Review paper

Spray drying and nano spray drying as manufacturing methods of drug-loaded polymeric particles

Suszenie rozpyłowe i nanosuszenie rozpyłowe jako metody sporządzania cząstek polimerowych z substancjami leczniczymi

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Abstract

In this review, benefits and drawbacks of the process of spray drying and nano spray drying with regard to the manufacturing of polymeric particles for pharmaceutical applications are discussed. Spray drying has been used for many years in the food, chemical and pharmaceutical industries for converting liquids into solids, in order to form products of uniform appearance. The construction of spray dryer enables to atomize the liquid into small droplets, which ensures a large surface area for heat and mass transfer, and significantly shortens the processing. Each droplet dries to an individual solid microparticle of characteristic features that can be tailored by optimizing formulation variables and critical process parameters. Since spray drying technology is easy to scale up and can be used for drying almost any drug in a solution or suspension, there are numerous examples of products in clinical use, in which this process has been successfully applied to improve drug stability, enhance bioavailability or control its release rate. In recent years, nano spray drying technology has been proposed as a method for lab-scale manufacturing of nanoparticles. Such an approach is of particular interest at early stages of drug development, when a small amount of new chemical entities is available. Here, the nebulization technique is used for feed atomization, while laminar gas flow in the drying chamber ensures gentle drying conditions. Moreover, electrostatic collectors have gradually replaced cyclone separators, ensuring high effectiveness in producing solid nanoparticles, even if a small volume of the sample is processed.

Key words: nano spray drying, spray drying, polymeric particles, microparticles, nanoparticles

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Streszczenie

W artykule omówiono zalety i wady procesu suszenia rozpyłowego i nanosuszenia rozpyłowego w odniesieniu do wytwarzania cząstek polimerowych do zastosowań farmaceutycznych. Suszenie rozpyłowe jest procesem stosowanym od wielu lat w przemyśle spożywczym, chemicznym i farmaceutycznym. Służy do przekształcania próbek ciekłych w jednorodne ciała stałe. Konstrukcja suszarki rozpyłowej umożliwia rozpylenie cieczy na drobne krople, co zapewnia dużą powierzchnię suszenia i prowadzi do skrócenia tego procesu. Właściwości stałych mikrocząstek można projektować przez optymalizację zmiennych, zależnych od receptury i krytycznych parametrów procesu. Ponieważ technologia suszenia rozpyłowego jest łatwa do zastosowania w skali przemysłowej i może być stosowana do suszenia niemal każdej substancji leczniczej w postaci roztworu lub zawiesiny, istnieje wiele przykładów zarejestrowanych produktów leczniczych opracowanych przy użyciu tej metody. Dzięki zastosowaniu suszenia rozpyłowego możliwe było zwiększenie trwałości i biodostępności lub kontrola szybkości uwalniania wielu substancji leczniczych. W ostatnich latach zaproponowano technologię suszenia nanorozpyłowego jako metodę przeznaczoną do wytwarzania stałych nanocząstek w skali laboratoryjnej. Takie podejście jest szczególnie interesujące na wczesnych etapach opracowywania nowych leków, gdy są one dostępne w ograniczonej ilości. W tej metodzie technika nebulizacji jest wykorzystywana do atomizacji cieczy, natomiast laminarny przepływ gazu w komorze zapewnia łagodne warunki procesu suszenia. Z kolei separatory cyklonowe zastąpiono kolektorem elektrostatycznym, co zapewnia wysoką wydajność procesu wytwarzania stałych nanocząstek, nawet w przypadku małych próbek.

Słowa kluczowe: nanosuszenie rozpyłowe, suszenie rozpyłowe, cząstki polimerowe, mikrocząstki, nanocząstki

Introduction

Spray drying is a well-known industrial technology that is used to transform liquids into powders.[1,2] Due to the fact that both aqueous and organic solvents can be used for such processing, this technology is suitable for combining compounds of different physicochemical properties with the aim of enhancing their functionality. The opportunity to design the particle size, shape, surface roughness, and surface composition of the final product by optimizing critical process parameters and formulation variables makes spray drying a suitable method of modifying unfavorable properties of both drugs and excipients. Importantly, spray drying is a one-step, continuous, cost-effective, and easy-to-scale process that can be used for manufacturing various polymeric drug delivery systems, including aseptic formulations.[3,4]

Advantages of spray drying

Multiple studies provided evidence that upon spray drying, it is possible to transform crystalline drugs into amorphous microparticles. A reduction of particle size followed by an increase of specific surface area, together with the modification of the physical form may translate into better solubility of the drug in water and, finally, in the enhancement of bioavailability.[5,6] Hence, the combination of drugs with polymers allows for manufacturing complex polymeric drug delivery systems that can control drug release, which remains stable for a long period of time.[7,8] Furthermore, the preparation of spherical particles may improve the flowability of the powder bed, which is an important factor in compaction or capsules filling.[9,10] In turn, the porous surface of spray-dried particles may be crucial in ensuring compactibility, facilitating mechanical interlocking of particles upon compaction and, as a result, ensuring a high mechanical strength of tablets. Importantly, such processing can be used even for thermolabile compounds, as their exposition to high temperature is very short.[3] Thus, the spray drying process is used for the encapsulation of labile compounds with the aim of improving their stability in contact with water vapor, oxygen, ultraviolet (UV) radiation, incorrect pH, or other incompatible compounds.

Therefore, during the last 2 decades, the spray drying process has been used in manufacturing of several drug products for both systemic and topical drug delivery. These products are mainly administered orally, by inhalation or via parenteral route.[11,12] Due to the fact that the spray drying process is considered one of the most commonly used industrial methods of ASD manufacturing, among the examples of commercially available spray-dried drug products there are formulations loaded with polymeric amorphous solid dispersions (ASD), e.g., immunosuppressive Prograf (tacrolimus, Astellas Pharma, 1994) and Zortress (everolimus, Novartis, 2010).[13] Recently, several fixed-dose combination drugs with polymeric ASD composed of 2 or 3 active pharmaceutical ingredients (API) have also been launched, such as Orkambi (lumacaftor/ivacaftor, Vertex, 2015), Zepatier (elbasvir/grazoprevir, Merck, 2016), Trikafta (elexacaftor/tezacaftor/ivacaftor, Vertex, 2019), and Symdeko (tezacaftor/ivacaftor, Vertex, 2019).[14,15] The spray drying process is also suitable for preparing protein formulations, e.g., inhaled insulin powder Exubera (Pfizer Inc./Nektar Therapeutics, 2006) or Afrezza (MannKind Corp., 2015), microsphere suspension loaded with lanreotide acetate for intramuscular injections Somatuline (Ipsen, 2013), or a powder fibrin sealant Raplixa for topical bleeding control during surgery (fibrinogen/thrombin, Nova Laboratories, 2016).[3,16,17]

Spray drying technology in a nutshell

The spray drying process consists of 3 main phases, namely atomization, evaporation of the solvent and collection of particles.[18] Atomization is the process of turning a liquid into a fine spray. For this purpose, 3 kinds of atomizers can be used, i.e., rotary atomizers, hydraulic nozzles or pneumatic nozzles.[18] The size of the droplets formed is controlled by the type of nozzle, as well as surface tension, viscosity and density of the fluid.[19] To prepare feed solutions water, organic solvents and their mixtures are used. Table 1 shows the characteristics of organic solvents that are often utilized in spray drying, while a scheme of a spray drier is shown in Fig. 1A. The atomized droplets pass through a drying chamber flushed with drying gas. The droplet–drying gas contact can be of countercurrent, cocurrent or mixed flow type. Cocurrent contact systems are widely used for pharmaceutical purposes.[20] Atmospheric air, previously filtered and preheated, is usually applied as drying gas.[2] However, if flammable organic solvents are used or compounds are prone to oxidation, the air in the drying chamber is replaced by inert gases, i.e., nitrogen. In this way, the level of oxygen can be considerably reduced, which limits the risk of chemical degradation or explosion. In such cases, the drying is carried out in tightly close systems (loops), where an aspirator is used for the circulation of the inert gas. The vapors of organic solvents are condensed in a refrigerator and collected in a closed receiver. The cleaned gas stream is preheated and flows back to the spray dryer. It is worth mentioning that modern spray dryers are also equipped with

Table 1. Characteristics of organic solvents used in spray drying and nano spray drying

Solvent name	Methanol	Acetone	Acetonitrile	Ethanol	Dichloromethane
Structure	CH_3OH	CH_3COCH_3	CH_3CN	CH_3CH_2OH	CH_2Cl_2
Density at 20°C [g/cm^3]	0.792	0.784	0.786	0.789	1.33
Freezing point [°C]	–98	–94.8	–45.7	–114	–95
Boiling point [°C]	65	56.1	81.6	78	40
Flammability	highly flammable liquid and vapor				non-combustible danger of explosion with: alkali metals, nitric acid, aluminum, amines, nitrogen oxides (NOx) exothermic reaction with: alkaline earth metal, metal powder, strong alkali
Auto-ignition temperature [°C]	455	465	524	455	605
Lower (LEL) and upper (UEL) explosion limits [vol. %]	5.5–44	2.6–12.8	4.4–16	2.5–13.5	13–22
Solubility in water at RT [g/L]	freely soluble	freely soluble	1	freely soluble	≈20
Viscosity at RT [mPas]	0.60	0.32	0.39	0.54–0.59	0.43
ICH solvent class	2	3	2	3	2

ICH – International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; RT – room temperature.

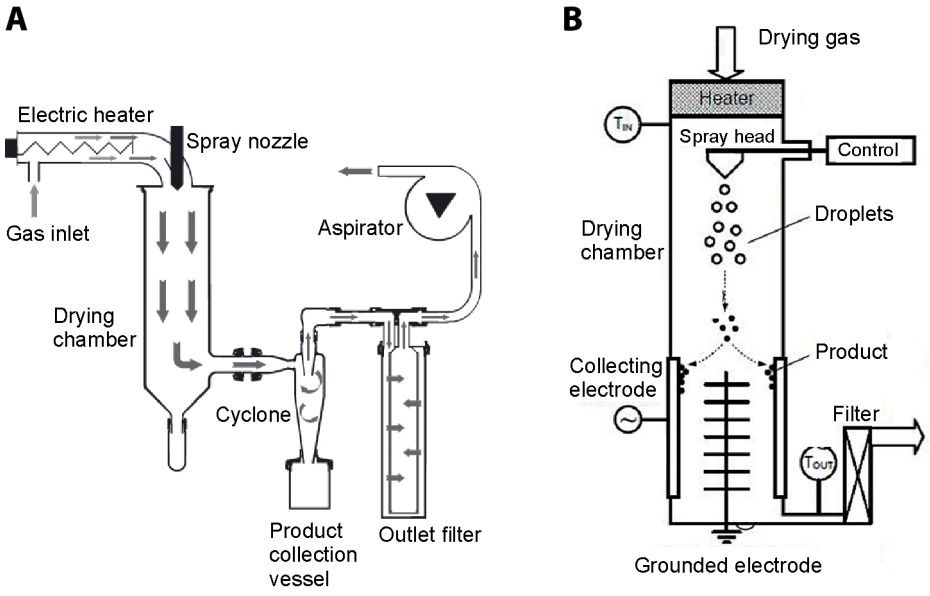

Fig. 1. The comparison of a spray dryer (A) and a nano spray dryer (B)

dehumidifiers. For water-organic solvents, strict control of the drying gas inside the drying chamber ensures robust process conditions and uniform product characteristics, and prevents the deposition of the product on the walls of the drying chamber.[21]

The size of the drying chamber determines the drying time, which is of particular importance for aqueous feed solutions. Two types of drying chambers of different height-to-diameter ratio (5:1 for tall and 2:1 for small chambers) are used.[18,22] Since the drying time is longer in large chambers than in small chambers, the former are recommended for aqueous fluids.[1,23]

To separate dry solid particles from the air stream, centrifugal separators in the form of cyclone units are commonly used. The drying gas enters the cyclone at the top and is set in a circular, spiraling motion. In consequence, solid particles moving in the gas stream under the influence of centrifugal force are thrown against the cyclone walls and fall down into the receiver, where they are collected. In turn, the exhaust gas is filtered and removed from the chamber. Unfortunately, particles can also settle on the walls of the drying chamber or cyclone, reducing the efficiency of the process. To prevent the product from being deposited on the walls and to protect it from the mechanical scraping, nonstick coatings and the receivers of cone-shaped bottoms can be applied.[23,24] It should be stressed that a significant limitation of cyclone is its inability to separate particles smaller than 2 μm from drying gas. If high-performance cyclones are used, particles bigger than 1.4 μm can be separated, but if submicrometer particles are formed, they are removed from the chamber in the exhaust gas.[25–27]

Optimizing spray drying process

The quality of the spray-dried product is determined by critical process parameters and formulation variables. Therefore, the application of the quality by design (QbD) approach together with process analytical technology (PAT) considerably shortens the transfer of this technology from the laboratory scale to the production plant.[23] Since there are many parameters that can be controlled in such a processing, the relationships between them are complex and sometimes difficult to predict. Therefore, a risk analysis is often combined with statistical tools such as design of experiment (DoE), with the aim to effectively optimize the properties of the spray-dried product, e.g., the morphology of particles.[28] In general, particles obtained in this process can be in the shape of spheres with surrounded cores, spheres with empty cores, porous solid foams, microparticles consisting of nanoparticles, composite shells, nanocomposites, or particles with irregular shapes.[29,30] Until now, multiple research studies have shown that the particle engineering is possible by tuning the value of critical process parameters (CPPs) to finally meet previously defined critical quality attributes (CQA).[31]

One of the most important CPPs is the inlet temperature of the drying gas. In conventional spray driers, it can be regulated up to 220°C. High inlet temperature ensures a high solvent evaporation rate, which has an impact on the particle formation process and the stability of the final product. Particles formed at high temperatures are bigger than those prepared at low temperatures, because of the agglomeration of primary microparticles. The surface of such particles may also be rough. Moreover, the solvent evaporation rate determines the kinetics of nucleation, which is crucial when amorphous forms are prepared. If the inlet temperature is too high, the solvent evaporates immediately and crystallizing solids may clog the nozzle, not to mention the risk of thermal degradation of thermally sensitive compounds.[23] Yet, it should be noted that the transition from the droplet to the particle takes milliseconds, which limits the risk of thermal degradation of compounds.[23]

In turn, the outlet temperature of the drying gas cannot be regulated directly by an operator, because its value depends on solvent vaporization enthalpy, solid load in the feed, inlet temperature, and flow rate of the drying gas. In theory, this is the highest temperature at which the compound can be heated without stability concerns. For amorphous systems, the outlet temperature should not be higher than the temperature of the glass transition, due to the risk of recrystallization. Furthermore, under such conditions, the particles become sticky and easily form deposits on the walls of the drying chamber, which has a negative impact on the yield.[32] The outlet temperature influences the level of residual organic solvents or the moisture in the spray-dried product. If its content is too high, an additional drying procedure might be necessary. Attention should be paid to spray-dried biomolecules, as organic solvents or their mixture with water may cause rigidification of their conformation, aggregation, dehydration, and even damage to their molecular structure.[17]

An important formulation variable that has an impact on the product morphology is the viscosity of the feed.[33] In conventional spray drying, the atomization of liquids that have viscosity lower than 300 mPas is possible.[30] The higher the viscosity, the more difficult it is for droplets to form, and finally, the more energy is needed for atomization. Since the viscosity value is usually related to the solid content in the feed, it is estimated that for a proper droplet formation, it should be below 30%. Moreover, the grade and the concentration of the polymeric carrier are other important factors. In turn, adding surfactants to the feed reduces the surface tension, leading to a small droplet size. The velocity of these droplets is high, and, consequently, a wide spray pattern is obtained.[1,2,29,33]

Polymeric drug carriers used for spray drying

Table 2 presents the examples of polymers used as carriers for various drugs in order to prepare microparticulates in the spray drying process. They are derivatives of the following:

– cellulose – hydroxypropylmethylcellulose (HPMC)[34], hydroxypropylmethylcellulose acetate succinate (HPMCAS)[35];
– aminopolysaccharides – chitosan[36];
– vinylpyrrolidone – polyvinylpyrrolidone (PVP),[37] copolymer of polyvinylpyrrolidone and vinyl acetate (PVPVA)[38];
– poly(methacylic) acid – Eudragit[39];
– poly(vinyl) alcohol (PVA)[40,41];
– poly(ethylene oxide) – Macrogols[29,42];
– aliphatic polyesters – poly(lactide) acid (PLA),[43] poly(lactide-co-glycolide acid) (PLGA).[44]

In recent years, the application of aliphatic polyesters to form drug delivery systems in the spray drying technique has been widely investigated because of the reputation of biocompatible, biodegradable and bioabsorbable drug carriers. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved the use of PLGA in humans in various ratios and molecular weights.[45] Different forms of this polymer can be obtained by manipulating the ratio of lactide to glycolide during polymerization. The glass transition temperature (Tg) of PLGA ranges from 43°C to 55°C and decreases as the amount of glycolide increases. The grades with low molecular weight and high glycolide content are characterized by high hydrophilicity and amorphousness, which reduces the degradation time.[46] All aliphatic polyesters are prone to hydrolysis in contact with water or water vapor. As a result, hydroxycarboxylic acids are formed, e.g., PLGA is hydrolyzed to lactic and glycolic acid.[47] Importantly, the degradation rate of PLGA in vivo can be controlled by tuning the physicochemical properties of the polymer, i.e., crystallinity, hydrophobicity, copolymer ratio, and molecular weight.[46] The results of multiple studies provided evidence stating that PLGA are suitable for the manufacturing of diverse drug delivery systems composed of microparticles formed in the spray drying process, as they are soluble in many organic solvents, e.g., chloroform, ethyl acetate, ethyl formate, or dichloromethane (DCM).[48] The latter has a low boiling point (40°C, Table 1), which facilitates processing and prevents polymer agglomeration at high temperatures.[49,50] The size of PLGA microparticles ranges from 1.3 μm to 15 μm, whereas the yield can be up to 75%. The drug release rate is mainly governed by the content of individual monomers in the copolymer.[51] When hydrophilic excipients such as trehalose, sucrose or PVA are combined with PLGA, proteins and enzymes can be successfully transformed into stable dry powder.[48,52,53] Therefore, while using PLGA, the development of controlled release drugs suitable for various routes of administration, including long-acting parenteral drugs, is possible.

Principles of nano spray drying technology

In 2009, Büchi Labortechnik AG (Flawil, Switzerland) launched the first nano spray drier (B-90) that enables the preparation of nanoparticles (understood here as the particles < 1 μm) of a precisely tailored morphology and a narrow particle size distribution.[54] Importantly, such processing can be performed with high efficiency (up to 96%) and while using a small amount of the drug (10 mg (2.7 g)).[16] The construction of a nano spray dryer can be compared with that of a conventional spray dryer in Fig. 1, while the comparison of the most important features of a spray dryer and a nano spray dryer is presented in Table 3. Briefly, this technology enables nanosizing of drugs, their nanoencapsulation, structural change (crystalline-to-amorphous transition), or preparing nano spray-dried dispersions in matrix-forming excipients.[55,56]

In contrast to conventional spray dryers, where nozzles of various kinds can be used, a nebulizer mounted on the spray head is responsible for creating tiny aerosol droplets in a nano spray dryer. Importantly, the construction of the nebulizer based on vibrating mesh technology ensures droplet formation with a high precision and reproducibility with regard to its size.[57] As a result, the particle size distribution of the final product is narrow. Essentially, the feed is circulating over the surface of a thin, perforated metal plate with laser-drilled holes of 4.0 μm, 5.5 μm or 7.0 μm in diameter. Under high-frequency vibrations of a piezoelectric actuator, the spray mesh moves rapidly upwards and downwards, ejecting droplets through the cylindrical holes into the drying chamber (Fig. 1B).[30,42] The laminar flow of drying gas directs droplets, and then solid particles, into the lower part of the drying chamber, where the latter are electrostatically charged in a high electrostatic field, created between a star-shaped discharge electrode (cathode) and a cylindrical collecting electrode (anode).[60,61] A high voltage (15–17 kV) at the collecting electrode ensures high efficiency of separation of submicron particles from the drying (up to 99%), even for small samples.[16,59,60,62] Interestingly, such a separation method is gentle and can be used for collecting even brittle nanoparticles without destroying them. In the end, the dried powder is removed from the surface of the collecting electrode using a scraper.[16]

Similarly to the conventional spray drying process, it is possible to adjust the properties of the nano spray-dried product, optimizing both formulation variables and critical process parameters.[16,18] In general, the particle size of nano spray-dried products ranges between 0.2 μm and 5 μm. Thus, the manufacturing of nanoparticles or microparticles is possible. The most important variables

Table 2. Examples of polymers used as carriers for preparing spray-dried formulations

Drug and route of administration	Carrier	Drug:carrier ratio (w/w)	Solvent	Process parameters	Yield [%]	Particle size [μm]	Particle morphology	Advantages
Carbamazepine[34] for oral administration	Chitosan HPMC	1:1 7:3 9:1	for crude drug: ethanol 96% for samples loaded with HPMC: ethanol/water 2:3 (v/v) for samples loaded with chitosan: 0.5% acetic acid	inlet temperature: 120°C outlet temperature: 75°C spray flow rate: 0.25 L/h air flow rate: 700 N×L/h	~30	~3	Spherical micro-spheres	drug amorphization; faster drug release from chitosan-HPMC composite microparticles than those made of HPMC; sustained drug release possible
Andrographolide[37] for oral administration	PVP	1:2 1:3 1:4	methanol	inlet temperature: 60°C outlet temperature: 45°C feed rate: 6–8 mL/min atomization air pressure: 2 kg/cm^2	60–70	2.8–3.6	spherical micro-particles	micronization; drug amorphization; stabilizing effect of hydrogen bonds; 5-fold solubility increase
Felodipine[38] for oral administration	PVPVA	1:4	acetone	inlet temperature: 72–184°C outlet temperature: 32–61°C feed rate: 110–188 g/min atomization air pressure: 2.11 kg/cm^2 cyclone: 10.2 cm or 15.2 cm two-fluid nozzle or pressure swirl nozzle	66–90	4–115	intact, collapsed or fractured hollow spheres	drug amorphization; flowability of amorphous solid dispersions suitable for compaction; high mechanical resistance of tablets
Diltiazem[39] for oral administration	Eudragit RS & Eudragit RL	1:2 1:4 1:8	DCM	inlet temperature: 70°C outlet temperature: 57–60°C feed rate: 2–5 mL/min spray-flow: 700 N×L/h 0.5 mm nozzle	N/A	1–9	smooth micro-spheres	narrow particle size distribution; drug amorphization; high drug load results in faster release rate
Caffeine or progesterone[43]	PLA	for progesterone: 10:90 20:80 35:65 50:50 for caffeine: 25:75 40:60 60:40 75:25	DCM	inlet temperature: 70°C outlet temperature: 40–45°C spray flow: 600 N×L/h 0.5 mm nozzle	N/A	<5	micro-particles with proges-terone: spherical; those loaded with caffeine: needle-shaped	drug micro-encapsulation; retarded drug release
Vancomycin[7] for topical ocular delivery	PLGA	1:2 1:3 1:4	for drug: water for polymer: DCM	inlet temperature: 80–85°C outlet temperature: 68–70°C spray rate: ~10 mL/min 0.7 mm nozzle	<55	10.96–11.75	almost spherical particles with smooth surface, agglo-merates visible	controlled drug release; enhanced pharmacokinetic parameters of drug from aqueous suspensions of microspheres shown in rabbit model

DCM – dichloromethane; HPMC – hydroxypropylmethylcellulose; PVP – poly(vinyl)pyrrolidone; PVPVA – poly(vinyl)pyrrolidone/vinyl acetate; PLA – poly(lactic) acid; PLGA – poly(D,L-lactide-co-glycolide); N/A – not available.

that are crucial in particle engineering using a nano spray dryer are listed in Table 3. The majority of nano spray-dried particles are spherical, but they can be wrinkled or doughnut-like in shape as well. Their internal structure may be hollow, solid or porous. With regard to the feed composition, the same solvents can be used as in spray

Table 3. Differences between spray drying and nano spray drying technology with critical process parameters (CPPs) of nano spray drying

Characteristics	Spray dryer	Nano spray dryer	CPPs in nano spray drying
Feed kind	solution suspension emulsion	solution nanosuspension nanoemulsion	• feed type and composition • viscosity max. 10 mPas • surface tension • sample volume • circulation pump rate • inlet temperature • chamber length • drying gas type (air, N_2/CO_2) • drying gas humidity • drying gas flow • aspirator speed • vibration frequency • spray rate intensity • spray mesh size • electric field
Solvents	water; organic solvents, water–organic mixtures		
Minimal sample volume [mL]	30	2	
Maximal drying temperature [°C]	220	120	
Particle size [µm]	2–100	0.2–5	
Particle size distribution	broad	narrow	
Drying gas flow	turbulent	laminar	
Nozzle type	hydraulic, pneumatic, ultrasonic	piezoelectric spray head	
Particle separation	cyclone	high voltage collecting electrode (15 kV)	
Yield [%]	50–70	70–90	
Processing scale	lab [g], pilot [kg], industrial [t]	lab [g]	

drying, yet when organic solvents are used, the outlet temperature is higher than that typical of the aqueous feed. Taking into account the mechanism of nebulization, attention should be paid to the particle size of the solids in dispersed feed systems, the solid load and the viscosity of this liquid formulation. Only solutions, nanosuspensions or nanoemulsions can be applied in nano spray drying, because the coarse particles dispersed in suspensions would block the mesh of the nebulizer.[50,62–65] If the solid concentration in the feed increases, the particles of the final product become larger, the yield may be higher, and at the same time, the feed rate and the process are longer. Thus, it is recommended that the optimal viscosity of the feed should be less than 10 mPas. This value is twenty times lower than that of the maximal viscosity of the feed suitable for spray drying. If the viscosity of the feed is high, doughnut-like particles can form.[30,66] When smooth surface is preferable, the addition of a surfactant into the feed can give favorable results, as the reduction of the particle size is observed.[60,62,63] Similarly, organic solvents combined with surfactants promote hollow particles.[67]

In terms of CPPs, slow drying results in more compact particles, whereas fast drying generates hollow particles.[68] When the mesh size is increased, the droplet size also increases, and then the particle size of the final product increases as well. Therefore, the application of the mesh with the biggest holes (7 µm) requires a higher feed rate during processing. A high spray rate intensity results in lower outlet temperature, which may be favorable for amorphous drugs. However, in such a process, slightly larger particles are formed, and their stability can be low. Additionally, when the drying gas flow rate increases, the outlet temperature increases as well, and the solvent content in the product is reduced. Yet, if the humidity of the drying gas is high, the moisture level and the outlet temperature increase, and the yield may decrease.

Applications of nano spray drying

Throughout the last 2 decades, nano spray drying technology has been applied for the manufacturing of nanocrystals, amorphous nanoparticles, and amorphous or crystalline solid dispersions of various drugs in polymeric, protein or carbohydrate carriers (Table 4).[56] It is worth mentioning that not only nanoparticles, but also microparticles can be formed upon such a processing. They can be used for systemic or topical drug delivery. Moreover, there are reports stating that combining microparticles formed in conventional spray drying with nanoparticles prepared using nano spray drying technology can be an interesting option in the development of modern therapies. Thus, multiple studies proved that nano spray drying can be a powerful method that enables the formation of complex systems destined for oral, inhalation, nasal, intravenous, ophthalmic, or dermal administration.[16,69,70] Their application can be useful in the treatment of pulmonary,[71] oncological[72] and immune diseases,[50] as well as mental disorders.[73] They can help control cerebral vasospasm[74] and coat medical implants with the aim of making them biocompatible.[75,76]

Baba and Nishida developed nanocrystals of calpain inhibitors that prevent programmed cell apoptosis and can be used in the therapy of Alzheimer's disease and Parkinson's disease.[77] Moreover, they reported that an aqueous dispersion of these nanocrystals could be applied in the form of eye drops for the treatment of Fuchs' endothelial dystrophy of the cornea. To prepare nanocrystals, the ethanolic feed solution loaded with 0.05% or 0.5% of the drug was prepared using 3 types of mesh sizes available (4.0 µm, 5.5 µm and 7.0 µm), and 2 gas flow rates (100 L/min or 150 L/min). The results showed that the particle size of the nanocrystals increased along with an increasing mesh size. Interestingly, the inlet temperature and the high gas flow rate did not influence the particle size. The same relationship was found for dexamethasone or fluorometholone (Table 4).[78]

Table 4. Examples of nano spray-dried drugs, protein and polymeric formulations with process parameters

Drug/year	Carrier	Drug:carrier ratio (w/w)	Solid concentration/ solvent/ in feed	Process parameters	Particle size [µm]	Particle morphology	Product properties
Calpain inhibitors[77] 2012	–	–	0.05% 0.50% ethanol solution	inlet temperature: 50°C outlet temperature: 35°C feed rate: 25 mL/h frequency: 60 kHz drying gas: N_2/CO_2 gas flow rate: 100 L/min or 150 L/min mesh size: 4.0; 5.5; 7.0 µm	0.38–0.85	spherical smooth surface	nanocrystals
Dexamethasone, Fluorometholone[78] 2013	–	–	for dexamethasone: 1% for fluorometholone: 0.1% ethanol solution	inlet temperature: 50°C outlet temperature: 35°C feed rate: 25 mL/h frequency: 60 kHz drying gas: N_2/CO_2 gas flow rate: 100 L/min mesh size: 4.0; 5.5; 7.0 µm	for dexamethasone: 0.83–1.34 for fluorometholone: 0.60–0.86	spherical shape; smooth surface	nanocrystals; particle size increases with increasing mesh size and solid concentration
Vildagliptin[79] 2015	Gelatin	1:1	0.5% (0.25% of drug) solution in water	inlet temperature: 120°C outlet temperature: 27°C gas flow rate: 100–110 L/min mesh size: 4.0 µm	0.45	spherical shape, smooth but undulated surface	mucoadhesive nanospheres of gastroretentive properties
Cyclosporin A, Dexamethasone[50] 2012	PLGA	1:5	0.5–2% of solids in DCM and ethanol mixture (70:30)	inlet temperature: 29–32°C outlet temperature: 28–32°C feed rate: 25 mL/h frequency: 60 kHz drying gas: N_2/CO_2 gas flow rate: 102–132 L/min spray rate: 50–100% pressure: 36–51 mbar mesh size: 4.0; 5.5 µm	0.90–2.23	spherical micro- and nanoparticles; narrow particle size	cyclosporin A molecularly dispersed in PLGA; dexamethasone in crystalline form dispersed in PLGA
Sildenafil[80] 2015	PLGA	1:9	1–10% of solids in acetone solution	inlet temperature: 45°C outlet temperature: 25–30°C frequency: 60 kHz drying gas: N_2/CO_2 gas flow rate: 100 L/min mesh size: 4.0; 5.5 µm	4–11	spherical particles, agglomerates visible	prolonged drug delivery to lungs; mesh size and solid load determine particle size
Simvastatin[72] 2018	PLGA	1:10	O/W emulsion O: 0.25% of drug & 2.5% of PLGA in DCM W: 1% PVA aqueous solution emulsion diluted 3 times with water before processing	N/A apart from the mesh size: 7.0 µm	0.26	spherical particles	polymeric nanoparticles for breast cancer treatment

N/A – not available; DCM – dichloromethane; PLGA – poly(D,L-lactide-co-glycolide); O/W – oil-in-water; PVA – poly(vinyl alcohol).

Furthermore, it was stated that when the concentration was increased 10 times, the nanocrystals were 2 times larger than those prepared with a low-concentrated feed solution.

Harsha et al. prepared mucoadhesive nanospheres with vildagliptin, using aminated gelatin to form the matrix.[79] These nanoparticles were developed to improve the oral treatment of diabetes by creating a gastroretentive formulation. Both compunds were dissolved in water and the solution of 0.5% was nano spray-dried at 120°C. As a result, a narrow particle size distribution and a high yield (over 80%) were obtained. In vitro drug release studies showed a slower release of vildagliptin from the gelatin nanoparticles compared to the crude drug. Drug release was controlled by diffusion. The results of the wash-off test showed that after 8 h, more than 85% of the formulation remained at the application site. These findings were confirmed in a rat model where 98.2% of the formulation was retained after 12 h. In addition, these nanospheres were stable for 12 months after storage at room conditions.

Among polymeric carriers, PLGA are universal matrix-forming or encapsulating excipients not only in conventional spray drying but also in nano spray drying technology (Table 4). They have been used for manufacturing of nano spray-dried particles loaded with, e.g., cyclosporine A, dexamethasone,[50] nimodipine,[74] simvastatin,[72] and sildenafil.[80] Importantly, the majority of these formulations ensure a controlled drug release.

An interesting application of PLGA in the nano spray drying process was described by Amsalem et al.[81] They developed solid nano-in-nanoparticles (double nano carriers in the form of powder) loaded with siRNA. These nanoparticles could be a model platform for systemic delivery of nucleic acids. As a rule of thumb, the encapsulation of biomolecules, such as siRNA, proteins and peptides, provides the opportunity to enhance their stability, reduce their toxicity and achieve targeted drug delivery (PEGylated surface). In this study, smooth surface spherical nanoparticles with particle size ranging from 580 nm to 772 nm were prepared with the aim to treat genetic disorders. The primary nanoparticles consisted of siRNA-loaded cross-linked human serum albumin. They were coated with an organic solution of PLGA or PLGA combined with PEG (1:1) during nano spray drying. Such an approach enabled co-processing at low temperatures (30–60°C). As a result, the activity of siRNA was preserved, processing using small amount of siRNA was possible, and the yields higher than 60% were achieved. Then, in vitro studies confirmed a controlled release of siRNA from solid nano-in-nanoparticles for 12 h or 24 h. Finally, cellular safety and uptake were also shown for PEGylated nanoparticles.

Conclusions

Spray drying and nano spray drying can be used as complementary technologies.[61] Due to its low efficiency in producing particles below 2 μm, standard spray drying is incapable of producing nanoparticles. In this case, nano spray drying allows to achieve submicrometer particle sizes with narrow particle size distribution.[82] The engineering of the polymeric particles is possible by modifying the formulation variables and process parameters. Moreover, spray drying yields are typically maximum 70% and nano spray drying yields are around 90%, even for small sample volumes. However, it should be noted that nano spray drying is difficult to scale up, which is not a problem with traditional spray drying. Another advantage of spray drying is a much higher viscosity of fluids that can be used compared to nano spray drying. Among dispersed systems, only nanosuspensions or nanoemulsions can be processed; otherwise, mesh blockage can occur.

Despite these limitations, several research studies show the potential of nano spray drying in the manufacturing of polymeric nanoparticles, especially in the field of targeted drug delivery or controlled drug release.

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