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Review

Spray drying of pharmaceuticals and biopharmaceuticals: Critical parameters and experimental process optimization approaches

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ABSTRACT

Spray drying is increasingly becoming recognized as an efficient drying and formulation technique for pharmaceutical and biopharmaceutical processing. It offers significant economic and processing advantages compared to lyophilisation/freeze-drying techniques even though the optimisation of process parameters is often a costly and time-consuming procedure. Spray Drying has primarily been used in formulating small molecule drugs with low solubility however it is increasingly being applied to the processing of large biomolecules and biopharmaceuticals. This review examines the basics of spray drying process, current technology and various components used in spray drying process. Moreover, it is focused on introducing critical formulation and processing factors in spray drying of small molecule drugs and large biomolecules, their similarities and differences. Finally, it provides an overview of the experimental optimisation strategies designed to achieve optimum spray drying results in the shortest possible timeframe while utilising minimum product.

1. Introduction

Spray drying is the process of converting a solution, suspension or emulsion into dried powder in a single step by passing an atomized spray through a high-temperature gaseous medium, and was first developed in 1860 (Pency, 1872). The dairy (Schuck, 2002; Schuck et al., 2016) and food (Gharsallaoui et al., 2007; Truong et al., 2005) processing industries were the first examples of the industrial use of spray drying technology followed thereafter by the pharmaceutical industry. Despite the technological challenges of spray drying on an industrial scale, it has become an indispensable part of the pharmaceutical, food, ceramic, and dairy industries. Spray drying is known to offer the following advantages: (1) consistent powder quality throughout the entire drying process; (2) controllable continuous processing; (3) wide range of dryer designs for specific applications and capacities; (4) applicable to both heat-sensitive and heat-resistant materials; (5) suitable for various type of feedstocks including slurrys, emulsions, pastes, or melts; (6) a low cost, scaleable and consistent technique for formulating low solubility small molecule drugs *via* preparing amorphous solid dispersions; (7) significant time/cost savings in processing large biomolecules when compared to lyophilization. Despite many significant advances in the field of spray drying, the application of this technique to biologically complex, high-value therapeutic products such as biopharmaceuticals still requires extensive research that can only be achieved by a combination of experimental protocols, statistical analysis, and advanced computational modelling (Van Eerdenbrugh and Taylor, 2011).

Experimental protocols are extensively used for optimising the process and formulation factors of spray drying specifically in pharmaceutical research. Statistical design of experiment (DoE) approaches are exploited in order to devise a sufficient number of experiments for defining the multidimensional relationship between factors and responses, and such approaches have played a significant role in the optimisation of spray drying operating parameters for a variety of products (Couto et al., 2013; Dufour et al., 2015; Liu et al., 2016).

Mathematical modelling and Computational Fluid Dynamics (CFD) based modelling techniques offer enormous potential when developing predictive models of the spray drying process, thereby potentially reducing the time required for process optimisation (Keshani et al., 2015b; Straatsma et al., 1999). However, there are still significant gaps in understanding the real advantages of these modelling techniques in topics such as spray drying of biomolecules and amorphous solid dispersions (ASDs) for formulating active pharmaceutical ingredients (APIs). Thus, other modelling techniques such as single-droplet drying

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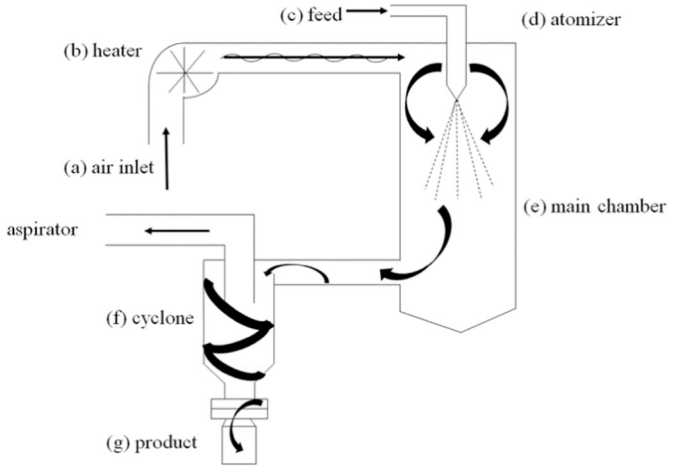

Fig. 1. Schematic representation of spray drying without recirculation loop (BUCHI-290), (a) air is sucked by aspirator; (b) air is heated up to defined inlet temperature and flows into drying chamber; (c, d) feeding liquid is pumped into atomizer with predefined flow rate; (e) heated air comes in contact with atomized feed and drying takes place in main chamber, (f) dried particles are separated from air stream in the cyclone due to the pressure drop; (g) the final particles are collected (Ameri and Maa, 2006).

models are required to effectively predict the critical attributes such as morphology, radial chemical composition and thermal degradation of the biomolecules.

This article reviews experimental considerations and techniques in relation to the spray drying of pharmaceuticals, biopharmaceuticals and optimisation techniques. The spray drying process itself is described in the first section of the review. Subsequent sections discuss the critical process parameters in relation to the spray drying of ASDs of poorly soluble small molecule drugs. The production of biopharmaceuticals suitable for pulmonary delivery and vaccine stabilization as two of the most recent and fastest expanding applications of spray drying are covered subsequently. Finally, an overview of different approaches to optimise the spray-drying process *via* experimental techniques is given.

2. Background and fundamentals of spray drying

2.1. General principles of spray drying

Fig. 1 shows a schematic of a laboratory scale spray dryer. A typical spray dryer consists of four main components, namely the drying chamber, atomizer (nozzle), aspirator, and collection cyclone (Ameri and Maa, 2006). A standard spray drying process consists of the atomization of the prepared feedstock to produce droplets of a certain size. Various atomizers can be used depending on the required droplet size, solution viscosity and desired feed rate. Atomized droplets encounter a high-temperature gas stream (temperature depends on many factors such as type of solvent or solvents, materials degradation or denaturation temperature, glass transition temperature, *etc.*) resulting in solvent evaporation and the production of solid particles. Finally, the dried particles will be separated from the outlet gas stream, by cyclone. The whole process occurs in a timeframe of few seconds. The properties of the final powder can be altered by variation of the process and formulation parameters.

2.2. Spray drying setup and configuration

The modular characteristic of lab scale spray dryers enables them to manipulate the particle properties. The process can be modified in terms of its cycle mode, types of atomizer and air flow pattern which are reviewed briefly in the following sections. However, this modularity becomes limited in industrial scale due to the financial and technological difficulties for instance, while changing atomizer or airflow are feasible in industrial scale changing cyclone or drying chamber geometry might be very costly.

2.2.1. Cycle mode

Typical spray drying process can be done in one of two cycle modes, the choice of which is dependent on the type of solvent (organic/aqueous) entering main drying chamber. In order to prevent the release of organic solvents into the environment, decrease the risk of explosion at high temperatures and reduce the vulnerability of final product to oxidation, reduce cost and recover solvents for reuse, a *closed loop* setup in combination with a condenser is preferred. During this process the outlet gas stream is directed to the condenser where organic solvent vapour is condensed and collected while the dried gas stream is returned to the drying chamber. In addition, an inert gas such as nitrogen is typically used as the gas flow stream to reduce the chance of organic solvent explosions at high temperatures. Moreover, *closed loop* may be preferred for aseptic formulation preparations even if the solution is aqueous. The *open loop* setup is employed in cases where an aqueous or water-based feedstock is to be dried. In this case, ambient air can be used as the drying gas stream without the necessity of using condenser as the outlet gas goes directly to exhaust (Aundhia et al., 2011).

2.2.2. Atomization

In terms of the spray-drying process, atomization is a critical step in the production of droplets with a specific size distribution and desired morphology (Ledet et al., 2015). The atomization process influences physical properties of the final product including particle size, drying chamber residence time and product morphology. Regardless of the type of atomizer used, the atomization process is affected by complex interrelated factors such as shearing and inertial forces, surface tension, droplet viscosity and droplet size distribution, all of which affect the angle and velocity of the atomized spray. Internal geometry of the atomizer is also highly influential in defining final properties of the powders (Gaspar et al., 2014). There are several types of atomizer/nozzles used in the spray drying industry, the most prevalent of which are discussed below.

2.2.2.1. Rotary atomizer. Rotary atomizers are available in two categories: (a) atomizer wheel and (b) atomizer disc. Rotary atomization is based on centrifugal energy created by the atomizer motor. As the liquid feed passes across or through a rotating wheel or disk. The liquid feed breaks into droplets due to the centrifugal force of the rotating disc (Lefebvre and McDonell, 2017). With this type of atomizer, the range of possible droplet sizes is typically broader compared with other nozzles (10–500 μm) (Miller et al., 2016). Given that the evaporation rate is proportional to the diameter of the atomized droplet squared, larger droplets will require much longer drying time and a wider drying chamber to enhance the drying process. The average droplet and particle size is dependent on the size and diameter of the grooves within the nozzle core, speed of the wheel and feed rate. This atomizer is often preferred for viscous fluids where it has been shown to produce a relatively uniform droplet size. Also, high feeding capacities of wheel designs (up to 200 t/h) make them a suitable choice for industrial applications (Fig. 2) (Aundhia et al., 2011). Numerous equations are available for estimating median droplets size (D50), with an example being:

$$D_{50} = 0.008 \times F_{feed}^{0.15} \times D^{-0.18} \times N^{-0.05} \times \omega^{-0.75} \times \mu_{feed}^{0.07} \quad (1)$$

where F_{feed} is feed flow rate, D is the disk diameter, N is the number of blades, ω is the blade speed and μ is the feed viscosity (Masters, 1985).

2.2.2.2. Single-fluid (hydraulic or pressure) nozzle. Single-fluid nozzles are operated by pumping the fluid through a die or orifice under

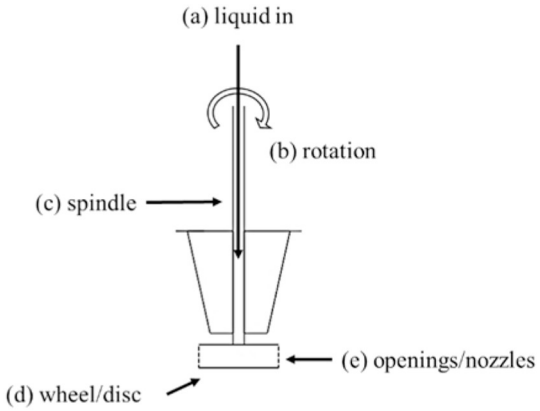

Fig. 2. Schematic representation of a rotary atomizer, (a) liquid feed goes through the spindle tube; (b) and (c) the spindle which is attached to the wheel/disc rotates with the defined rotation speed; (d) wheel/disc rotates with the defined speed; (e) due to the centrifugal force liquid feed is thrown out of the openings (Aundhia et al., 2011).

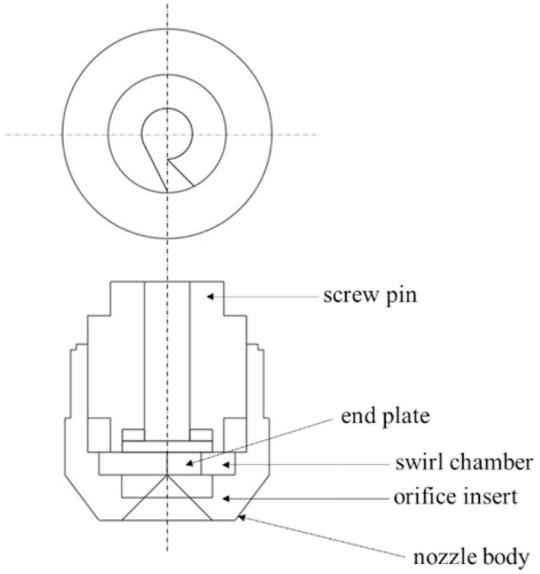

Fig. 3. Schematic representation of single-fluid (hydraulic/pressure) nozzle; the feedstock enters the swirling chamber with high pressure and as it exits the tip of the nozzle it breaks into droplets (Aundhia et al., 2011).

pressure and are typically used when a narrow droplet size distribution (mean size 10–400 μm) is required (Miller et al., 2016). The feed swirls within the swirling chamber of the atomizer and departs the nozzle as a cone shaped spray. The average droplet size is a function of feed rate, viscosity and pressure. For highly viscous feeds, pressures up to 800 atm are required for proper atomization (Fig. 3). Eq. (2) provides an estimation of D50 of droplets produced through pressure nozzles (Lefebvre and McDonell, 2017):

$$D_{50} = 4.0 \times F_{feed}^{0.25} \times \Delta P_{feed}^{-0.5} \times (\sigma_{feed} \times \mu_{feed})^{-0.25} \times \rho_{feed}^{0.07} \quad (2)$$

where, F_{feed} is feed flow rate, ΔP_{feed} is the pressure, σ_{feed} is the surface tension, μ_{feed} is the viscosity and ρ_{feed} is the density of the feed.

2.2.2.3. Pneumatic (multi-fluid) nozzle. In a pneumatic or multi-fluid nozzle the liquid feed is atomized by a gas stream (air or an inert gas such as nitrogen) which breaks up the feed stream into droplets at the tip of the nozzle (Fig. 4). The average droplet size in this case is controlled by feed rate, atomizing gas rate and pressure. Pneumatic nozzles are used for making extremely fine droplet size (10–100 μm)

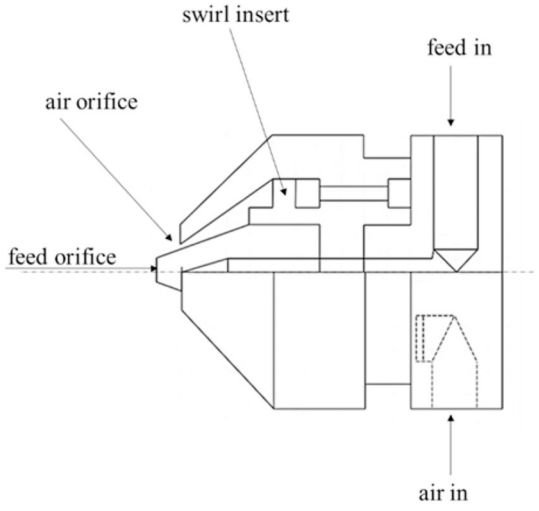

Fig. 4. Schematic representation of a two-fluid nozzle; the feedstock meets atomizing air at the tip of the nozzle and breaks up into droplets (Aundhia et al., 2011).

and are widely used in the pharmaceutical sector (Miller et al., 2016). Lubanska presented the following equation for predicting D50 of the sprayed droplets *via* the two-fluid nozzle as a type of multi-fluid nozzle:

$$D_{50} = K_d D_n \left[\frac{\eta_{feed}}{\eta_{gas} \times We} \left(1 + \frac{F_{feed}}{F_{gas}} \right) \right]^{0.5} \quad (3)$$

where K_d is a constant, D_n is the orifice diameter in the atomizer, η_{feed} and η_{gas} are the kinematic viscosities of the product and gas, F_{feed} and F_{gas} are the feed and drying gas flow rates (Lubanska, 1970).

2.2.2.4. Ultrasonic nozzle. An ultrasonic nozzle works by employing a high-frequency electrical signal to two electrodes that are placed between two piezoelectric transducers which then begin to vibrate (Fig. 5). The final vibration is then amplified by a titanium nozzle tip (Cal and Sollohub, 2010). This type of nozzle produces more uniform and larger droplets and is less prone to clogging due to its self-cleaning ability. Moreover, it produces droplets with relatively lower velocity which provides longer residence time in the drying chamber. Ultrasonic nozzle is capable of producing the widest range of droplets with median size of 5–1000 μm (Miller et al., 2016).

Overall, selecting the type of atomizer is dependent on the viscosity of the feed and the amount of energy available for atomization. In general lower viscosity liquids can be atomized to smaller droplets compared to liquids with higher viscosity at constant level of atomization energy (Wisniewski, 2015). Increasing the atomization energy leads to smaller droplet size. Droplet size affects final particle size

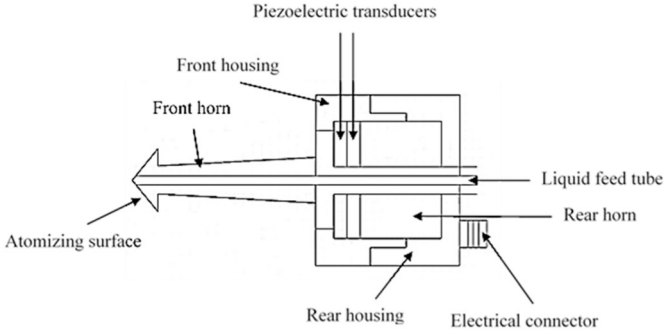

Fig. 5. Schematic representation of ultrasonic nozzle; the liquid feedstock breaks up into droplets at the tip of the nozzle due to the ultrasonic vibrations of piezoelectric transducers (Wisniewski, 2015).

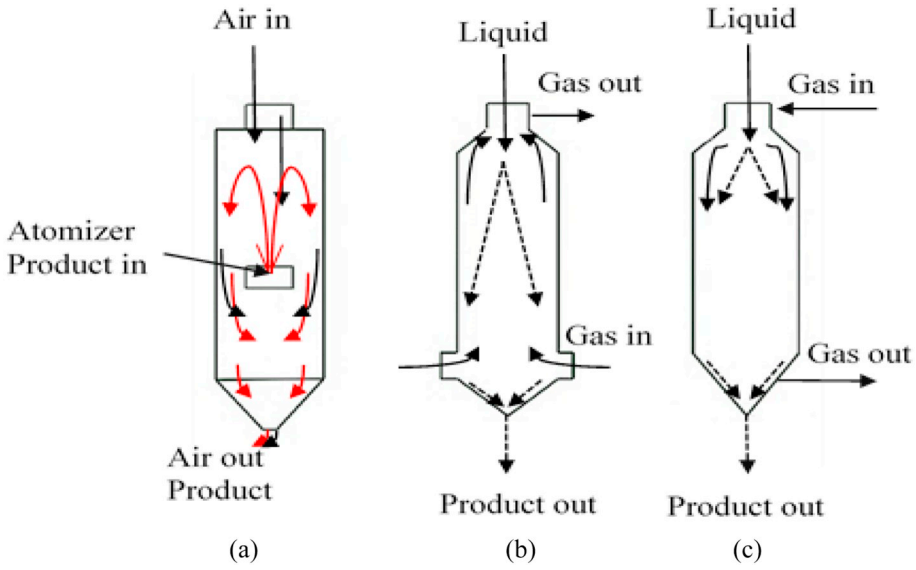

Fig. 6. Types of airflow in spray dryer (a) mixed flow, (b) counter current, (c) co-current (Wisniewski, 2015).

which can be a critical quality attribute in applications such as pulmonary drug delivery. Selecting the proper atomizer depends on the feed properties (suspended particles, viscosity, rheological behaviour), particle size distribution requirements of the final product and feed flow capacity requirements (Miller et al., 2016).

2.2.3. Airflow

Spray dryers are classified based on the flow pattern within the drying chamber. This is an important factor defining the air-droplet interaction. It is based on the position of atomizer in relation to the inlet air flow.

Fig. 6 shows three types of air flow pattern that are commonly used, namely *co-current*, *counter-current* and *mixed flow*. In the *co-current* arrangement, the drying air and droplets move in the same direction from the top of the drying chamber to the bottom (Fig. 6a). This setup would be suitable option in the case of spray drying of heat sensitive materials (Masters, 1985), however, they are in use for other type of materials as well. In this arrangement, the overall temperature of the droplet is lower compared with *co-current* and *mixed flow* arrangements during the most intense stage of drying where the droplet temperature is below the wet bulb temperature (T < wet-bulb temperature). Thus, the droplet temperature does not rise markedly as it is in contact with lower temperature gas. In the *counter-current* arrangement (Fig. 6b), the feed and drying gas, flow in opposite directions. As droplets encounter hot gas at the end of the drying chamber (at this stage droplets must be in the last stage of drying process, *i.e.* wet-bulb temperature), their outlet temperature is higher compared with the *co-current* setup. Thus, the *counter-current* arrangement provides higher thermal efficacy for drying materials with a longer drying cycle (Masters, 1985). However, it might not be the best option for thermally sensitive materials (*e.g.* biopharmaceuticals) due the higher outlet temperature compared with *co-current* arrangement. Moreover, final particle size is usually double the diameter of those in the *co-current* process because of the intensive agglomeration and as such is widely used in production of detergents, fertilizers and certain food substances (Chhabra and Kreith, 2017).

Mixed flow is a combination of *co-current* and *counter-current* air flows. The atomizer is placed in the central part of the drying chamber and the solution is sprayed upward or downward (based on its thermal stability) while the airflow is downward. *Mixed flow* mode offers greater flexibility for drying materials with varying degrees of thermal stability. For drying powders with high thermal stability, the upward spraying direction may be used while for thermally sensitive materials the downward stream is used to decrease the air-droplet contact time (Masters, 1985).

3. Critical factors for successful spray drying

3.1. Particle formation

Regardless of the application, control of the size and morphology of the particles is considered to be critical. Drug performance will be highly affected by its physical and chemical properties, namely aerodynamic properties, dissolution rate, flowability, compressibility and particle size distribution (Liversidge and Cundy, 1995; Vicente et al., 2013). In the last decade, the trend has been moving from empirical design of particles to fundamental modelling of the underlying phenomena of particle formation (Vehring, 2008).

The key factor in successful particle engineering strategies is understanding the underlying mechanisms and controlling the radial distribution of components during spray drying process (Vehring et al., 2007). Surface activity and evaporation rate have been shown to be two of the most critical factors in defining the radial distribution of individual components. Surface activity may lead to the preferential orientation of the components on the surface while, by evaporation from the surface, the concentration of the components at the surface increases resulting in aflux of concentration away from the surface. Thus, understanding that evaporation is a coupled mass and heat transfer issue is essential. Various numerical models have been developed for multicomponent droplets drying (Adhikari et al., 2004; Chen, 2004; R. S. Miller et al., 1998). Vehring introduces a fundamental model for drying of droplets in the absence of internal convection *i.e.* the chemical components in an evaporating droplet can be described by the non-linear diffusion coefficient (Vehring, 2008; Vehring et al., 2007). Fick's second law of diffusion for droplets with constant evaporation rate, at constant diffusion coefficients and negligible interactions between the solutes, has an analytical solution:

$$d^2(t) = d_0^2 - \kappa t \tag{4}$$

where, d is the diameter of the droplet, d_0 is the initial diameter of the droplet, κ is the evaporation rate and t is time.

Based on this equation, drying time could be approximated as well as evaporation rate. Moreover, rearranging the solution of the diffusion equation, leads to the calculation of surface enrichment, E_i, which is the surface concentration of component i in proportion to its average

concentration in the droplet:

$$E_i = \frac{c_{s,i}}{c_{m,i}} = \frac{\exp(0.5Pe_i)}{3\beta_i} \quad (5)$$

where, $c_{s,\ i}$ is the surface concentration of component I, $c_{m,\ i}$ is the average concentration of component I, β_i is the profile function and Pe is the Peclet number:

$$Pe_i = \frac{\kappa}{8D_i} \quad (6)$$

The Peclet number is a dimensionless number showing the ratio of diffusional motion of the solutes to the radial velocity of the receding droplet surface (Vehring et al., 2007) where κ represents the evaporation rate and D_i is the diffusion coefficient of solute i.

A low Peclet number ($Pe < 1$) at a specific feed concentration leads to the droplet surface receding at a normal pace while solid particles have enough time to rearrange, leading to limited void space, a denser particle and, therefore, higher bulk density of the final powder. Compounds with a higher diffusion coefficient can keep up with the rate of shrinkage of the droplet surface so will be distributed homogeneously throughout the final particle. In a solution containing several compounds, the compound with the lowest diffusion coefficient will most likely precipitate at the microsphere surface. The Peclet number can be affected by a mixture of material properties of solutes and solvents and process factors that determine the evaporation rate. Hence, surface enrichment could be manipulated by extremely high or low evaporation rates. The effect of solvent evaporation rate and solute diffusion coefficient on the final morphology of the spray dried particles has been reported elsewhere (Rizi et al., 2011; Vehring, 2008).

The differential diffusion coefficient of various components of the solution affects the physical properties of the powder. At constant evaporation and feed concentration rates, a low diffusion rate/high evaporation rate ($Pe > 1$) denotes the slow diffusional movement of the solute compared to the receding speed of the droplet surface. Depending on the type of solute, different solidification scenarios may happen. Molecules with high initial saturation and fast crystallization kinetics may have crystalline phase separation while others may not have enough time for crystallization. This results in the formation of particles with decreased density since shell formation occurs earlier in the evaporation process. Large biomolecules such as peptides (Stahl et al., 2002; Zijlstra et al., 2004) and proteins (Maury et al., 2005) are usually reported as forming hollow, wrinkled or dimpled particles. The diffusion coefficient can be expressed using the Stokes-Einstein equation:

$$D = \frac{K_B T}{6\pi\eta r} \quad (7)$$

where D is the diffusion coefficient, K_B is the Boltzmann constant, r is the globular radius, T is the absolute temperature, and η is the solution viscosity. The diffusion coefficient is inversely related to the viscosity of the solution and the hydrodynamic radius of the components in the droplet.

As the diffusion coefficient and evaporation rate are not constant, thus the Peclet number is also not constant. It means that the Peclet number might vary as the droplet evaporation progresses. This is in the co-solvent system where there are two different evaporation rates. Moreover, in cases where a phase transition *e.g.* crystallization might happen during the process, the Peclet number can change dramatically. Some of the low solubility peptides or amino acids are in this category (Vehring, 2008). The Peclet number could have a significant role in optimising the desired final particle properties. Therefore, it is necessary to be familiar with the process and formulation factors that influence it during the drying process. The next section will introduce these factors in spray drying of small and large molecules.

3.2. Pre-requisites of producing amorphous solid dispersions with spray drying

The influential factors in the spray drying process fall into two main categories: feed solution factors, and process factors. The former consists of the feed solution viscosity, surface tension, density, chemical stability and feed composition. The process factors are mostly machine-related factors such as inlet/outlet temperature, feed rate, atomizing gas flow rate, atomizing gas type, nozzle type, air flow pattern and drying gas flow pattern. The interrelations of these factors make optimisation of the spray drying process a complex procedure. In an attempt to overcome this challenge, researchers have adopted a DoE approach thereby allowing effective interpretation of the interplay between different variants (Cerpnjak et al., 2015; Dufour et al., 2015; Liu et al., 2016).

Understanding the reasons behind the morphology of a particle, size, functional layers or aerodynamic properties requires a sound knowledge of a particle formation process. This leads to further research into physical and chemical mechanisms controlling the drying process and particle formation during spray-drying process. Several experimental techniques have been devised for investigating these phenomena including suspending droplets from glass filaments (Lin and Gentry, 2003), levitating droplets using ultrasonic waves and moving chains of similar droplets.

3.3. Feed solution properties

3.3.1. Excipients

Spray drying can be used for the production of ASDs. An ideal ASD is a one-phase system in which all molecules of the API are fully mixed with the carrier molecules (Van den Mooter, 2012). Melting point and enthalpy, thermal stability, constant of ionization, hydrogen bond (H-bond) donating/accepting nature, parameters of solubility/interaction and partition coefficients are properties that could be helpful in identifying ideal poorly soluble candidates for ASD formulations. Active pharmaceutical ingredient, solvent and excipient are main components of a solution used for ASD. Thus, a combination of these components dictates the spray drying process factors required for specific final powder properties.

With respect to excipient selection for spray drying, a key requirement is considerable solubility and chemical stability of solution state of the API and excipients in a regular volatile solvent or a mixture of solvents (Paudel et al., 2013). Therefore, the solubility screening of the solid components is a necessary step prior to spray drying of formulations (Davis et al., 2016; Friesen et al., 2008). The role of the polymeric carrier is not only to stabilize the amorphous API but also to improve drug dissolution and absorption (Teja et al., 2013).

Several factors need to be evaluated and established before excipient selection includingglass transition temperature (T_g), nature of polymer (anionic/cationic), presence of functional groups, hygroscopicity of polymer, solubility in common organic solvents, polymer molecular weight and thermal stability (Baghel et al., 2016). Glass transition temperature is one of the most frequently used criteria to characterize amorphous solids and examine the interactions between API and excipients in ASDs. Moreover, it is one of the factors that should be considered before selecting input temperature for spray drying since high input temperatures may lead to wall deposition due to the softening of the particles and, subsequently, give low yields. Generally, amorphous systems with higher T_g are superior in order to improve the stability of the ASD formulation as they normally exist in a glassy state at room temperature with significantly higher viscosity ($> 10^{13}$ P) reducing API mobility and the risk of recrystallization (Chokshi et al., 2008). Thus, polymeric excipients with high T_g are exploited with APIs as they are capable of providing ASDs with T_gs of 75 °C or higher (at least 50 °C above the room temperature) (Shah et al., 2012).

Intermolecular interaction between API molecules and the excipient is one of the most critical aspects that should be considered in developing new ASD formulations (Qian et al., 2010). The stronger the intermolecular interactions (hydrogen bonding, electrostatic, ionic or hydrophobic bonding) the higher the miscibility between the API and the excipient. Excipient screening based on structure is typically the first step in identifying the most favourable carriers for a drug with known chemical structure (Van Eerdenbrugh and Taylor, 2011). There are some systematic approaches to rationally predict and design ASD formulation (Korhonen et al., 2017). Calculating solubility parameters (Forster et al., 2001; Marsac et al., 2006), use of partition coefficients (Yoo et al., 2009), lattice-based solution models (*e.g.* Flory-Huggins theory) (Laitinen et al., 2014) and molecular modelling (Van Eerdenbrugh and Taylor, 2011) are examples of systematic techniques for studying ASD formulations. For instance, Greenhalgh et al. reported the miscibility of the API and polymer when the difference of their solubility parameter was $< 7\,MPa^{0.5}$, while samples with solubility differences above $10\,MPa^{0.5}$ were immiscible (Greenhalgh et al., 1999).

Additionally, hygroscopicity of the polymeric excipient is considered as another influential factor on the physical stability of amorphous products during storage and should therefore be considered in structure based analyses. Unlike adsorption of water in crystalline materials which depends on the available surface area, water uptake in amorphous solids is mostly mass dependent. Water weakens molecular hydrogen bondings and expands free volume of ASDs (Ahlneck and Zografi, 1990; Andronis et al., 1997; Imaizumi et al., 1980; Makower and Dye, 1956). This leads to lower miscibility of the drug in the polymer and decreased T_g of the formulation, thereby producing drug-rich phases that prompt phase separation and recrystallization (Shah et al., 2012). Moreover, water affects the viscosity of solids by lowering their T_g (Andronis et al., 1997). For instance, a decrease of about 150 °C in T_g of PVP K-12 after storage at a relative humidity of 53% was observed (Teng et al., 2010). Therefore in many cases the use of a hydrophobic polymer such as Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) is recommended to provide enhanced stability (Chokshi et al., 2008). In addition, formulating spray-dried ternary ASDs with inclusion of a hydrophobic and a hydrophilic polymer has been tried. This approach has led to an increase in both the solubility and stability of ASDs (Davis et al., 2017; Six et al., 2004; Ziaee et al., 2017).

Table 1 presents a comprehensive list of polymeric carriers most frequently used in the formulation of ASDs. The associated physical characteristics and commonly used solvents are also presented.

3.3.2. Solvents

Appropriate solvent selection is as important as choosing a suitable excipient. Generally, the initial criteria for the selection of suitable solvents include: (1) high solubility of drug and excipients in the selected solvent ($> 50\,mg{\cdot}ml^{-1}$), (2) final solution viscosity, (3) low toxicity and environmental hazards, (4) high volatility for fast evaporation over the course of drying (5) chemical stability of the API and excipients in the solvent, (6) non-combustion in spray drying environments (Chokshi et al., 2008). Table 2 shows some of the most frequently used solvents in the spray-drying process and their physical properties.

According to the International Council for Harmonization (ICH), all class II and III solvents are suitable to be used in the spray drying process (Anon, 2009b). Relative volatility of the solvent should be considered as the primary criterion to achieve reasonable yield and reduce residual solvent in the final powder. Droplet viscosity and surface tension are crucial factors for effective feed atomization during the spray drying process (Lefebvre and McDonell, 2017). Dielectric constant and polarizability of the solvent are also significant in determining the crystallinity or amorphicity of the powder (Ansari and Sunderland, 2008). It is reported that the higher the dielectric constant and dipole moment, the higher the amorphicity of the final solid dispersion leading to higher equilibrium solubility (Ansari and Sunderland, 2008). The Hildebrand solubility parameter of the solvents can be an informative tool during solvent selection as it provides an estimation of the solubility of drug and other excipients in the solvent. Kamlet-Taft (KT) solvent parameters that measure the hydrogen bond donor (α) and hydrogen bond acceptor (β) separately gives understanding about the possibility of presence of H-bond donor or acceptor pairs and the strength of H-bonding in the solutions (Kamlet et al., 1983). Solvents with higher (α) are efficient in dispersing drugs or polymers with H-bond acceptor functionality. The higher the β value of a solvent the more suitable it is for API or polymers with stronger H-bond donor groups (Paudel et al., 2013). Solvent evaporation rate is another aspect that should be considered with respect to final properties of particle, specifically morphology and radial distribution of the components.

Viscosity of the solution is dependent on the polymer concentration and its molecular weight, which is related to the polymer dispersity in the chosen solvent and non-covalent interaction between polymer-solvent-drug. Paudel et al. concluded that the use of a mixture of solvent and anti-solvent (*e.g.* acetone for PVP in a formulation of naproxen:PVP) leads to solid dispersions with improved miscibility and physical stability (Paudel and Van den Mooter, 2012). Rheological properties of the feed stock (*e.g.* Newtonian/non-Newtonian liquids, shear thinning/shear thickening) can also impact the droplet formation.

3.4. Process factors

3.4.1. Feed concentration

The feed concentration is the solid particle fraction in the volume of the solution. Littringer et al. (2012) proposed that higher solution concentrations of mannitol aqueous solutions lead to particles with a rougher surface compared to low feed concentrations. They reported the formation of hollow spray dried particles with higher porosity and lower bulk density at high feed concentrations. A higher feed concentration corresponds to less solvent in each droplet. This leads to higher *Pe* values, shorter evaporation times and porous particles with less density in the final stage. Higher feed concentrations increase the chance of agglomeration or formation of multimers between polymer chains or API molecules which result in more porous particles with lower density and rougher surfaces (Kim et al., 2003; Tomasko and Timko, 1999). Suhang et al. reported markedly lower residual moisture content in the final spray-dried honey powder at higher solid concentrations. This was attributed to the increase in feed solid content and decrease of total moisture to be evaporated (Suhag et al., 2016).

3.4.2. Feed rate

Feed rate in the spray-drying process is commonly reported as the mass of transferred powder per unit of time. It controls the amount of solvent and solid content entering the drying chamber. Thus, physicochemical properties such as solvent evaporation rate, morphology, particle size and density can be altered by varying the feeding rate. It has previously been demonstrated that higher feed rates result in higher moisture content in final particles (Tonon et al., 2008). Moreover, higher yields were also reported at decreased feed rates. Increased feeding rate of the feedstock at the same atomizing gas flow rate leads to enlarged droplets (*i.e.* particles) due to lower atomization energies (Billon et al., 2000; Stahl et al., 2002). Moreover, in terms of technological limitations, very high feeding rates might result in overloading the condenser in closed loop setup.

3.4.3. Inlet/outlet temperature

Inlet temperature has a direct effect on heat and mass transfer during the droplet drying process. Singh et al. have reviewed the effect of inlet temperature on the final properties of amorphous solid dispersions (Singh and Van den Mooter, 2016). Higher inlet temperatures influence the particle formation process due to the high rate of solvent evaporation. This process can lead to a pressure gradient inside and outside the droplet with subsequent effects on the final morphology of

Table 1
Overview of typical carriers for ASD preparation and relevant physical properties (Paudel et al., 2013; Teja et al., 2013).

Carriers	M. Wt (range) (kDa)	T_g (T_m) °C	Solubility parameter	Hygroscopicity	pH solubility	Commonly used solvents
HPMC 2910	10–1500	148.2–151.1	23.8	~10%	1–10	EtOH, MeOH, EtOH/DCM, water, DCM, MeOH/DCM, acetone and water
HPMCAS-MF	80	117.3–120	31.2	6–7%	> 6.5	Ethyl acetate, acetone or MeOH, acetone/ water, THF, methyl acetate: MeOH, Water
HPMC-E5 (2906)	10–1500	152	–	–	1–10	
Na-CMC	90–700	–	–	–	–	
HPMC-P55	10–1500	138	28	7–8%	> 5.0	Acetone
HPMC-AS HG	55–93	117.9–120	–	–	–	
HPC (L-HPC)	50–1250	105 (220)	–	–	–	MeOH, diluted, ammonia solution
MCC	36	(260–270)	–	–	–	
PVP K 30	50	170–174	27.7	40%	1–10	EtOH, IPA/H2O, water, MeOH, DCM, EtOH/ water, MeOH/DCM, EtOH/acetone, IPA
PVP K 25	28–34	–	–	35–40%	1–10	DCM, IPA
PVP VA64	45–70	106.0–110.0	–	< 10% (50% RH)	1–10	Acetone, water/EtOH, DCM, water, MeOH/ DCM, IPA
PVP VA37	–	–	–	–	1–10	
Kollicoat IR	45	–	–	–	–	Water with or without HCl/ethanol, DCM
PVA 22000	20	–	–	–	–	Hydroalcoholic or DCM, water
Gelucire 44/14	–	(44)	–	≈1% (< 60% RH)	–	Water
Gelucire 50/13	–	(50)	–	–	–	MeOH, DCM
Compritol 888/ATO	–	–	–	–	–	DCM
Sterotex K NF	–	–	–	–	–	DCM
PEG 4000	2.6–3.8	(50–58)	–	< 25%	1–14	DCM/MEOH, water, EtOH
PEG 6000	7.3–9.3	−22.71 (55–63)	–	< 1%	1–14	DCM/MEOH, hydroalcoholic or DCM, EtOH
PEG 8000	7–9	(60–63)	–	NH	–	DCM/MEOH, DCM
PEG 20000	15–25	−41 (60–63)	–	NH	–	
Poloxamer 407	9.84–14.6	–	–	–	–	Water, DCM or acetone
Lactose	0.3423	(232)	–	–	–	Water
Arabia gum	–	–	–	–	–	Water
Stevia-G	–	–	–	–	–	EtOH/H_2O
Glucosyl hesperidin	–	–	–	–	–	EtOH/H_2O
PHPMA (poly[*N*-(2-hydroxypropyl) methacrylate])	20	–	–	–	–	
Eudragit E 100	47	48	19.3	–	–	EtOH, DCM, IPA, Ethyl acetate, THF
NaPMM	135	–	–	–	–	Water
Polyacrylic acid (PAA)	100	100–105 &126	–	–	–	MeOH/DCM
Carbopol 940	104.4	100–105	–	–	–	
Chitosan hydrochloride (Chitosan)	10–1000	203	–	–	–	
Soluplus	90–140	~70	–	–	–	

the powder such as surface roughness. A higher inlet temperature leads to rapid formation of a solid skin on the outer surface of the droplet which entraps the solvent vapours (Singh and Van den Mooter, 2016). Depending on the type of API and excipient polymer used, the solvent vapour pressure may collapse the whole particle, or result in a particle with a porous surface (Vehring, 2008; Vehring et al., 2007).

Furthermore, faster drying due to higher temperatures is appropriate for the formation of ASDs with higher T_g, which in turn is more desirable for product stability. This is primarily due to the rapid drying of the equilibrium fluid into non-equilibrium glass form. In contrast, slower drying rates can result in low T_g products having stickier particles which reduce the final yield due to wall deposition. This will in turn increase the stickiness of the powders to the cyclone and lower the final yield of the spray-dried material (Singh and Van den Mooter, 2016).

3.4.4. Atomization and drying gas (type and flow rate)

Drying and atomization gas type and flow rate selection is crucial

Table 2
Solvent ICH limit relevant physical properties of commonly used spray drying solvents (Patel et al., 2015; Paudel et al., 2013; Vasconcelos et al., 2016).

Solvents	ICH limit (ppm)	B.P. (°C)	ΔH_v (kJ·mol^{-1})	P (Torr)	η (mPas)	γ (mN·m^{-1})	ε	δ (cal·cm^{-3})$^{1/2}$	μ (D)	Kamlet taft (KT) parameter	
										α	β
Water	–	100.0	40.7	17.5	0.89	71.690	78.4	23.4	1.84	1.17	0.47
Methanol	3000	64.7	35.3	128	0.54	22.10	32.6	14.5	1.60	0.98	0.66
Ethanol	Class 3	78.3	38.7	59	1.08	22.00	24.3	12.7	1.70	0.86	0.75
Isopropanol	–	82.3	45.7	44	2.07	18.30	18.3	11.4	1.66	0.76	0.84
DCM	600	39.8	28.0	475	0.42	27.20	8.9	9.7	1.60	0.13	0.10
Acetone	Class 3	56.3	29.1	240	0.30	22.68	20.7	9.6	2.70	0.08	0.43
Methyl ethyl ketone	Class 3	79.6	31.2	105	0.40	23.04	18.5	9.3	2.76	–	–
Dioxane	380	101.3	38.0	41	1.26	33.00	2.2	10.0	0.40	0.00	0.37
Tetrahydrofurane	720	66.0	26.9	200	0.46	26.40	7.5	9.1	1.60	0.00	0.55
Ethyl acetate	Class 3	77.1	31.9	97	0.43	23.20	6.0	9.0	1.78	0.00	0.45
Chloroform	60	61.2	30.8	210	0.54	26.60	4.7	9.3	1.01	0.20	0.10
Acetonitrile	410	81.6	33.8	97	0.34	28.45	37.5	11.9	–	3.44	–

B.P.: boiling point, ΔH_v: enthalpy of vaporization, P: vapour pressure at 20 °C, η: viscosity at 25 °C, γ: surface tension at 25 °C, ε: dielectric constant, δ: total solubility parameter, μ: dipole moment, α: KT hydrogen bond donor (acidity), β: hydrogen bond acceptor (basicity).

for defining the droplet size, density, velocity, and the properties of the final particles. Various atomization gases such as compressed air, N_2 and CO_2 have been used previously for spray drying. Atomization gas properties such as density and specific heat capacity are decidedly important in defining the final properties of spray dried powders. For instance, N_2 with lower density ($1.1233\ kg{\cdot}m^{-3}$) has been shown to produce smaller particles with different surface morphologies compared to CO_2 ($1.7730\ kg{\cdot}m^{-3}$) (Paudel et al., 2013; Singh and Van den Mooter, 2016). Moreover, an inert gas such as N_2 is typically used with non-aqueous solutions (organic solvents) and for solutions containing easily oxidized solutes. The differing morphology has been attributed to variations in heat and mass transfer of different drying mediums. The effect of atomization and drying gas type on crystallization has been studied by Langrish and co-workers (Islam and Langrish, 2010a, 2010b). They stated that the crystallinity of the resulting spray dried lactose was affected by the drying and atomizing gas in the order of most crystallinity to least: N_2 > air > CO_2. A possible reason for this is due to the higher temperature and mass transfer of CO_2 compared to N_2 and air which in turn provides better conditions for production of amorphous materials. Kudra et al. reported higher efficiency in the drying process with CO_2 compared to air due to its higher heat transfer rate. This leads to up to 20% faster drying which offers 4% energy savings on the heat input (Kudra and Poirier, 2007).

3.4.5. Atomization device

In addition to all aforementioned spray-drying process factors, the type of atomization device also affects the droplet size distribution, velocity, spray-cone diameter and incident angle. An overview of the various types of atomizers has been given in Section 2.2. One-fluid nozzles can produce larger particles compared to the other types of atomizers as such particles produced using this method can often be used directly in tablet pressing without a granulation step (Dobry et al., 2009). However, these nozzles are not compatible with high-viscosity non-Newtonian feed stocks. The most common type of atomizer used in production and research of amorphous solid dispersions is the two-fluid nozzle (Cal and Sollohub, 2010). In these systems, the atomizing gas and solution feed rate are the main factors in defining final particle size distribution thereby permitting a high level of control of the atomization process. Higher gas flow rates in tandem with lower feed rates typically result in smaller particle sizes (Mandato et al., 2012). In two-fluid nozzle, droplet size decreases to a plateau with an increasing air (or gas):liquid ratio (ALR) (Snyder and Lechuga-Ballesteros, 2008). The main drawback of two-fluid nozzles is the limitation in achieving high throughputs. Another disadvantage of two-fluid nozzles is that all formulation components are required to be solubilized in one type of solvent. However, in multi-fluid nozzles *i.e.* three-fluid (with two liquids and one gas channels) and four-fluid (with two liquids and two gas channels) nozzles, two solutions can be atomized simultaneously. Multi-fluid nozzles have previously been used for spray drying of amorphous solid dispersions (Kondo et al., 2014). The API indomethacin was successfully spray dried in amorphous form with a four-fluid nozzle and HPMC as polymeric excipient (Chen et al., 2007). In addition, the solubility of artemisinin was increased due to partial amorphization by employing a four-fluid nozzle in tandem with polyethylene glycol (PEG) as the polymeric excipient (Sahoo et al., 2011).

The main concern during spray drying of small molecule APIs is formulating them properly in order to achieve higher solubility, stability and bioavailability. However the spray drying of large biomolecules that are sensitive to thermal degradation is a significantly more complex process. In either of cases, these properties can be controlled by understanding and optimising the interrelations of process and formulation factors during the spray drying process. The next section provides more insight on the critical quality attributes of spray drying process that should be considered during optimisation process.

3.5. Critical quality attributes

Based on ICH Q8 definitions, an important stepin pharmaceutical product development is the identification of critical quality attributes (CQAs) in a way that those product characteristics having an impact on product quality can be studied and fully controlled (Anon, 2009a). Moreover, it is recommended to use the enhanced product and process understanding along with quality risk management to establish an appropriate control strategy including a design space. A CQA is a physical, chemical, biological or microbiological property or characteristic of a material that should be within an appropriate limit range or distribution to ensure the desired product quality. Critical formulation and processing factors of spray drying process were introduced, however depending on the application of spray dried powders, different CQAs are required to be screened. In the following section, CQAs of spray dried pharmaceutical powders are introduced.

3.5.1. Particle size distribution

Particles size distribution is critically important for formulating powders especially where pulmonary delivery applications are concerned. (Baldinger et al., 2012). It has been recognized that the optimal aerodynamic particle size distribution for pulmonary delivery application is in the range of 1–5 μm (Hickey, 2016). Maltesen et al. studied the effect of various processing and formulation factors such as nozzle gas flow rate, feed flow rate, inlet gas temperature aspirator capacity and solid concentration on final aerodynamic particle size distribution using near infrared spectroscopy (NIR) (Maltesen et al., 2012). Moreover, LeClair et al. found the significance of Peclet number, and solid content on particle size distribution (LeClair et al., 2016). Higher solid contents in tandem with higher Peclet number led to lower particle size distribution.

3.5.2. Yield

The process yield is highly affected by two main factors, namely loss due to the non-optimal process factors and the material formulation. This could be prevented by selection of an appropriate spray dryer with optimal design features such as wide drying chamber for rotary atomizers or high efficiency collection cyclone in tandem with clearly defined and optimised processing factors. In addition, wall deposition during spray drying due to low T_g of the sprayed formulation decreases the yield. This can be avoided by spray drying at lower outlet temperatures or introduction of polymeric excipients with higher T_g to the formulation. Low drying temperatures can cause incomplete drying of the particles (residual solvent in the particles) and stickiness of the particles to the drying chamber. Thus, optimising the drying conditions improves drying resulting in higher yields.

3.5.3. Morphology

The morphology of the spray-dried product is extremely significant, especially for biopharmaceutical applications whereby the product is to be delivered *via* oral inhalation (Paluch et al., 2012; Prinn et al., 2002). Formulation factors such as solvent evaporation rate and diffusion rate of solute from the inner core to the outer crust of the particles has been shown to significantly affect the final morphology of the particles (see Section 3.1). It is well known that the higher the feeding rate, the larger the particle size. Moreover, lower solid contents and smaller nozzle tips (typically in two-fluid nozzle) lead to smaller droplets and thus finer final particles. Paluch et al. introduced a new system of morphology classification for spray-dried biomolecules. In this system, the shape of particles was described as spherical or irregular, and the surface was categorized as smooth or crumpled (Paluch et al., 2012). This classification system is helpful in enhancing our understanding of the effect of morphology on aerosolization of spray dried particles. It has been reported that smooth and flat surface of particles results in increased adhesion forces between the particles. Moreover, the flat surface

promotes the large contact area between the particles which leads to higher cohesive forces between particles (French et al., 1996; Steckel and Brandes, 2004). The effect of surface active components such as amino acid L-leucine on the morphology and aerosolization of spray dried powders has been studied (Eedara et al., 2018). It was shown that its application leads to reduction in surface cohesiveness and dimpled particles with reduced contact area (Sou et al., 2013; Vehring, 2008; Walton and Mumford, 1999).

4. Applications

4.1. Spray drying of poorly soluble small molecule drugs

Spray drying has attracted significant interest in fields such as ceramics (Lukasiewicz, 1989), pharmaceuticals (Baghel et al., 2016; Paudel et al., 2013), biopharmaceuticals (Ameri and Maa, 2006; Ledet et al., 2015), dairy and food processing (Gharsallaoui et al., 2007). With respect to biopharmaceutical and pharmaceutical production, spray drying has been utilised as a method of enhancing bioavailability in addition to solubility enhancement of drugs *via* amorphous solid dispersion (Patel et al., 2015). Encapsulation of active pharmaceutical ingredients (APIs) within an inert protective matrix has been carried out by spray drying (I Ré, 1998). Spray drying is also employed in the production of dry powder vaccines offering significant advantages when compared with liquid formulations, due to increased stability against chemical and physical hydrolysis, particles aggregation, structural irreversible denaturation/degradation or fluctuations in pH (Ameri and Maa, 2006).

Based on the Biopharmaceutics Classification System (BCS) as depicted in Fig. 7, drugs are classified according to their aqueous solubility and intestinal permeability as these factors are a key determinant of their oral bioavailability (Saluja et al., 2010). It is known that 40% of the newly developed drugs are poorly soluble or lipophilic in nature (Patel et al., 2015; Snyder and Lechuga-Ballesteros, 2008).

In order to compensate for low solubility of pharmaceutical APIs, many physical and chemical techniques are employed such as: (a) salt formation of ionisable compounds (Huang and Tong, 2004), (b) particle size reduction (Liversidge and Cundy, 1995), (c) amorphous solid dispersions (ASDs) (Caron et al., 2011; Chen et al., 2006; Leuner and Dressman, 2000; Li et al., 2008; Sekiguchi and Obi, 1961; Serajuddin, 1999; Teja et al., 2013), (d) crystal engineering approaches: co-crystallization, modification of crystal habits and polymorphs (Hickey et al., 2007; Shan and Zaworotko, 2008), (e) solution containing solvents, co-solvents, and lipids (Savjani et al., 2012), (f) micelle based approaches (Lee et al., 2007; Shin et al., 2009; Yu et al., 1998), (g) complexation (Becket et al., 1999; Memişoğlu et al., 2003), salt formation (Savjani et al., 2012).

Solid dispersion is historically defined as a dispersion of drug in a solid matrix where the matrix is either a small molecule or polymer. The dispersed state may include many forms such as eutectic mixture, crystalline/glass solutions, and amorphous/crystalline suspension (Chiou and Riegelman, 1971; Sekiguchi and Obi, 1961). Amorphous solid dispersion can now be more precisely defined as a dispersion of drug in an amorphous polymer matrix, preferably at molecular level (Huang and Dai, 2014). Traditional methodologies such as rapid condensation of vapour, super cooling of melt, crystalline mass mechanical activation and fast precipitation from solutions have previously demonstrated ASDs with enhanced solubility (Angell, 1995). Disordered structure and higher Gibbs free energy of amorphous compared with crystalline state leads to improved solubility and higher dissolution rates (Zhang et al., 2012). However thermodynamic instability leads to structural relaxation, nucleation and undesirable crystal growth often during subsequent storage of amorphous formulations (Van den Mooter, 2012). Glass transition temperature (T_g) as one of the characteristics of amorphous materials is the temperature at which materials transform from a disordered glassy state to a softer rubber-like state (ISO, 2013). Thus, at temperatures higher than T_g adequate molecular motion is available for the phase transformation. As a basic rule of thumb storage of amorphous APIs at 50 °C below their T_g reduces the molecular motions leading to lower chance of recrystallization of these compounds (Hancock et al., 1995; Paudel et al., 2013). Van den Mooter has mentioned phase instability as a function of time and/or storage conditions such as temperature and humidity as a primary reason for the low number of ASD formulations currently available in the market (Table 3) (Van den Mooter, 2012; Vasconcelos et al., 2016). However, this can be overcome by preparing a homogeneous amorphous dispersion of API with high T_g polymeric excipients (Chan et al., 2015; Li et al., 2008; Shen et al., 2011). Due to high molecular weight and high entropy, polymers often inhibit mobility of individual API drug molecules thereby preventing subsequent crystallization. Thus, binary or ternary amorphous mixtures of drug and polymer-based excipients are often combined to form ASD (Davis et al., 2017; Kadir et al., 2011; Taylor and Zografi, 1997; Ziaee et al., 2017). To qualify a solid solution, the drug/polymer system should comply with two criteria: the formulation should depict a single glass transition temperature (T_g), and the drug should be in amorphous form (Goldberg et al., 1966). Taylor et al. showed that the stability enhancement of the ASD formulations is due to new assembly of bonding between API and polymeric carriers (Taylor and Zografi, 1997). Van den Mooter et al. refer to the anti-plasticizing effect of the polymers as another stabilizing factor (Caron et al., 2011).

In addition to the traditional routes for the manufacture of ASDs, new technologies such as hot melt extrusion (Albadarin et al., 2017; Douglas et al., 2016a; Douglas et al., 2016b), spray-drying (Cho et al.,

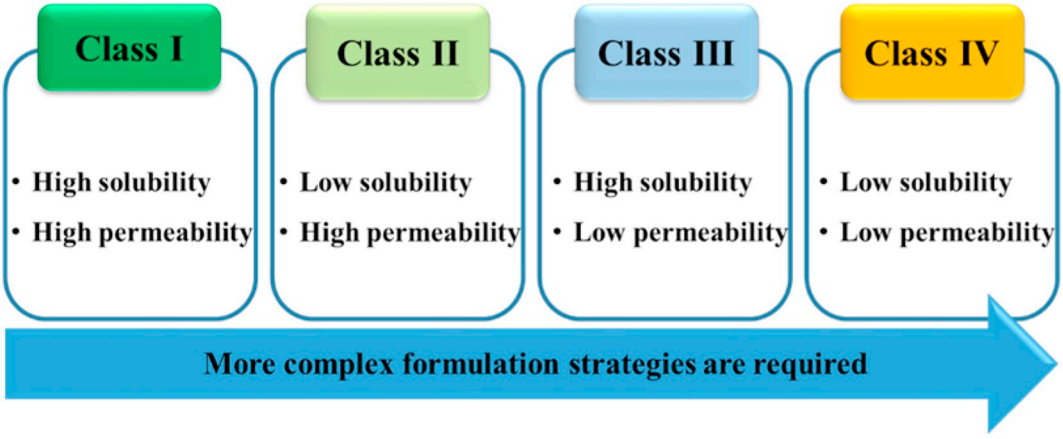

Fig. 7. Biopharmaceutics classification system (BCS) (Saluja et al., 2010).

Table 3
Examples of commercially available pharmaceutical products using amorphous solid dispersion technologies (Kawabata et al., 2011; Rumondor et al., 2016; Van den Mooter, 2012; Vasconcelos et al., 2016; Vo et al., 2013).

Product name	API	Carrier	Preparation method	Year of approval
Gris-PEG™	Griseofluvin	PEG	Melt extrusion	1975 (FDA)
Isoptin®	Verapamil	HPC/HPMC	N/A	1982
Nimotop	Nimopidine	PEG	N/A	1985
Cesamet™ (US)/Canemas®(Austria)	Nabilone	PVP	N/A	1985 (FDA)
Nivadil®	Nivaldipine	HPMC	N/A	1989
Prograf™	Tacrolimus	HPMC	**Spray drying**	1994 (FDA/MHRA)
Nezulin®	Troglitazone	PVP	N/A	1997
Afeditab®	Nifedipine	PVP/poloxamer	N/A	2001
Cymbalta®	Duloxetine	HPMCAS	N/A	2004 (EMA/FDA)
Crestor®	Rosuvastatin	HPMC	**Spray drying**	2004 (EMA), 2002 (FDA)
Kaletra®	Lopinavir/ritonavir	PVP-VA	Melt extrusion	2005 (FDA), 2001 (EMA)
Eucreas® Galvumet™	Vildagliptin/metformin HCL	HPC	Melt extrusion (metfotrmin)	2007 (EMA)
Fenoglide®	Fenofibrate	Poloxamer/PEG	N/A	2007
Intelence®	Etravirine	HPMC	**Spray drying**	2008 (EMA/FDA)
Modigraf®	Tacrolimus	HPMC	**Spray drying**	2009 (EMA)
Samsca®	Tolvaptan	HPMC	Granulation	2009 (EMA/FDA)
Certican®	Everolimus	HPMC	N/A	2009
Zotress™(US) Certican®/Votubi® (EU)	Everolimus	HPMC	**Spray drying**	2010 (EMA/FDA)
Onmel™	Itraconazole	HPMC	Melt extrusion	2010 (FDA)
Fenoglide™	Fenofibrate	PEG/poloxamer 188	Spray melt	2010 (FDA)
Novir®	Ritonavir	PVP-VA	Melt extrusion	2010 (FDA) 2009 (EMA)
Incivek™ (US)/Incivo® (EU)	Telaprevir	HPMCAS	**Spray drying**	2011 (EMA/FDA)
Kalydeco®	Ivacaftor	HPMCAS/SLS	**Spray drying**	2012 (EMA/FDA)
Zelboraf®	Vemurafenib	HPMCAS	Co-precipitation	2012 (EMA) 2011 (FDA)
Noxafil®	Posaconazole	HPMCAS	Melt extrusion	2014 (EMA) 2013 (FDA)
Viekira™(US)/Viekirax® (EU)	Ombitasvir/Paritaprevir/Ritonavir	PVP-VA/TPGS	Melt extrusion	2014 (EMA/FDA)
Belsomra®	Suvorexant	PVP-VA	N/A	2014
Hravoni®	Ledipasvir/Sofosbuvir	PVP-VA	**N/A**	2014
Orkambi®	Lumacaftor/Ivacaftor	HPMCAS/SLS	**Spray drying**	2015 (EMA/FDA)
Envarsus®	Tacrolimus	Poloxamer/HPMC	N/A	2015

2017; Janssens et al., 2008; Paradkar et al., 2004; Paudel et al., 2013; Wlodarski et al., 2016), freeze-drying (Xu et al., 2016), milling (Wlodarski et al., 2016), melt-quenching (Watanabe et al., 2004) and spray-congealing (Tong et al., 2011) have been employed. As can be seen from Table 3, spray drying is a leading technology among all solvent evaporation methods to produce commercialized ASD formulations. For spray drying to be considered an effective technique to produce ASDs, the dried product should enhance the absorption of poorly water-soluble drugs in gastrointestinal fluid (GI) and provide physical stability for the API (hindering crystallization and phase separation) leading to longer shelf-life, and easier shipment and storage (Friesen et al., 2008). Previous studies have shown that larger API molecules with low numbers of aromatic rings, a low level of molecular symmetry, branched carbon skeleton and electronegative atoms are capable of forming amorphous solid dispersions (Baird et al., 2012; Baird and Taylor, 2012; Baird et al., 2010; Mahlin et al., 2011). The following sections will be focused on presenting the most critical factors for successful preparation of ASD formulation by spray-drying.

4.2. Spray drying of large molecule drugs (biopharmaceuticals)

At ambient temperatures, many biopharmaceuticals such as proteins and peptide-based drugs are more stable in solid state compared to liquid state (Yuh-Fun and Steven, 2000). Hence, for improved long-term storage and stability, the need for processing techniques capable of producing solid product free from moisture content is essential. Moreover, with the advent of new drug delivery systems such as long-acting microspheres (Tracy, 1998), vaccine powders for intradermal delivery (Chen et al., 2002) and fine powders for pulmonary delivery (Maa et al., 1999), the biopharmaceutical sector will see increased demand for new powder formation techniques.

Lyophilization or freeze drying is commonly used for powder preparation of many commercially available biopharmaceuticals (Wang, 2000). However, in addition to its denaturising effect, it requires a secondary procedure for breaking apart the freeze-dried cakes into finer particles. As a direct result of this requirement there is less control over the particle properties such as particle size distribution, morphology, porosity, density, *etc.* Spray drying has shown huge promise as a single step liquid to powder conversion method which gives the user significant control over the final properties of the powder. A major difference between the two techniques which is often underestimated is the presence of different types of stresses. Ice formation stress, freeze concentration of the solutes and pH swing are some of the stresses due to the freeze-drying process while, spray-drying applies mostly thermal and mechanical stresses to the samples.

Spray congealing has also been applied for processing particle engineering of biopharmaceuticals. It is a hybrid technology between spray drying and hot melt extrusion therefore shares advantages and disadvantages of both methodologies. It has been used for formulating controlled release formulations of proteins such as insulin (Maschke et al., 2007).

Table 4 presents a comparison between freeze drying and spray drying technologies for biopharmaceutical products.

As regards spray drying of biopharmaceuticals, a clear limitation of the spray-drying process is the high temperature required for solvent evaporation which may destabilize or denature thermo-labile biopharmaceuticals. The drying process in spray drying consists of three steps outlined as follows (see Fig. 8): (1) the droplet experiences initial heating (path 0–1) (2) at this stage evaporation starts and the solvent is readily available at the surface of the droplet. The mass of the droplet decreases while the temperature stays constant at the wet bulb temperature of the solvent and the diameter of the droplet shrinks (path 1–2); (3) at this stage the droplet size has decreased and a solid outer crust has formed around a wet core and the droplet is treated as a wet particle with constant outer diameter (d_p) The temperature of the droplet starts to rise as well (path 2–3). The evaporation from the wet core continues and as a result, the thickness of the solid crust increases and wet core shrinks (d_i). The drying can be stopped at the desired

Table 4
Advantages and disadvantages of spray drying and lyophilisation techniques (McAdams et al., 2012).

Technique	Advantages	Disadvantages
Freeze drying	Established technology within the biopharmaceutical industry Equipment widely available Limited process losses Straightforward aseptic processing Avoidance of high temperature, decreases the risk of biomolecule denaturation	Large space and maintenance requirements High power consumption Requirement for further processing to make final powder Difficulty associated with scale up Time consuming
Spray drying	Highly controllable leading to the engineered particles properties (size, morphology) Can be incorporated into continuous processing techniques Capacity to engineer particle morphology Particles delivery routes can be tailored	Process losses greater than freeze drying (can be significantly reduced by proper process optimisation) Complex and interrelated process parameters Time consuming process optimisation

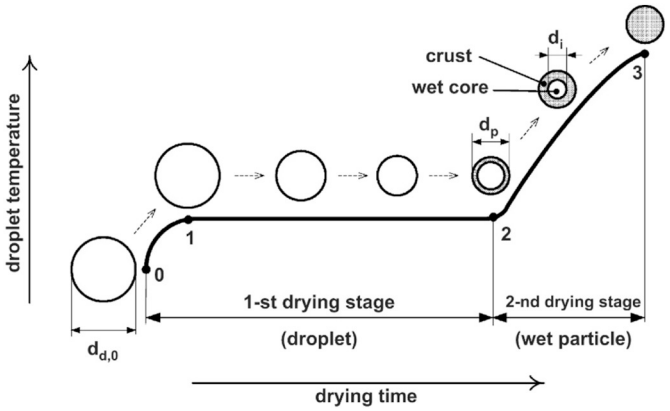

Fig. 8. Typical temperature profile and morphology of a droplet during drying process containing solid. (The picture reprinted with permissions from Mezhericher et al. (2008)).

residual liquid level. (Mezhericher et al., 2008; Singh and Van den Mooter, 2016).

The spray drying process often exerts certain thermal stresses on the product however with the appropriate process optimisation these can be minimized/controlled. For instance, outlet temperature is a key process parameter. If the outlet temperature is higher than thermal degradation temperature (depending on the degradation kinetics), the dried powder can undergo thermal degradation. On the other hand, if the outlet temperature is too low, the material experiences less thermal degradation but shorter shelf life due to residual water or lower yield due to wall stickiness. The challenge therefore is to optimise the process to produce a sufficiently dry powder, yet not incur unacceptable degradation.

Table 5 shows a number of biomolecules that have been spray dried and the corresponding spray drying conditions. This table shows the wide range of biomolecules that have been spray dried using various lab scale up to pilot scale spray dryers. The outlet temperature in all cases is well below 100 °C along with very low feeding rates. It is obvious that the researchers have tried to keep the outlet temperature as low as possible while maintaining a reasonable drying process. This clarifies the general optimisation conditions for spray drying of biomolecules. Irreversible denaturation happens during the dehydration process owing to the change in the secondary structure of the proteins (Hasija et al., 2013). This is attributed to the removal of hydration water molecules which are required to form hydrogen bonds to stabilize the protein's secondary structure (Carpenter and Crowe, 1989; Costantino et al., 1996; Prestrelski et al., 1995). However, some proteins such as lysozyme experience both reversible and irreversible thermal denaturation (Blumlein and McManus, 2013). To improve the stability of the spray dried proteins, it is advisable to use excipients including sugars (*e.g.* sucrose and trehalose (Hulse et al., 2008; Ogain et al., 2011)), and polyols (*e.g.* sorbitol (Maury et al., 2005)) that could function according to the water-replacement theory. Moreover, surfactants (*e.g.* pluronic F-127® (Haj-Ahmad et al., 2013)), polymers (*e.g.* dextran and polyethylene glycol (S. Jacob et al., 2006)), antioxidants (*e.g.* ethylenediaminetetraacetic acid (Akers and DeFelippis, 2012)), amino acids (*e.g.* arginine and glycine (Ajmera and Scherließ, 2014)) and chelating agents (*e.g.* ammonium sulfate (Hiroyuki et al., 2009)) can be used as excipients for improving biomolecules stability during processing (Li and Mansour, 2011). Various mechanisms have been proposed to explain the role of excipients in protecting proteins from denaturation (Ajmera and Scherließ, 2014):

(1) Water replacement theory: proteins are usually bound to many water molecules in solutions. Excipients that form hydrogen bonds with proteins during water removal process, help to protect and strengthen the tertiary structure of proteins by creating a water-like environment for them (Carpenter et al., 1994). For instance, sucrose and trehalose (Hulse et al., 2008; Ogain et al., 2011), and polyols (*e.g.* sorbitol (Maury et al., 2005)) could function according to the water-replacement theory.
(2) Amorphous state stabilization: the glass forming excipients limit the molecular mobility of proteins and prevent aggregation by effective dispersion of protein molecules (Green and Angell, 1989). As an example, trileucine has been used for improving the physical stability of a wide range of drugs (*i.e.* asthma therapeutics such as albuterol and cromolyn) due to its high glass transition temperature (~104 °C) compared to room temperature which enables the long-term room temperature stability of the aerosols (Lechuga-Ballesteros et al., 2008).
(3) Surface adsorption reduction: the excipients acting as surfactant reduce the protein concentration at the surface because of their own surface activity thus preventing interfacial induced denaturation (Maa et al., 1998; Yuh-Fun and Steven, 2000). For example, pluronic F-127® (Haj-Ahmad et al., 2013) could act as surfactant which occupies the surface of the droplets and protects proteins from air-liquid interface tension.

Additionally, effects associated with high shear force during the spray drying process may lead to denaturation of protein based biopharmaceutical materials. While it has been reported that shear force alone does not cause denaturation of biomolecules, in combination with the air-liquid interface effect it may cause aggregation in some sensitive proteins (Ameri and Maa, 2006; Maa et al., 1998). Typically proteins are able to tolerate shear rates as high as $10^5\,s^{-1}$ without protein aggregation or activity loss (Maa and Hsu, 1996). However, as most of the proteins are amphiphilic, in air-liquid interfaces their hydrophobic regions are exposed to the non-aqueous surface which results in denaturation (Ledet et al., 2015). The sources of stress on biopharmaceuticals can be circumvented by optimisation of the process and formulation parameters. Parameters that are typically screened after spray drying are yield, morphology, chemical stability, therapeutic

Table 5
Spray dried biomolecules and the corresponding spray drying conditions.

Biomolecule	Type of spray dryer/congealer	Inlet/outlet temperature (°C)	Feed rate ($ml \cdot min^{-1}$)	Nozzle type	Atomizing air flow ($L \cdot h^{-1}$)
Lysozyme (Haj-Ahmad et al., 2016)	Büchi B-290 mini spray dryer	110/55	5	Two-fluid	600
Plasmid (Lane et al., 2005)	Büchi B-290 mini spray dryer	165/85	7	Two-fluid	800
Lactoferin (LF) (Wang et al., 2017)	Spray dryer FT30 MKII	180/70 and 95	17–20	Two-fluid	–
Papain (PAP) (Gaspar et al., 2017)	Büchi B-290 mini spray dryer	103/85	5	Two-fluid	400
Recombinant human deoxyrebonuclease (rhDNase) (Zijlstra et al., 2009)	Büchi 190 mini spray dryer	135/55 and 75	2.37 (setting 3)	Two-fluid	400, 600 or 800
Interfering RNA/poly (lactic-*co*-glycolic acid) (siRNA/PLGA) (Jensen et al., 2010)	Büchi 290 mini spray dryer	45/30	0.3	Two-fluid	473
Liposomal DNA (Seville et al., 2002)	Büchi B-191 mini spray dryer	150/80–85	7.5	Two-fluid	600
Human parathyroid hormone (PTH) (Cordons et al., 2003)	LabPlant laboratory-scale spray dryer	100/52–62	10	Two-fluid	Atomizing air pressure: 0.5 bar
Anti-immunoglobulin E (IgE) monoclonal antibody (Maa et al., 1999)	Büchi 190 mini spray dryer	100–105/50–55	15	Two-fluid	1050

activity and flow properties of the final powder. The most significant factors affecting the powder properties are excipient type, protein/excipient ratio, feed solid concentration, instrument design, inlet/outlet temperature, liquid feed rate, type of atomizer and atomizing air pressure. All these parameters are interrelated, thus optimising one parameter often requires optimisation of many other parameters. However, many research groups have attempted to model spray drying process with different approaches. DoE, computational fluid dynamics (CFD), and heat-mass balance modelling has been used to understand the intercorrelations of the process and formulation factors in both lab scale and industrial scale spray dryers (Grasmeijer et al., 2013; Hennigs et al., 2001; Huang et al., 2004; Jamaleddine and Ray, 2010; Keshani et al., 2015a; Lin and Chen, 2006; Maltesen et al., 2008; Woo et al., 2008). Moreover, single droplet drying models in conjunction with experimental setups are another approach to studying the basic heat and mass transfer phenomena within one droplet (Perdana et al., 2015; Perdana et al., 2011; Schutyser et al., 2012).

4.2.1. *Applications of spray drying of biopharmaceuticals*

Spray drying of biopharmaceuticals has been carried out by both academic research groups and the biopharmaceutical industry. Spray drying has been used for engineering specific particle sizes for pulmonary delivery applications *e.g.* insulin for treatment of diabetes. Stabilization of active biopharmaceuticals including vaccines with excipients is another field of immense interest (Hasija et al., 2013). The next section of this review gives a brief overview of the technological requirements and final powder properties for vaccine stabilization and pulmonary delivery applications.

4.2.1.1. Pulmonary delivery. Micronized APIs are the most common technology used for production of inhalation powders (Chow et al., 2007; Seville et al., 2007). However, the micronization process itself offers limited control over final particle size and morphology as observed in jet milling (the typical approach for the production of micronized particles). Spray drying has been a promising technique for producing powders for inhalation since its first application as an alternative to milling processes in the 1980s (Fourie et al., 2008).

A spray dried powder suitable for pulmonary delivery applications should satisfy the following properties: (1) aerodynamic particle diameter between 1 and 5 μm. The aerodynamic diameter of an irregular particle is defined as the diameter of the spherical particle with a density of 1000 $kg \cdot m^{-3}$ and the same settling velocity as the irregular measured particle (Hinds, Jan. 1999); (2) narrow particle size distribution; and (3) powder should be readily aerosolizable at relatively low aerodynamic dispersion forces (Chow et al., 2007); (4) the employed excipient should be able to protect the protein from destabilization/denaturation and improve its storage time/shelf-life at room temperature; (5) to ensure the biopharmaceutical product has not been denatured during the spray drying process therapeutic activity of the protein should be certified in *ex vivo* experiments (Zijlstra et al., 2009); (6) Finally, it is critical that particle properties (*e.g.* density, morphology, surface energy and composition, *etc.*) of an aerosol be maintained during manufacture, storage and administration (Lechuga-Ballesteros et al., 2008).

In line with the main mechanisms of particle deposition in lungs, namely inertial impaction, gravitational sedimentation and Brownian diffusion, the size of the inhalation particles is of extreme importance. Large particles (larger than 5 μm) with high density and momentum travel in one direction only without the ability to change direction and collide on the airway's wall in the respiratory tract. Particles smaller than 1 μm typically follow the Brownian deposition mechanism in the alveolar region where there is very low airflow. Gravitational mechanism in the central and peripheral regions of the lung is the dominant adsorption mechanism for particles with an intermediate size (1–5 μm). Therefore, 1–5 μm is the desired range of particle size for maximizing the absorption through pulmonary delivery. (Seville et al., 2007).

Insulin is suitable for pulmonary delivery. It has high permeability through the alveolar membrane and exhibits high thermal stability. In 2006 Pfizer and Inhale Therapeutic Systems received FDA approval for Exubera® spray-dried insulin for inhalation applications. It consists of recombinant insulin (60%), sodium citrate, mannitol, glycine and nominal amounts of sodium hydroxide (for adjusting the pH to 7.2–7.4) (Ledet et al., 2015; McAdams et al., 2012; White et al., 2005). However, it was withdrawn from the market after only one year in the market due to poor sales numbers (Heinemann, 2008). Lutz Heinemann has reviewed the main reasons behind the failure of Exubera and has attributed these to a number of reasons such as the size of the inhaler, which was large and cumbersome. Additionally, the procedure for preparing and activating the air pump was time consuming and was reported to be annoying from the patients' perspective. Moreover, the selection of specific doses was not possible using Exubera upon initial product introduction (Neumiller and Campbell, 2010). The MannKind Corporation has previously developed technologies for pulmonary delivery of insulin (Technosphere®) using freeze drying technology. Marketed as Afrezza, the formulation consists of a novel excipient fumaryl diketopiperazine (FDKP) and polysorbate 80 which was approved by FDA in 2014 (Anon, 2018). However, based on the market analysis four years after approval it is still experiencing low sales numbers. Although it is not used for pulmonary delivery of biomolecules, a successful example of a commercial spray dried biopharmaceutical product is the FDA approved Raplixa®. It is the first spray dried fibrin sealant which can be used to help control bleeding in adults during surgery. It is comprised of spray dried thrombin and fibrinogen which are blended and filled aseptically (McKeage, 2015). It has been developed by ProFibrix BV and manufactured through Nova Laboratories' aseptic spray drying technique. The two components are spray dried individually with a protective coating of trehalose in order to prevent the conversion of fibrinogen to fibrin *via* reacting with thrombin. The free-flowing powders are then blended in specific ratios to prepare a ready to use product.

Excipients, such as sugars *e.g.* trehalose and raffinose and amino acids *e.g.* arginine and leucine have been investigated as protein stabilisers (Table 6) (Ogain et al., 2011). Using trehalose increases the cohesion tendency of the particles resulting in particle aggregation (Bosquillon et al., 2001b; Lo et al., 2004) and is therefore a suboptimal stabilizer. Lactose produces smooth, spherical particles with a narrow fine particle size distribution (Andya et al., 1999). It is efficient in increasing the shelf life of the spray dried powder though it has little effect on humidity resistance (Andya et al., 1999) whereas erythritol, a non-hygroscopic carbohydrate, has been shown to significantly improve the stability of the final powder against humidity. The concerns/risks of Maillard reactions of lactose, discourages its employment as an excipient to stabilize proteins (Bharate et al., 2010; Vinjamuri et al., 2017). Sucrose is not a suitable excipient for the spray drying process as it does not improve stability against humidity. Dextran and mannitol are two frequently used excipients (Bosquillon et al., 2001a; Bosquillon et al., 2004; Chougule et al., 2006) as stabilizing agents for proteins. Lechuga-Ballesterol et al. investigated the use of trileucine for improving the physical stability of a wide range of drugs (*i.e.* asthma therapeutics such as albuterol and cromolyn). Its high glass transition temperature (~104 °C) compared to room temperature enabled the long-term room temperature stability of the aerosols (Lechuga-Ballesteros et al., 2008). Moreover, low aqueous solubility of trileucine led to the formation of corrugated particles and promoted the formation of trileucine coated particles with superior aerosol performance. Its high surface activity contributed to the formation of powders with reduced cohesiveness. Lastly, it competed with proteins on the air/water interface resulting in decreased surface tension in solution and less denaturation and aggregation in the solid state (Lechuga-Ballesteros et al., 2008).

Table 6
Excipients used for spray drying of biopharmaceutical powders for inhalation. This list is mostly compiled from reference number (Ajmera and Scherließ, 2014; Seville et al., 2007).

Carbohydrates	Sucrose
	Trehalose
	Dextran
	Erythritol
	Mannitol
Amino acids	Arginine
	Aspartic acid
	Glycine
	Leucine
	Phenylalanine
	Threonine
	Trileucine
	Histidine

4.2.1.2. Vaccines. Spray drying increases the stability of vaccines at ambient temperature (Plotkin, 2008). Dry vaccines are preferable to liquid because of the reduced risk of chemical and physical damage due to hydrolysis, aggregation, denaturation, degradation or pH fluctuations (McAdams et al., 2012). Most vaccines require storage between 2 and 8 °C. Improper storage conditions lead to denaturation of the API. This restriction inhibits the delivery of vaccines in developing countries that may have insufficient cold storage facilities. Table 7 outlines some examples of vaccines that have previously been spray dried as well as the drying conditions.

A vaccine for cholera was spray dried using Eudragit® L 30 D-55 or Eudragit® FS 30D as excipients with 1:10 vaccine to excipient w/w ratio. Significantly, a lower yield was observed at lower inlet temperature (60 °C) compared with 80 and 100 °C. However, the antigenicity of the samples produced with Eudragit® L 30 D-55 at the highest inlet temperature (100 °C) was only 88% compared with 98% at 60 and 80 °C which was mainly due to the high processing temperature (Ano et al., 2011).

Saluja et al. compared spray drying and freeze drying of the influenza subunit vaccine for pulmonary delivery (Saluja et al., 2010). It was shown that spray drying produces smaller particles (mass median size 2.6 μm) compared with spray freeze drying (mass median size 10 μm) at same processing conditions. Live, attenuated measles virus vaccine was also spray dried and freeze dried (Ohtake et al., 2010). Different stabilizing excipients have been employed to enhance vaccine stability at room temperature; sucrose-trehalose (17% w/v) were employed for stabilization against dehydration; L-arginine (4% w/v) to prevent the protein to protein interaction and aggregation; human serum albumin (4% w/v) to stabilize the vaccine by a combination of enhanced T_g, increased viscosity and surfactant effect, glycerol (1.25 wt%) as plasticizer to increase the interaction between glassy sugar matrix and the vaccine molecule. Moreover, potassium phosphate buffer (50 mM) was used in conjunction with divalent cations ($CaCl_2$ and $ZnCl_2$) to reduce process loss and maintaining the virus structure during processing, respectively.

To date there has been limited commercial success with respect to spray dried biopharmaceutical products. This can be attributed to two reasons. Firstly, freeze drying is well-established as a drying technique at industrial scales in both the pharmaceutical and biopharmaceutical industries, and within highly regulated regimes such as these, the adoption of newer technologies is often slow. Secondly, the high processing temperatures associated with spray drying have the potential to denature or reduce activity in protein based biologics. While this can be overcome by the use of suitable excipients, appropriate modelling techniques and optimised processing conditions, establishing such parameters requires significant research and development efforts in the initial stage. Insight into the techniques used for the optimisation of spray drying processing conditions with respect to biopharmaceuticals is provided in the next stage of this review. While freeze drying may be the current mainstay technique for the drying of biopharmaceuticals it

Table 7
Spray-dried vaccines.

Vaccine	Spray Drying Conditions	Excipients	Application and Reason for Spray Drying
Cholera vaccine (vibro cholerea) (Ano et al., 2011)	**Büchi 191 Mini Spray Dryer** Two fluid nozzle, 0.7 mm tip Feed rate: 5 L/min, Atomizing air flow: 600 L/h, Inlet temperature: 60, 80 and 100 °C.	Eudragit®L30 D-55/Eudragit®FS 30D	Mucosal delivery
Influenza subunit vaccine (Saluja et al., 2010)	**Büchi 190 Mini Spray Dryer** Two fluid nozzle, 0.5 mm tip Feed rate: 5 mL/min, atomizing air flow: 800 Ln/hr, inlet temperature: 100-105 °C, outlet temperature: 50-55 °C, aspirator air flow: 1000 L/min.	Sucrose, Trehalose, L-arginine, Human serum albumin, Glycerol	Pulmonary delivery
Attenuated measles virus vaccines (Ohtake et al., 2010)	**Büchi B-190Mini Spray Dryer** Feed rate: 0.5 mL/min, Atomizing nitrogen pressure: 15 psi, Inlet temperature: N/A, Outlet temperature: 40 °C.	Sucrose, Trehalose, Mannitol	Enhancing stability at ambient temperature.
- Aluminium-salt for hepatitis B virus (Chen et al., 2010) **- Polysacharide-protein conjugate vaccine for meningitis A** (Chen et al., 2010)	**GEA Niro Mobile Minor™ pilot plant** Feed rate: 520 g/h, Atomizing gas flow: 6kg/h, Nozzle pressure: 1.9 bar, Inlet temperature: 90-95 °C, Outlet temperature: 61 °C.	Sucrose, Trehalose	Thermostability
Insulin (Exubera, Pfizer) (White et al., 2005)	**Büchi B-190Mini Spray Dryer** Feed rate: 5 mL/min, Atomizing air flow: 600 L/h, Inlet temperature: 110 – 200 °C, Outlet temperature: not mentioned	sodium citrate, mannitol, glycine and nominal amounts of sodium hydroxide (for adjusting the pH to 7.2-7.4)	Pulmonary delivery of insulin.
AERAs-402, live virus vector (Jin et al., 2010)	Inlet temperature: 65-125 °C, drying gas flow: 439-538 L/h, Outlet temperature: 34-50 °C, aspirator rate: 35 m^3/h.	Mannitol, Leucine, Sucrose, Histidine, Dextran	Pulmonary delivery
Newcastle disease, live virus (Huyge et al., 2012)	**Büchi B-290Mini Spray Dryer** Feed rate: 7.5 ml/min, Inlet temperature: 150 °C, Outlet temperature: 70-75 °C.	Mannitol, Trehalose, inositol, PVP, BSA	Pulmonary delivery
Hep B, alum-adjuvanted subunit (Cape et al., 2008; Chen et al., 2010; Maa et al., 2003)	GEA Niro pilot plant	Trehalose	Freeze sensitive

has the disadvantage of being a batch process and in addition suffers from high energy consumption. The ongoing transformation within the pharma and biopharama industries from batch to continuous processing represents a significant opportunity for the adoption of continuous spray drying techniques. Relative to freeze drying spray drying is highly advantageous in terms of energy consumption and being a continuous and gentle drying process. These factors in tandem with the possibility to achieve higher drying efficiencies represent the best motivation for the biopharmaceutical industry to invest in developing new spray drying facilities and processing methods.

4.3. Optimisation of the spray-drying process

Optimising spray drying as a multivariate process with interconnected effective factors is highly challenging for process optimisation engineers and scientists. Traditionally, experimental approaches were focused on one factor at a time studies. However, by introduction of the Quality by Design (QbD) philosophy (Juran, 4 May 1992) into the pharmaceutical industry, the significance of statistical methods for designing and analyzing the results of experiments were emphasized by regulatory authorities (FDA, EMA) (Anon, 2009b). QbD has been defined as “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.” by ICH Q8 (R2) (Anon, 2009b). DoE is a structured and organized method for determining the relationship between factors affecting a process and the output of the process. The application of QbD in pharmaceutical product development process is based on analyzing multivariate experiments using process analytical technology (PAT) and DoE to identify the CQAs and working environment of the process. DoE is recognized as the main toolbox for employing QbD in drug formulation and process development. In this section, a brief overview of recent developments in optimising spray drying *via* experimental procedure based on DoE is given.

4.3.1. Design of experiment (DoE)

DoE is a method for clarifying and optimising the effect of process and formulation factors on final powder with decreased number of experiments and lower amount of required materials. The interactions between factors are estimated systematically using DoE. Additionally, it gives experimental information in a larger region of the factor space (Czitrom, 1999). Employing DoE approaches for mapping the effect of interrelated parameters and their interactions on multiple responses are highly recommended by pharma and biopharma regulatory agencies (Anon, 2009b). Note that users of DoE as a process optimisation technique need to be aware of all process and formulation factors, their possible effects and interrelations on the spray-drying process. Otherwise, the designed DoE might not lead to a comprehensive understanding of the process.

Several DoE approaches and software packages have been used in the literature for optimisation of the spray-drying process in either pharma or biopharma applications. Vinjamuri et al. used a two-phase DoE for optimising spray dried ipratropium bromide microspheres for oral inhalation. In phase I, a 2^{7-3} fractional factorial design was used to evaluate the individual formulation and process parameters and their possible effect on yield (%), particle size, particle size distribution and T_{out}. A screening design is informative in terms of defining the approximate working environment and determining the most critical factors affecting the output responses. Phase II was based on a response surface design to identify the critical individual, interaction and non-linear effects of input factors (*i.e.* the factors that were found to be significant in the screening design) (Vinjamuri et al., 2017). The effect of five input variables (solution pH, solid content, inlet temperature, atomizer gas flow rate and feedstock feeding rate) on final yield and aerodynamic properties of spray dried antibiotic (ciprofloxacin hydrochloride) and nutrient dispersion compound (glutamic acid) was

studied. A central composite design with 32 runs revealed that final yield is primarily controlled by variables that determine cyclone efficiency *i.e.* atomizer gas and feedstock flow rate and solid content. It would be informative if the authors could study the effect of drying air flow rate on the final yield of the process, as this effect is missed in this study (Ross et al., 2017).

In our research group, we used a custom design with JMP® Pro Version 13.0 (SAS Institute Inc., Cary, NC) for formulating an amorphous solid dispersion of ibuprofen *via* spray drying (Ziaee et al., 2017). The effect of solid content, feedstock flow rate, inlet temperature and formulation factors such as API/excipient and composition of solvents on physical and chemical properties of the final powders were studied. Contours and empirical equations were derived by post analysis of 16 runs revealing the intercorrelations between the process and formulation factors. For instance, higher yield was achieved at formulations with higher excipient contents and solid contents between 5 and 10 wt %.

Mao and co-workers used a central composite design to identify the optimal drug:excipient ratio and spray drying temperature. Using Design-Expert® software (Stat-Ease, Inc., Minneapolis, MN) they managed to figure out 4:5 and 120 °C as mannitol:itraconazole optimal ratio and inlet temperature, respectively (Sun et al., 2015).

Table 8 describes pharmaceutics and biopharmaceutics that have previously been optimised for spray drying. This table summarizes the input factors and output responses, the DoE methods and the software used for statistical analysis. It provides helpful information on the most critical factors of spray drying of biomolecules that have been addressed so far by other researchers. More interestingly, in some cases a two-step DoE has been used for an initial screening of critical factors and subsequent analysis of the intercorrelations of factors and responses. It should be noted that a sound understanding of various DoE methodologies and their applications is a must for concise analysis of the results.

5. Conclusions

Spray drying is increasingly being used in the biopharmaceutical sector and is currently being used in the pharmaceutical industry for producing amorphous solid dispersions and improving the solubility of low solubility APIs. As the biopharmaceutical sector continues to expand with new products, there is increased demand for new single step processing techniques such as spray drying. This paper reviewed the fundamentals of the spray drying process and its application in the pharmaceutical and biopharmaceutical sectors. The highly influential process and formulation factors were reviewed with respect to their effect on final powder products, and an overview of the interrelation between these parameters was explained. Examples of commercially available spray dried pharmaceuticals and biopharmaceuticals were also highlighted.

Formulating ASDs *via* spray drying has progressed immensely, however, there are still numerous challenges to be addressed. Low solubility of small molecules in organic solvents, very low T_g and stickiness, low flowability and compressibility of spray dried powders are some of the current challenges. Moreover, the need for precise experimental analytical methods for examining the radial distribution of components in spray dried particles is of extreme importance to particle engineering. There is still a need to address the gap in the literature on examining the effect of downstream processing on the stability of ASDs.

Spray drying of biopharmaceuticals remains a developing area of research. The emergence and subsequent withdrawal of Exubera® from the market highlighted both technical and non-technical challenges. In spite of the challenges for spray drying of pharmaceuticals and biopharmaceuticals, this technology is highly promising in terms of its wide range of applications and versatility. Moreover, increasing interest in advancing continuous manufacturing has put technologies such as spray drying at the centre of focus for formulation processing of pharmaceuticals and biopharmaceuticals. Thus, the research in this field is increasingly expanding with exploring new opportunities for spray drying and more fundamental understanding.

Notes

The authors declare no competing financial interests.

Table 8
DoE methods, software packages, optimised input parameters and output responses.

Input factors	Output responses	DoE method	Software
Atomizer gas flow rate, solid content, aspiration rate, feedstock feeding rate, inlet temperature	Yield, volume median diameter, span, outlet temperature	Two phases: 1) 2^{7-3} factorial, 2) Response surface	JMP® Pro Version 10.0.2 (SAS Institute Inc., Cary, NC) (Vinjamuri et al., 2017)
pH, solution concentration, inlet temperature, atomizer gas flow rate, feedstock feeding rate	Yield, (mass median aerodynamic diameter)	Central composite design, 32 samples	Statgraphics® (Warrenton, VA) (Ross et al., 2017)
Solid content, feedstock flow rate, inlet temperature, API/excipient and composition of solvents	Yield, residual solvent, density, crystallinity, dissolution rate, particle size, morphology of ASD formulation of ibuprofen	Custom design, 16 samples	JMP® Pro Version 13.0 (SAS Institute Inc., Cary, NC) (Ziaee et al., 2017)
Inlet temperature, mannitol:drug ratio	Particle size	Central composite design	Design-Expert® software (Stat-Ease, Inc., Minneapolis, MN) (Sun et al., 2015)
Water:organic solvent ratio, feedstock feed flow rate, solid content, atomizing air flow rate, type of organic solvent	Dissolution rate, yield, actual drug load, particle size and crystallinity of diazepam and mannitol	Central composite design, 60 samples	Design-Expert® 10.0.2 software (Stat-Ease Inc., Minneapolis, USA) (Kauppinen et al., 2018)
Inlet, aspiration rate	Yield, α-tocopherol recovery rate	Central composite design	Stat Graphics 5.0, Statistical Graphics Corporation, MD, USA (Bonferoni et al., 2018)
The excipient (PVP K25) concentration, inlet temperature, feedstock feeding rate	Size of redispersed nano crystals of hesperidin	Two phases: 1) Screening, 11 samples, 2) Response surface, 11 samples	MODDE 9 software (Wei et al., 2018)
Acetalated dextran nanoparticles wt%, total feed concentration of mannitol and nanoparticles, inlet temperature	Drug loading, encapsulation efficiency, water content, mass median aerodynamic diameter, geometric standard deviation, fine particle fraction, respirable fraction, emitted dose, percent size change, and percent polydispersity index	Box-Behnken design, 15 samples	Design Expert (Version 8 Stat-Ease, Inc.) (Wang and Meenach, 2017)

CRediT authorship contribution statement

Ahmad Ziaee: Writing - original draft, Writing - review & editing. **Ahmad B. Albadarin:** Writing - original draft, Writing - review & editing. **Luis Padrela:** Writing - original draft, Writing - review & editing. **Tim Femmer:** Writing - original draft, Writing - review & editing. **Emmet O'Reilly:** Writing - original draft, Writing - review & editing. **Gavin Walker:** Writing - original draft, Writing - review & editing.

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