bovine serum albumin (65 kDa) BSA/PLA (w/w) 1:2 – 1:6	1,2-Dichloroethane	Distilled water/0.84 – 3.95 μm	12.5 kV/1 ml/h/18-gauge needle	[41]
Polylactic acid (PLA 2000 g/mol), (1 – 6.7% w/v)	Beclomethasone dipropionate, salbutamol sulfate (0.1 – 0.7%)	Dicloromethane (61 – 66% v/v), ethanol (26% v/v), ammonium hydroxide (0.02 – 0.2%), propylene glycol (6.5% v/v), polyoxyethylated sorbitan ester (Tween 80, 0.1 – 0.2% v/v), water (1.5 – 3% v/v)	70% ethanol + 0.01 – 0.1% Tween-80/150 – 800 nm	2.7 – 6.2 kV/0.12 – 0.6 ml/h/ 0.05 mm i.d., 0.1 mm o.d.	[39]
Chitosan (Mw 176 kDa; 92.8 % deacetylation) (1 – 5% w/v)	Ampicillin sodium (ampicillin/polymer 1:15 w/w)	Acetic acid (10 – 90% v/v)	Aluminum foil/520 nm	22 – 34 kV/20 – 26-gauge needle	[48]
Poly-lactide-*co*-glycolide (PLGA 75:25 90 – 126 kDa)	BSA, lysozyme	Proteins in water, polymer in dichloromethane	Solid/5.4 – 10 μm, 0.8 μm protein-loaded PLGA nanofibers	Nozzle-ground difference 8 – 15.5 kV/0.2 – 1 ml/h (protein solution), 3 – 5 ml/h (polymer solution)/3 mm o.d. 2 mm i.d., 0.72 mm o.d.	[43]
Elastin-like polypeptides (ELPs 17.8;70.2 kDa), (0.5 and 1.0% w/v)	Doxorubicin (20% w/w)	Trifluoroethanol/ethanol	Solid/300 – 400 nm	8 kV/0.05 – 0.1 ml/h	[49]

API: Active pharmaceutical ingredient.

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used [40,47-49]. By using a stabilizer in the spraying liquid and/or in the receiving liquid, aggregation, flocculation and coagulation tendencies of the forming particles can be prevented [29,39].

3. Spray drying

To prepare true pharmaceutical formulations and dosage forms, the nanoparticles often need to be processed further into microparticles – and further again to tablets and capsules. Spray drying is a process that is utilized in the processes of nanoparticle manufacture, and also in manufacturing microparticles for the further processing steps. In spray drying, a drug-containing fluid is forced through a nozzle, producing a mist that is dried to produce a fine powder. The process consists of four steps: i) atomization of the feed into a spray; ii) spray–air contact; iii) drying of the spray; and iv) separation of the dried product from the drying gas (**Figure 2**) [3].

The process has the advantages of being continuous, easy to scale-up, simple, cost-effective, and well suited for heat-sensitive products, in which physical properties of the resulting product can be controlled. It can also be fully automated. By spray drying, dry particles can be produced by atomization of different kinds of fluid, such as solutions, suspensions or emulsions [61-63]. Products are relatively monodisperse particles and drug entrapment efficiency is normally very high [64].

3.1 Nozzle types

The technique uses a variety of different types of nozzle such as kinetic energy nozzles that exist in the form of two-fluid or pneumatic nozzles [65,66]. Here, atomization occurs by interaction of the liquid and compressed air or the second fluid. High air speed generated within the nozzle breaks up the feed into the fine droplets. Hydraulic pressure nozzles [67] that force the liquid through a small orifice under pressure are also widely used. The pressure provides the energy to form a sheet of liquid, which then breaks up to form the spray. As the pressure is raised, there will be an increase in liquid flow, the angle at which the spray liquid is emitted is wider and the size of droplets is smaller.

One more atomizer type is centrifugal atomizers that apply a rotating disk or a wheel to spray the liquid into a gas environment [67,68]. The atomization energy is provided by the rotation speed of the wheel and the droplet size will decrease with increased wheel rotation. Ultrasonic nozzles are used to generate fine droplets without the use of high pressure or atomizing air [69]. This type of nozzle uses high-frequency (20 – 120 kHz) vibration to produce very narrow droplet size distribution and low-velocity spray from a low-viscosity liquid. In air-jet nozzles single or multiple jets are introduced to feed the liquid slowly into a high-velocity gas stream producing fine droplets [69]. Besides the mentioned atomization techniques, it is also possible to apply sonic energy and vibrations for atomization [3].

The pharmaceutical industry typically uses commercial spray dryers with a two-fluid nozzle. The particle sizes achieved with this equipment range from hundreds of nanometers to several micrometers [65,70-72]. Also, very small particle sizes are feasible, for example, nickel oxide nanoparticles with a mean diameter of 140 nm have been produced by ultrasonic spray drying [73].

3.2 Particle size

The one-droplet-to-one-particle (ODOP) mechanism during the spray drying sets the lower limit of the particle size to ~ 100 nm owing to the problems of generating small droplets during spraying [65,74]. The final size of the spray-dried particles is determined by the droplet size obtained in the atomization process and the volume reduction occurring during the drying, which is often dependent on the drying temperature [74]. For example, if the droplets are formed by an ultrasonic equalizer, the frequency of the vibration of the generator controls the droplet size: for example, droplet sizes with a frequency of 1.7 MHz have mean diameters ~ 5 μm, whereas the corresponding value for 0.8 MHz is 8 – 10 μm [70]. Besides the atomizer, the droplet size depends also on the liquid flow rate and the atomization gas flow rate [74]. Drying time is typically from 1 to 5 s depending on the sprayed droplet size. The outlet temperature of the drying gas is normally between 50 and 120°C owing to the cooling effect of the evaporating solvent. However, the temperature of the dried particles is often lower than the outlet temperature of the gas.

3.3 Process parameters

Factors influencing the properties of the final product have been widely studied [65,66,75-81]. In summary (**Table 4**), the size of the droplets formed during the atomization and, thus, the size of the resultant dried particles are affected by process parameters such as atomization type, atomizer settings (atomization pressure, size of the nozzle), physical concentration/composition and flow rate of the feed, drying temperature, and chemical and physical properties of the non-volatile substances. One very important variable involved in the control of the droplet size is the mass ratio of airflow to feed rate, which is also known as the air-to-feed ratio. An increase in this ratio causes a decrease in droplet size. It is also important to note that highly viscous materials cannot be atomized by pressure nozzles [74].

As mentioned earlier, one droplet forms one particle during spray drying. Hence, the concentration of the non-volatile material in the sprayed liquid has a significant influence on the resulting particle size: the less non-volatile material the droplet contains, the smaller the particle size will be [82]. Also, the finer the aperture of the nozzle, the higher the kinetic forces generated at its base and, thus, the finer and more wide-reaching the spray [65]. Owing to the fact that

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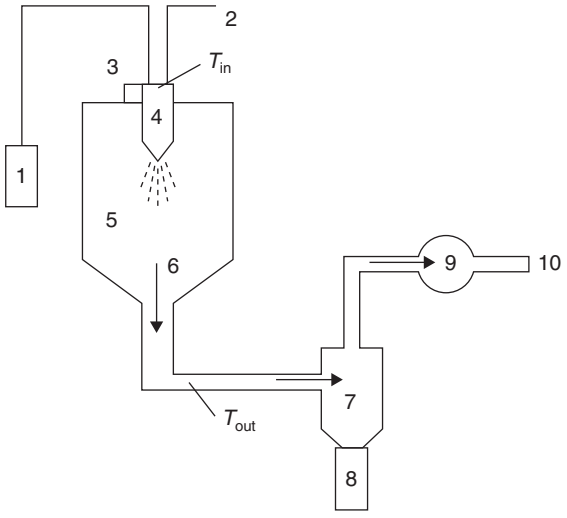

Figure 2. Schematic presentation of spray dryer equipment.
1: Feeding liquid; 2: Drying gas flow; 3: Heater for drying gas; 4: Nozzle; 5: Drying chamber; 6: Dried product and process gas flow; 7: Cyclone (product separation); 8: Product collection vessel; 9: Aspirator; 10: Exhaust gas.

Table 4. Effect of spray drying process parameters on product properties.

Parameter	Particle size	Yield	Powder density	Moisture	Ref.
Nozzle diameter ↑	↑				[65,66]
Feed concentration ↑	↑		↓		[65,66,75-77]
Air flow ↑	↓			↑	[3,76,77]
Feed flow ↓	↓	↑			[75,78]
Outlet temperature ↑		↑		↓	[3,78,79]
Ethanol concentration ↑	↑	↓		↓	[3,80,81]

the dimensions of the nozzle will influence the size of the droplet produced during atomization, choosing the right nozzle is of great importance in order to produce nanometer-size particles.

An efficient spray drying process results in dried particles suspended in the drying air. These particles are typically removed from the air stream using a cyclone, and the geometry of the cyclone is also important for effective particle recovery. Cyclones with smaller radii generate higher resistance to airflow compared with larger cyclones, resulting in the collection of finer particles that would otherwise be exhausted - and higher yield [83].

3.4 Nanoparticle production by the spray drying technique

Although spray drying is most often used to produce microparticles, nanoparticle production is also possible with the technique. Nanoparticle production by spraying of volatile solvent and poorly water-soluble propylparaben microemulsion has several advantages over the commonly used techniques. For example, owing to the spontaneous formation of microemulsions, no high energy is required and the size of the microemulsion droplets is as small as a few tens of nanometers [84]. This leads to possible formation of nanoparticles with a diameter <100 nm. Furthermore, the powder produced has good flow properties and is easily redispersed in water in the presence of a crystal growth inhibitor such as poly(vinyl pyrrolidone) (PVP).

Polymeric nanoparticles have also been produced by spray drying. Pamujula and co-workers [64] spray dried amifostine nanoparticles with mean particle sizes of 240 – 257 nm. A water-in-oil emulsion of amifostine with PLGA was spray dried. When the emulsion was fed to the nozzle, atomization occurred by the force of the compressed air, which disrupted the emulsion into small droplets. In the formed nanoparticles part of the amifostine formed a solid solution with PLGA and the remaining amifostine was in crystalline form dispersed into the polymer matrix. The drug encapsulation efficiency was very high, from 91 to 100%. The lower drug entrapment efficiency was caused by the mixing of the emulsion before the spray drying, meaning that the drug loss during the spray drying was almost zero. The particles were spherical and smooth and the achieved particle size was highly reproducible. In this study the drug loading did not affect the particle size or

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morphology, but it changed the surface charge of the formed particles.

Spray drying can be used as an alternative technique for lyophilization in the production of dry solid lipid nanoparticles (SLNs) from an SLN dispersion [85]. The SLN dispersions were prepared using three different lipid materials: Cetylpalmitate (melting point [m.p.] 47°C), Compritol (glycerol behenate containing ~ 15% monoglyceride, m.p. 72°C) and Synchrowax (glyceroltribehenate and calcium behenate, m.p. 105 – 115°C). Spray drying of the dispersion containing Compritol was successful, even though the melting point of the lipid was below the melting point of the spraying medium (water). This was possible because, generally, the maximum temperature at the particle surface is ~ 15 – 20°C below the outlet temperature of the co-current dryer; in this case outlet temperatures of 60 – 65°C were reached [86]. Smaller particles were obtained by decreasing the lipid content. Owing to the strong adhesion of the granulates to the glass equipment, the yield was quite low, ~ 10%. Adhesion to the equipment walls is a common problem that causes poor yield when particles of extra-small size are aimed at.

High temperatures, which can cause melting, are extremely problematic with SLNs [85], especially when aqueous solutions are used. Melting is the principal reason for particle growth during spray drying. The minimum melting point of the lipids that can be used in the spray drying of aqueous SLNs is 65°C. Addition of small amounts of alcohol can also accelerate the drying and decrease the aggregation or the adhesion of the wet granules to the glass walls of the drying chamber [85]. The addition of carbohydrates, which form a surface layer on the particles, can reduce the effects of temperature. Aqueous PVP solution has been shown to protect the SLNs during drying by forming a layer around the SLNs, which absorbs most of the heat [87].

In particle formation the drying is an external-to-internal process: the surface layer is heated first and often the interior of the particles differs from the surface. During the spraying, the maximum temperature the nanoparticles can reach is typically 30 – 35°C or more below the outlet temperature of the dryer (particle surfaces are typically 15 – 20°C below the outlet temperature) [86]. Even biological molecules have been spray dried, because it has been shown that the molecules are exposed to high temperatures for only a few milliseconds to seconds in the spray-dried chamber. If the powder temperature remains at a level of 40 – 45°C or less, no extensive damage is caused [117]. For the drying of heat-sensitive materials, co-current gas flow is preferable, because the dry product is in contact with the coolest gas [85].

The production of pure crystalline material is possible by *in situ* precipitation during the spray drying. *In situ* precipitation of hydroxyapatite (HA) was performed from saturated solution, which was obtained by dissolving in a dilute acetic acid solution or carbonic acid solution [88]. The solutions were dispersed using a spray nozzle and water and the volatile weak acid was evaporated inside a glass cylinder heated by electrical heating tapes. The particle sizes produced ranged from 10 to 100 nm. High-resolution transition electron microscopy showed that the particles consisted of packed crystalline HA particles 5 – 10 nm in size.

Preparation of nanometer-sized calcium fluoride particles for dental applications was reported by Sun and Chow [89]. In this study, a two-liquid nozzle was applied; cationic and anionic components of the salts were initially present in two separate solutions, and mixed during the process of atomization. As a result, particles with a size range from 50 to 500 nm were obtained. Furthermore, it has been shown that the bigger particles were formed by fusion of even finer particles (10 – 15 nm). Addition of surfactants to the reactant solution may lead to a significant increase in the surface area of the calcium fluoride nanoparticles and better dispersions. When the nanoparticles are produced during the atomization process, the content of the final product depends on the relative feeding rate and the mixing efficacy.

3.5 Nanostructured microparticles by spray drying

In addition to manufacturing nanoparticles, spray drying is also (mostly) used to form nanostructured microparticles by spraying suspensions of previously prepared nanomaterials such as nanocapsules, porous nanomaterials, nanoparticles, SLNs, nanocrystals, and so on [62,85,90-95]. Also, protein nanoparticles have been successfully spray dried into microparticles [61]. Consolidation of nanomaterials into microparticles by spray drying forms particulate systems where the properties of the nanomaterials are retained [93]. Pure nanoparticles can be dried, but often some bulking agents such as mannitol, lactose or trehalose are used to form a continuous matrix, where the nanoparticles are dispersed homogenously [74,93,94].

Spray drying of mesoporous silica nanoparticles with particle sizes from 20 to 1000 nm [90,91,95] has been performed, resulting in microparticles consisting of the individual silica nanoparticles. A hierarchical pore network was achieved owing to the intra- and inter-particle pore structures: the original mesopores were situated inside the individual primary nanoparticles, whereas inter-particle porosity was formed during the spray drying. If the particles do not melt during the spray drying, the original nanostructure can be retained [92].

During the spraying process, stability problems arise mainly as a result of the high temperature and shear forces, which increase the kinetic energy of the system, leading to an increase in particle collisions. The influence of the shear forces can be decreased by the addition of protectants, for example sugars such as lactose and mannitol, or polymers that are located between the particles, or by decreasing the particle concentration in the sprayed liquid [85,93,94]. High temperature may also cause problems with polymeric nanoparticles. For example, spray-dried PLGA nanoparticles were redispersible and retained the original particle size [96,97]. However, the nanostructures may also be destroyed and drug release delayed if the nanoparticles are exposed to

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temperatures exceeding the glass transition temperature of the polymer [62]. With too high temperatures, the polymeric materials may form polymeric films [96].

Sugars with low glass transition temperature (T_g), such as dextrose and sucrose, have been noted to form sticky powders [13]. Lactose and mannitol with higher T_g make better powders; it seems that the glass transition temperature is more important than the melting point for successful spray drying. In particular, the outlet temperature should not be higher than the glass transition temperature [96]. With lactose, owing to the conversion to monohydrate form, typical residue moisture content after spray drying is 4 – 6%, whereas with mannitol the corresponding value is <2%. This may also affect the stability of the end product. Besides the polymeric surfactants or sugars, extra charged surfactant(s) may also be required to hinder the irreversible aggregation.

Dissolution studies of the spray-dried nanostructured microparticles show two separated regions in the dissolution profiles: an initial lag time when the disintegration of the loose aggregates takes place, and later a dissolution behavior similar to that observed for the original nanosuspensions [13]. It was noticed that high inlet temperature increased the initial lag time. Also, absence of a surface charge caused the formation of particles that were not redispersible.

Physicochemical properties of the spraying solutions and drying conditions determine the morphology and shape (spherical, hollow spheres, toroid-like, doughnut-like, etc.) of the particles produced. When the drying process is slow, the nanoparticles have time to diffuse, but with faster drying times the particles will be more homogenously localized and are therefore expected to be situated at the outer part of the grains [98]. Also, with slow drying, the dried particles are dense, as the particles have time to organize themselves during the drying. Spherical particles may be formed with small droplet sizes, when solid particles inside the droplets are very large or very small [70].

Different kinds of structure can be achieved when spray drying nanoparticles: evenly dispersed through the microparticles [99], or accumulated clusters [94]. Accumulation can be due to the adhesive nature of the nanoparticles and their surface energy. Chemical parameters, such as concentration and ionic strength, affect the formation of microspheres [100]. For example, titanium nanoparticles at low salt concentration have been shown to aggregate and form hollow particles and doughnuts, whereas high salt concentration favors the formation of solid nanoporous microspheres. The difference is due to the relative magnitudes of the Laplace and osmotic pressures before the process, which determine whether the compression or fragmentation of droplets is favored during the spray drying. Accordingly, salt addition may cause preaggregation of the nanoparticles before the spray drying.

Addition of surfactants may also hinder the unwanted surface aggregation. Maa and co-workers [101] found that addition of Polysorbate 20 to the spray-dried material decreased surface aggregation of recombinant human growth hormone by 2 – 15%. Adler and co-workers [102] noticed that increasing concentrations of Tween 80 or SDS reduced surface accumulation of BSA depending on the concentration. This tendency of proteins and peptides to accumulate on the surface of spray-dried particles, resulting from the suddenly expanding liquid/air interface during the spraying, is seen in many studies [102,103]. The surface aggregation is explained by the sudden expansion of the liquid/air interface.

Hadinoto and Cheow spray-dried hollow particles, whose shells were formed by nanoparticle aggregates [96]. Capillary and van der Waals forces held the shell-forming aggregates together while the particle core remained empty. Spray drying was performed without any protectants. During spray drying, evaporation of the spraying liquid from the droplet surface exposes the nanoparticles to the vapor phase at the receding liquid–vapor interface. To minimize the surface energy, the exposed nanoparticles tend to migrate towards the droplet center because the surface energy at the solid–vapor interface is greater than the corresponding energy at the liquid–vapor interface. Hollow particles are formed with fast drying, when diffusion of the nanoparticles is hindered because of the fast solidification. Also, the presence of surfactants has been suggested to favor the formation of doughnut-shaped particles [104]. Surface tension is increased with decreasing liquid temperature, which causes a hydrodynamic effect near the surface of the droplet. Added surfactants enhance this phenomenon. The surface tension gradient affects the tangential motion from the local cooling point, caused by the evaporation, to the surface [70].

Toroid-shaped particles are formed with large droplet size, high temperature and high gas flow rate, and the presence of a surfactant [70]. The toroid morphology can be explained to be the result of an initial deformation of the sprayed droplet. Change from spherical shape to mushroom-like or double-convex disk takes place during the drying, when the droplet loses its structural stability due to the macro- and microhydrodynamic effects. This can be due to the increased droplet size, increased fraction of solid nanoparticles or decreased surface tension of the droplet. Accordingly, particle shape and size can be controlled by process parameters. Increased drying gas velocity destabilizes the droplet shape. When the residence time of the droplet in the reactor is diminished owing to the increased gas velocity, the air temperature needs to be increased to get dry particles. When the liquid is evaporated, the heat flows from the droplet surface to the gas stream, which creates localized temperature gradients. Solid particles are moving towards the particle/droplet surfaces and particles are forming against the toroid shape [70].

4. Other electrostatics/atomization-related techniques to produce nano/micrometer-sized drug delivery systems

The aerosol flow reactor consists of a collision type air jet atomizer as the aerosol generator [17]. Drug-containing

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solutions are prepared and the liquid feed rate is adjusted with a crimped injection needle. The resulting droplets are suspended in nitrogen, which acts as an inert carrier gas. The generated aerosol is next passed through a heated tubular laminar flow reactor, which evaporates the solvent from the droplets and finalizes the formation of the nanoparticles [17]. Dry powder samples of the nanoparticles (particle diameters ~ 100 nm) are collected with the heated low-pressure impactor on aluminum foils, and mere refrigerator storage is feasible for the nanoparticles produced. Nanoparticles of non-steroidal anti-inflammatory drugs ketoprofen and naproxen have been prepared with various acrylic acid polymers (Eudragit L, Eudragit RS and Eudragit E), and optimized nanoparticle characteristics including sustained drug release profiles have been shown [17,105].

Congealing means the transformation of a melt from soft or fluid state into rigid or solid-state on cooling. Different droplet formation techniques (including spray drying) producing an efficient droplet–air contact are used to produce spherical particles/powders by congealing the melts (e.g., encapsulated materials, inorganic and organic melts such as drugs, fat/wax types of soft material, etc). It must be emphasized here that no submicrometer particles are formed with spray cooling/congealing. Particle sizes of 50 – 150 μm are produced by high-speed rotary atomizers connected to cooling chambers and 150 – 300 μm sized particles in fountain nozzle systems. Very recent examples of pharmaceutical spray congealing systems include, for example, particle size control and microencapsulation of glimepiride [106], preparation of high payload solid lipid microparticles containing sunscreen agents [107], comparison studies of spray congealing with emulsion-based microencapsulation methods [108], coupling of co-freeze drying and ultrasound-assisted spray congealing processes [22], preparation of insulin-loaded microparticles [109], and studies on the effect of disk speed and particle properties for rotary spray congealing of suspensions [110].

5. Conclusion

Several different liquid atomization-based techniques are available for the production and formation of nanosized or nanostructured microparticles for drug delivery purposes. Spray drying and electrospraying are the most utilized of the methods. The spray drying process has already been scaled up to industrial scale. So far, electrospraying has been used successfully on the laboratory scale, and the biggest challenge for the technique is just the scaling for industrial purposes. The most important advantage of these techniques is that the production of dried powders is possible and no further drying step is needed for stabilization. Also, a clear benefit of the techniques is that both hydrophilic and hydrophobic drug materials can be formulated to particles.

6. Expert opinion

Liquid atomization-based techniques are well suited for the production of pharmaceutical nanopowders. Properties of the final products can be controlled by selected process parameters, and particles from the nanoscale to the micrometer scale are achievable. A clear advantage compared with many conventional nanoparticle formation techniques is that the final product is often in dry form, which lowers the total costs of the formulation process as the number of process steps is minimized. However, electrospraying, for example, may also be utilized for the production of nanosuspensions. In these techniques the process time for an individual particle is very short, although the total process times may be very long. This is especially beneficial for thermolabile materials. Also, the mechanical stress against the particles may be avoided.

Electrospraying is a straightforward bottom-up method to manufacture polymeric nanoparticles of submicrometer diameters. When the physical processing parameters, such as voltage, spraying distance, flow rate and capillary diameters, are in balance with the sprayed solvent properties, stable cone jet mode can be attained and the production of monodisperse particles is possible. Within the limits of the Taylor cone jet mode, particle size and morphology can be controlled by changing the polymer concentration, molecular mass or solvent properties.

A widely studied field in pharmaceutical research is controlled drug release from biodegradable polymer matrices. Encapsulation of drugs to the polymer matrix can be achieved with electrospray. Uniform drug distribution in the matrix is reached for the controlled drug release from the particles, as well as high encapsulation efficiency and yield. Suitability of electrospray for both hydrophilic and hydrophobic drug substances, simple apparatus and suitability for versatile material requirements are also great advantages of the electrospray. Mild processing conditions, low temperature and normal air pressure ensure suitability for biotechnological (peptides, proteins) as well as for medicinal substances. The optimization of set-ups for the production of nanoparticles has been a major role. Physicochemical characterizations of the nanoparticles have been done infrequently, but in those studies where the end products were analysed, only minor changes were reported [39,46,47].

The electrospray method is most suitable in small-scale processes and the advantages are often restricted to research purposes. Scale-up for the industrial applications may be challenging considering the small production capacity. Throughput of a single electrospray set-up is inherently low owing to the low flow rates, which are in the range of microliters per minute. The only way really to increase the production would be to use several spraying nozzles or by increasing the number of spraying equipment. This requires investments in instrumentation and would increase the production costs. In theory, this obstacle could be

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overcome with arrays of spraying nozzles. With a few hundred nozzles, the production could already be acceptable. Therefore, the answer to this problem might come from microfluidics and/or lab-on-a-chip technologies.

In the spray drying technique, process parameters (nozzle diameter, feed concentration, feed rate, air flow, inlet and outlet temperature) influence the spray drying output. Alteration and interplay of these parameters is of great importance to achieve particles with optimal characteristics (size, density, morphology, moisture content, etc.). However, it is important to notice that the operation parameters are case-specific. For example, generally, an increase in feed concentration increases the particle size, but it is possible that only the powder density is increased [111]. Also, an increased aspirator rate and, hence, shorter residence time in the drying chamber, influence drying less efficiently and result in higher moisture content. On the other hand, an increased aspirator rate can also lead to more efficient collection of the powder in the cyclone and, therefore, higher yield, although this may cause exhaustion of fine particles. Further, applying a higher airflow rate generates higher atomization forces leading to more efficient dispersion of feed liquid, resulting ultimately in the production of smaller particles. To complicate the matter, this would lead to a larger difference between the inlet and outlet temperatures and, consequently, to a higher moisture content. This problem, in turn, could be solved with the addition of solvent with lower boiling point compared with water.

Thus, the general guidelines tend to suggest that, to produce particles that are as small as possible, a relatively low feed concentration should be spray dried using a low feed flow rate, a high drying airflow rate, a reasonably high aspirator rate to prevent exhaustion of fine particles, and an inlet temperature sufficient to maintain an outlet temperature that results in a reasonable moisture content in the resultant powders.

One very interesting application of spray drying is the production of well-defined nanostructured microparticles. A typical problem with powdered nanoparticles is how to perform the further formulation steps needed towards actual pharmaceutical dosage forms. The very electrostatic and thermodynamically unstable ultra-fine powders are poorly flowable, dusty, and may aggregate and therefore lose the beneficial properties of the nanoparticles. In nanostructured microparticles the original properties of the nanoparticles remain, but the handling of the micrometer-sized powders is easier. Compared with another widely utilized technique for the drying of nanosuspensions, namely freeze drying, spray drying is clearly a more cost-effective and faster technique. Also, the control against the original nanostructure(s) and maintenance of the particle size of the final product are more easily achievable.

Obviously the most beneficial technique(s) should be selected for each formulation and dosage form in question, whether electrospray/aerosol flow reactor method/encapsulation/emulsification, and so on, alone for nanoparticle preparation, or these in combination with scaled-up and established techniques such as spray drying/spray congealing/freeze drying, and so on. Interest in this research area and commercial applications thereof will increase in the future.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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