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Powder Production and Particle Engineering for Dry Powder Inhaler Formulations

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Abstract: Dry powder inhalers have become increasingly attractive for pulmonary delivery of locally and systemically effective medications. In comparison to the liquid counterparts, such as nebulisation and pressurised metered dose inhalers, the powder form generally offers better chemical stability, improved portability and potentially superior patient adherence. Currently, the aerosol performance between dry powder inhalers varies to a large extent due to differences in the design of inhaler device and formulation. The particulate properties have a significant influence on the inter-particle interactions, which impacts on the aerosolisation of the inhaled powder. In this review, critical particulate properties that affect aerosol performance are discussed. Recent advances in powder production and particle engineering techniques are also assessed, aiming to develop new inhaled powder formulations or improve the aerosolisation efficiency of existing products.

Keywords: Pharmaceutical aerosol, dry powder inhalers, particle engineering, particulate properties, aerosolisation.

1. INTRODUCTION

Inhaled formulations and pulmonary drug delivery systems have become increasingly attractive to deliver therapeutics for both local and systemic diseases. The direct treatment of respiratory diseases by delivering the active pharmaceutical ingredients (API) straight to the site offers rapid onset of drug action, high therapeutic efficacy and reduced systemic exposure [1]. These advantages are evident in the popularity of inhaled therapies for the treatment of asthma, chronic obstructive pulmonary disease (COPD) and respiratory infections over the last decade, particularly for drugs with low oral bioavailability and high systemic toxicity. For example, bioavailability of oral administration of fluticasone propionate, a corticosteroid, is generally < 1% [2], while inhaled forms of fluticasone provide satisfactory treatment with minimum side effects; its combination products (i.e. Advair® or Seretide®) are among the top pharmaceutical products by sales for many years. For drugs with high systemic toxicity, such as the antibiotic colistin, preclinical and clinical studies have shown that the inhalation route can achieve a markedly higher drug concentration in the airways and substantially lower systemic exposure than the intravenous route, leading to safer and more efficacious therapies against life-threatening respiratory infections [3].

There are three main forms (or inhaler devices) of inhaled therapy available in the market: nebuliser, pressurised metered dose inhaler (pMDI) and dry powder inhaler (DPI). Inhaler devices have been reviewed recently [1] and are only briefly introduced here. Nebulisation is a common practice in clinics for treatment of asthma and COPD, particularly for paediatric usage. Traditional jet nebulisers are bulky and the treatment is time-consuming and inefficient, though more recent devices including vibrating-mesh nebulisers have much greater portability and improved delivery efficiency. pMDIs were the mainstay in the past but are facing issues related to the transition of propellants in some countries like China. Moreover, pMDIs are not able to deliver high doses, which limit its use for high drug-dose medications such as inhaled antibiotics. Consequently, DPIs are becoming the most popular form because in general they are easy to use, portable and the APIs in the formulation are chemically more stable than the liquid counterparts. Therefore, this review focuses on the powder production and particle engineering of DPI formulations.

2. EFFECT OF PARTICULATE PROPERTIES ON AEROSOL PERFORMANCE

Aerosol performance of an inhaled powder depends on two critical steps: aerosolisation from the device, and subsequent deposition in the lungs. Typically, aerosol performance of pharmaceutical products is determined by impinger or impactors (such as the Anderson Cascade, Multistage Liquid Impinger and Next Generation Impactor) and is expressed as emitted dose (ED), fine particle fraction (FPF), fine particle dose (FPD) or mass median aerodynamic diameter (MMAD) [4, 5]. The emitted dose is defined as the total mass of drug recovered from the impactors excluding inhaler and capsule. The FPD is defined as total mass of drug particles with aerodynamic diameter ≤ 5μm. The FPF can be expressed as percentage of FPD to either the total drug dose, the amount recovered from the entire system (inhaler device, capsule, mouth piece and impactor stages), or the ED. MMAD is defined as the aerodynamic diameter at which 50% of the particles are smaller. Physiochemical properties (i.e. particle size, density, particle shape, surface roughness and crystallinity) are critical parameters [4, 6-9] that may be controlled or altered to achieve optimised performance with higher ED and FPF. The influence of particulate properties on aerosol performance is discussed in the this section.

2.1. Size

Particle size is the most influential particulate property that affects aerosol performance and may be expressed as either the geometric or aerodynamic diameter [10]. The geometric diameter refers to physical diameter of the particle, which can be directly measured using light scattering, laser diffraction or image analysis methods [4]. The aerodynamic diameter is defined as the diameter

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of a spherical particle with a unit density that has the same settling velocity as an irregular particle in a flowing air stream [8, 9, 11, 12]. A detailed description of the aerodynamic diameter is beyond the scope of this review, though readers are referred to previous literatures [8, 12]. In brief, a widely accepted model that describes the relationship between geometric diameter, density and the aerodynamic diameter is given by [4, 8];

$$D_a = D_g\sqrt{\frac{\rho}{\lambda\rho_0}} \quad (1)$$

where D_a is the aerodynamic diameter, D_g is the geometric diameter, ρ_0 is the unit particle density, ρ is the particle density and λ is the dynamic shape factor of the particle.

In DPIs, the aerodynamic diameter best describes the aerosolisation behaviour of particles as it considers the gravitational and inertial deposition of the drug in the lungs [4]. While the effect of aerodynamic diameter on deposition mechanisms in the lung has been reviewed elsewhere [13], the optimal aerodynamic diameter that achieves a desirable lung distribution is often quoted as 1–5 μm [8, 10, 12, 14, 15]. Submicron particles (less than 0.5 μm in diameter) are more likely to be exhaled, whereas particles greater than 5 μm in diameter tend to be deposited in the oropharynx/upper respiratory tract [12, 15]. Alternatively, the capillary-rich alveoli region can be targeted with particles in the range of 1–2 μm [9].

Based on Equation 1, decreasing the geometric size is a possible method to achieve particles with small aerodynamic diameters that could reach the deeper airways. On the otherhand, the flowability and dispersibility of powders with small geometric diameter are limited by strong inter-particulate forces, for example the Van der Waals that occur between drug–drug and drug–excipient particles [9, 16]. Therefore, following the same equation, another strategy to obtain a balance between dispersibility and deep lung penetration would be to formulate particles with large geometric diameters and low density.

2.2. Density

One of the widely adopted strategies to formulate particles with large geometric diameter and low density is to make the particle porous. Edward *et al*. pioneered the work that demonstrated large porous particles, with geometric diameters greater than 5 μm but with a low density of 0.4 g/cm^3, were highly inhalable and could be efficiently deposited in the lungs [17]. Furthermore, these porous particles with large geometric size were observed to escape the alveolar macrophage clearance in the lung [17]. Typically, these large porous particles are produced by Air®, which involves spray drying dipalmitoylphosphatidylcholine (DPPC) with albumin and saccharides using ethanol/water co-solvent system [18]. Air® pulmonary drug delivery system has been applied for pulmonary delivery of levodopa [19], salbutamol sulfate [20] and insulin [21].

Air® technology is not the only approach available to alter the density of the particles. PulmoSphere™ technology which involves spray drying a unique emulsion containing pore forming agent such as Perfluoroctyl bromide (PFOB), surface modifier such as calcium chloride ($CaCl_2$) and phospholipid as a dispersion stabilizing agent, was the first to be commercialised for inhaled products [22, 23]. Unlike Air® technology, the porous particles produced by PulmoSphere™ are small (geometric diameter between 1 and 5 μm) with a foam-like morphology [23, 24]. PulmoSphere™ has been applied to dry powder delivery for tobramycin [25], ciprofloxacin [26], budesonide [27], indacaterol, leuprolide, and amphotericin B [23].

Recently, a novel method has been developed for the production of excipient free porous particles [28]. This method involves spray drying a solvent/anti-solvent solution with or without a pore forming agent, such as ammonium bicarbonate. The ammonium bicarbonate decomposes into carbon dioxide (CO_2) producing porous particles that are excipient-free. It should be noted that the pore forming agents used in excipient free porous particles methods such as ammonium carbonate and ammnoum acetate were also discussed in the original Pulmosphere™ patent [24].

2.3. Shape

The dynamic shape factor, λ, is another property that is directly related to the aerodynamic diameter. Elongated particles have a larger dynamic shape factor, which leads to smaller aerodynamic diameters than spherical particles of equivalent mass or volume. In fact, the aerodynamic diameter of elongated particles is dependent on the width rather than their length [29]. This explains that despite having a physical diameter of greater than 10 μm, elongated particles could still be inhaled and deposited in the lungs. Chan *et al*. exploited this aerodynamic advantage [29] and formulated elongated particles of cromoglycic acid [30] and nedocromil [31] with superior aerosol performance for asthma prevention.

The application of elongated particle has been extended to DPIs [7, 32, 33]. Fults *et al*. investigated the effect of particle shape on the ED of dry powdered disodium cromoglycate (DSCG) in DPIs [7]. The $FPF_{(total\ drug\ dose)}$ of elongated DSCG was significantly higher compared with that of spherical DSCG. Likewise, an eight-fold increase in the FPF of steroid KSR-592, was observed when the shape was changed from plate-like to needle-like [33]. However, recrystallisation or polymorphic methods to produce these particles with various shapes would result in particles of different composition, surface structure and/or characteristics and, thus, introduce confounding variables. This would complicate the influence on aerosol performance, as suggested by Chan *et al*. [34]. Recently, Fromen *et al*. [35] utilised the particle replication nonwetting template (PRINT®) to fabricate powders of predetermined composition, shape, size, and surface functionality, allowing for direct comparison of aerosol performance between particles of different shapes. Unfortunately, Fromen *et al*. [35] made no comparison to examine the effect of particle shape on aerodynamic parameters such as FPF or ED. Nevertheless, the superior aerosol performances of elongated rifampicin [32] and rifapentine [36] are favorable for inhalation to deliver anti-tuberculosis therapeutics directly to the site of infection, i.e. the lungs.

Particle shape was also identified as an important factor in minimising device-dependent aerolisation performance [32]. When aerosol performance of spherical and elongated rifampicin were compared using two different inhalers, Aeroliser® and Handihaler®, the difference in performance was less significant for the elongated rifampicin. $FPF_{(total\ drug\ dose)}$ obtained using the Handihaler® and Aeroliser® for spherical rifampicin were 50.9% and 36.6%, respectively, whereas $FPF_{(total\ drug\ dose)}$ was at least 60% for the elongated rifampicin regardless of the type of device or flow rate.

The existing literature shows that aerosol performance is linked to the shape of drug particles [7, 11, 30-34, 37]. Thus, it should be carefully considered when designing DPI formulations. Recently, the efforts have been made towards identifying the optimal particle shape to achieve the maximised aerosol performance in DPIs. Several types of elongated particles have been assessed. For example, cube-, needle-, pollen-, and plate-shaped particles (Fig. **1**) [11] are expected to have different effects. The needle-shaped particles have a smaller contact surface area than plate-shaped particles, but has a relatively large dimension. Due to its large dimension, needle-shaped particles are susceptible to deposition by interception in the upper airway thereby resulting in lower $FPF_{(recovered)}$. Conversely, its smaller contact surface area reduces the Van der Waals forces, and consequently, possesses a higher ED than plate-shaped particle. Pollen-shaped particles seem to have the ideal shape for inhalation, because of its improved flowability, dispersibility and deposition properties compared with the particles of other shapes [11, 37]. However, it is important to note that current evidence supporting the effectiveness of pollen-shaped particles is based on hydroxyapa-

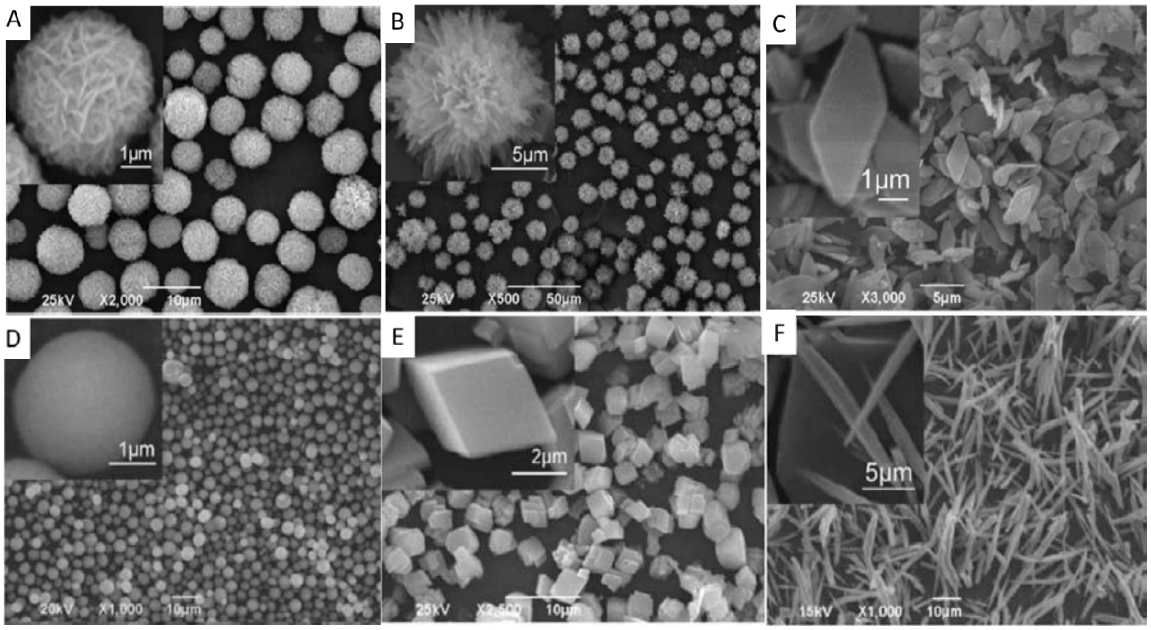

Fig. (1). Scanning electron microscopy images of (**a**) pollen-shaped I HA particles; (**b**) pollen-shaped II HA particles; (**c**) plate-shaped CaC_2O_4 particles; (**d**) sphericxal II HA partilces; (**e**) cube-shaped $CaCO_3$ particles; (**f**) needle-shaped $CaCO_3$ particle. Reprint from [11] with permission by Springer.

tite (HA), which was used as a carrier for inhalation drug delivery. The aerodynamic advantages of pollen-shaped particles are yet to be applied to API.

Alternatively, the aerodynamic advantage of elongated particles could be applied to carrier particles [38, 39]. Previously, a positive relationship was observed between the elongation ratio (ER) of carrier particles and the aerosol performance of the API [38, 40]. Increasing the ER of the carrier particles significantly increased the amount of API delivered to the lungs. This was attributable to longer flowing time of elongated carrier in the lung, which allowed more time for the API particle to detach from the elongated carrier particle [38]. Furthermore, the relative contact area between the API and elongated carrier may be reduced, thereby decreasing adhesion and promoting API liberation during the aerosolisation process [40, 41]. The aerosol performance could be further enhanced by combining elongated carrier with elongated API particles [42]. Unfortunately, the importance and underlying mechanisms of this combinatorial effect is yet to be fully investigated. Further studies are required to determine the optimal ER that can be used to enhance aerosol performance to the greatest extent.

2.4. Crystallinity and Polymorphism

Solid state properties influence both the aerodynamic behaviour and stability. The particles may exist in two different states, namely, crystalline or amorphous [12]. The crystalline state is defined by the degree of ordered structure in a solid particle [4]. An ordered structure comprises the repeating units of three-dimensional brick-like structures mutually connected by non-covalent forces, such as the Van der Waals and hydrogen bonding [12, 43, 44]. On the other hand, the amorphous state lacks long-range crystal order. A crystalline particle may exhibit both crystal and amorphous properties, i.e. being partially amorphous. One example is the formation of a local amorphous site on the surface of a particle as a result of structural dislocation following jet milling [45].

The effects of crystallinity on aerosol performance are complex because changes in crystallinity by particle engineering will also alter other properties (i.e., particle shape, electrostatistic charge and surface energy). Crystallisation processes may manufacture particles with different crystal habits [46]. Since shape is a strong determinant of aerodynamic behaviour, crystal growth processes should be carefully designed and controlled to ensure the production of stable crystalline particles for inhalation with better aerosol performance. Addition of polymers or surfactants such as polyvinylpyrrolidone (PVP), hydroxypropylmethyl cellulose (HPMC), span 85 or lecithin are able to alter the rate of crystal growth as well as the shape of the crystal [47-49]. For instance, PVP K25 was effective in inhibiting salbutamol sulfate crystal growth resulting in formation of block-like particles with a diameter of less than 10 μm. Conversely, the addition of HPMC, lecithin or span 85 to salbutamol sulfate produced needle-like particles [49].

Pharmaceutical crystals may also exist as different polymorphs that can exhibit extremely different physical properties such as solubility, moisture absorption and melting point [50]. More importantly, particles with different polymorphs may also have large variations in aerodynamic behaviour. While this may be attributed to differences in particle shape as well, the most desirable and stable polymorph should be identified and characterised using powder X-ray diffraction and thermal analysis (such as thermal gravimetric analysis and differential scanning calorimetry) [4, 51]. Furthermore, polymorphism in excipients also deserves attention. Lactose, commonly used as a carrier, showed significant differences in its aerodynamic behaviour between its polymorphs such as α-lactose anhydrous, α-lactose monohydrate and β-lactose due to differences in surface energy. The crystal with the highest surface energy (α-anhydrous with surface energy = 220 mJ/m^2) was found to possess the lowest $FPF_{(recovered)}$, approximately 5.5 ± 1.2%, compared to α-monohydrate (lowest surface energy of 120 mJ/m^2) that resulted in higher $FPF_{(recovered)}$ of 19.8 ± 1.1% [52] . Hence, higher surface energy tended to exhibit higher adhesive forces between drug and carrier particles, leading to fewer drug particles that could be liberated during aerosolisation. Another concern with polymorphism is the transformation of particle from unstable forms to stable forms [50], which may occur during the manufacture or storage that could contribute to instability issues in aerosol performance over time.

Additionally, amorphous solids may present another instability issue for DPIs, particularly for many small molecules. Amorphous solids are usually formed when a liquid containing the API is rapidly dried such that the molecules lose their mobility prior to the

formation of a crystalline structure [12, 50]. This often happens in the spray dried formulations of small-molecule APIs, where the thermodynamically unstable powders are prone to chemical degradation and crystallisation into the stable crystal form [51]. Such undesirable crystallisation may occur at ambient environment or at elevated temperature or humidity that depends on thermal properties such as glass transition temperature (Tg) [50]. For instance, amorphous mannitol was found to recrystallise at RH above 50% in a spray dried mixture, which demonstrates the importance of controlled crystallinity to achieve stable formulations [53]. Furthermore, the crystallinity could also influence the aerosol performance of DPIs. Amorphous salbutamol sulfate had an inferior aerosol performance compared with the crystalline form [54, 55]. Consequently, the use of amorphous particles for inhalation has been limited. However, the ability to formulate drugs as amorphous solids is becoming increasingly important in the pharmaceutical industry. Sugar derivatives such as glucose, lactose, saccharose, dextran or sorbitol have been examined to formulate stable amorphous particles that are suitable for inhaled therapy [56]. On the other hand, the instability of amorphous drugs could be minimised by handling and storing amorphous drugs in moisture control packaging. Exubera® and TOBI® Podhaler™are two examples of marketed amorphous drugs that utilised such packaging, thereby possessing a shelf life of 2 and 3 years respectively.

The general concept that crystalline phase possesses a greater stability than amorphous phase has been well established for small molecules, however, this may not be true in some biopharmaceuticals. Pikal *et al*. [57] discovered that amorphous insulin was more stable than its crystalline form. Furthermore, some biopharmaceuticals including proteins (i.e. bovine serum albumin) and peptides (i.e. colistin) were noted to remain stable in the amorphous form at the ambient environment. Zhou *et al*. demonstrated that an amorphous colistin (a polypeptide antibiotic) powder produced by spray drying was both physically and chemically stable over a 3-month period when stored at 25°C and 60% RH [58]. Currently, no studies have reported the underlying mechanism for the superior stability of amorphous biopharmaceuticals.

2.5. Inter-particulate Forces

The inter-particulate forces between particles determine the degree of de-agglomeration which have a significant influence on the aerosol performance of DPIs [9, 59]. There are four main interaction forces: (1) Van der Waal's, (2) capillary, (3) electrostatic and (4) mechanical interlock [4, 60]. Van der Waals' forces are predominately responsible for particle-particle interactions during aerosolisation of powders [60] and are dependent on many factors such as the geometric diameter, surface roughness and particle morphology [61]. The capillary and electrostatic forces are comparable with Van der Waals' forces under certain conditions [9]. Capillary forces become significant when the environmental humidity is relatively high [62], while the influence of electrostatic forces could be remarkable under dry conditions [63]. For DPIs, one typical strategy to improve aerosolisation is to alter the surface roughness of particles to decrease the Van der Waals forces.

2.6. Surface Roughness

Surface roughness of the drug or carrier particles determines the aerosolisation behaviour because it contributes to the particle packing in powder agglomerates and the magnitude of contact area between particles or between particle and inhaler device. For carrier free DPIs formulation, a more corrugated particle surface generally results in less contact area between particles, thereby improving the aerosolisation performance [41, 64].

However, in binary systems containing drug and carrier particles, the influence of surface roughness of carriers on the FPF has not been well understood and contradictory results have been reported. In some studies, the $FPF_{(recovered)}$ of APIs was improved by decreasing the surface roughness of the carrier particles [38]. Carrier particles with corrugated surface formed stronger inter-particulate bonds with drug particles due to physical entrapment of the fine drug particles within the surface clefts and indentations. These findings were in agreement with Kawashima's work which demonstrated that very corrugated surfaces of lactose produced by fluidised bed granulation and resulted in poor dispersion [65]. On the contrary, Chan *et al*. [66] showed that corrugated lactose carriers, produced by coating large lactose particles with fine lactose using a fluid-bed coater, resulted in better aerosol performance. The microscopic undulations produced by the fine particle coating resulted in less contact area between drug particles and lactose carrier surfaces. Hence, the Van der Waals forces between drug particles and carrier surfaces decreased due to less contact area.

These discrepancies are likely to be a result of the different roughness patterns of carrier particles. For lactose carriers, these encompass patterns such as microscopic cavities or large cavities (capable of accommodating one or more drug particles), the interactions between drug particles and carrier surfaces can vary to a large extent. In fact, the ratio between the geometric diameter of API and the width of the cavity is critical to determine the positive or negative effects on aerosolisation. When the drug particle is substantially larger than the carrier surface cavity, the contact area between drug and carrier particles are minimised and thus result in improved dispersion (Fig. **2**). However, if the width of the cavity is greater than the size of drug particle, as shown in Fig. (**2**), drug particle can be trapped in the cavity and lead to increased adhesion and decrease aerosol performance.

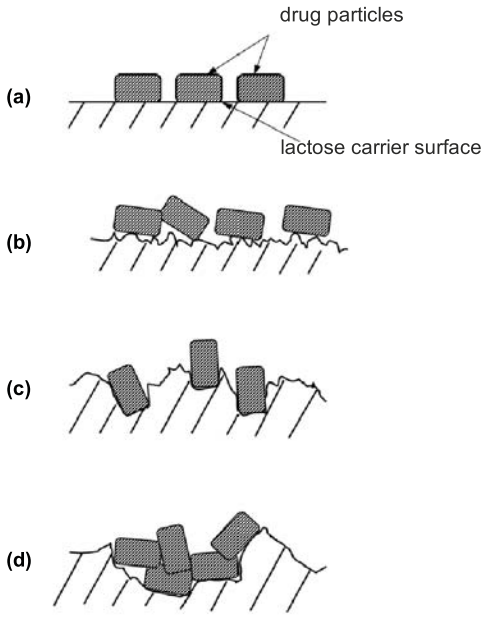

Fig. (2). Influence of surface roughness of carrier on particulate interactions between drug particle and carrier surface: (**a**) smooth carrier surface; (**b**) carrier surface with microscopic asperities that are smaller than drug particles; (**c**) individual drug particles trapped in the carrier surface; (**d**) drug cluster trapped in the carrier surface. Reprint from [184] with permission by Elsevier Limited.

3. POWDER PRODUCTION AND PARTICLE ENGINEERING

3.1. Milling

The conventional method of DPIs production involves crystallisation which provides very limited control in important particle characteristics such as morphology, particle crystallinity, shape and size distribution [12, 15]. In particular, the crystallisation process

usually produces poly-dispersed particles with a size of >10 μm, which is not suitable for pulmonary inhalation [12]. In the pharmaceutical industry, crystalline particles are jet-milled in order to achieve the inhalable particle size [67, 68].

There are several types of jet mills: fluid impact mills, opposed jet mills, spiral jet mills, oval chamber jet mills and fluidised bed opposed jet mills [69]. These have been comprehensively reviewed by Joshi *et al*. [70]. The excess energy supply during the milling process could leads to mechanical activation (i.e. the development of local amorphous site at the surface of the particle) [45, 46, 71-73]. Mechanical activation has been observed in milled salbutamol sulfate [45, 72]. Following micronisation, the local amorphous region could potentially recrystallise during manufacture or storage under ambient conditions [45, 46, 71, 74]. This involves the amorphous region sticking to neighbouring particles, causing particle fusion or aggregation, that undesirably increases the overall particle size [45, 74]. This uncontrolled particle growth following micronisation was reported for revetropate hydrobromide [75]. However, particle size reduction for milled budesonide was reported by Joshi *et al*. [76]. The difference in the observation was most likely a result of different storage environment post-milling, highlighting the importance of environmental conditions in controlling particle properties. For example, the particle size of micronised adipic acid could increase, decrease or remain unchanged depending on the storage conditions, particularly temperature and humidity [77].

In addition, the micronised particles produced by the milling process carry high amounts of charge [9] and are more surface-active [78], which makes the powder extremely cohesive and prone to aggregation and agglomeration [15, 79]. These undesirable characteristics potentially reduce the aerosol performance [80]. Due to the existence of these potential limitations, alternative methods like spray drying [81], spray freeze drying and supercritical fluid (SCF) precipitation [82-87] with enhanced production performance have been developed.

Over the past decade, many studies have attempted to solve the instability issue of jet milled particles. One current approach used by the pharmaceutical industry is to simply store the milled particles for an extended period of time until the particles are physically stable [41, 77]. During storage, the local amorphous sites of the particles undergo structural relaxation to a thermodynamically stable crystalline state but potentially causing the particle size to change [78]. Such a practise is very time consuming and economically impractical as storage time is largely dependent on the hydrophilic and hydrophobic properties of the API [69, 70, 77].

A conditioning or relaxation process was also introduced following jet milling [71]. This step allows the adjustment of the storage conditions to facilitate structural relaxation. Humidity and temperature have been shown to be important in controlling structural relaxation [45, 74, 78, 88-90]. Elevated temperatures may induce the micronised particles into the physically stable form by accelerating recrystallisation or stabilising the amorphous state. When the milled particles are stored at the temperatures below its Tg, the excess moisture of water was removed, thereby stabilising the amorphous state [71]. When the temperature exceeded the Tg, recrystallisation became possible [74], thereby reducing the degree of amorphous content. Regardless of the storage temperature utilised, an undesirable increase in particle size was observed [71]. On the other hand, increasing the humidity of the environment enhanced the conversion from the amorphous to crystalline state [71]. The higher humidity allows the absorption of water, lowering the Tg of the particle, making crystallisation possible [74, 78]. However, this recrystallisation could be accompanied with undesirable particle growth. To date, several optimised conditioning or relaxation process parameters have been proposed for DPIs. For example, conditioning parameters of elevated temperature of 60°C to 90°C for a period of 6-50 h for micronised glycopyloate bromide has been introduced [91]. Likewise, micronised tiotropium bromide was exposed to 25-40°C and 70-80% RH post-micronisation [92].

Temperature and humidity also have a significant impact on the physical stability of DPIs on storage [71]. Although the underlying mechanism remains unclear, particles stored at elevated humidity conditions showed a better physical stability on storage than particles stored at elevated temperatures. It should also be noted that the relative magnitude of cohesive-to-adhesive forces strongly depend on the conditioning parameters and duration [90]. These factors should be considered in particle engineering, as balance of cohesive-to-adhesive forces determine the performance of binary and tertiary carrier-based DPIs [78]. Currently there is a lack of fundamental understanding on the mechanisms affecting the balance of these forces. However, it is clear that humidity-based conditioning significantly altered the balance of the cohesive-to-adhesive forces between fluticasone propionate, lactose monohydrate and salmeterol xinafoate [90].

Lately, in-process conditioning with condition gas such as nitrogen gas has been investigated [89]. The condition gas is mixed with the micronised particles as it travels through the condition zone. Parameters such as humidity, flow rate, temperature, nature of the condition gas and contact time may be controlled in order to obtain the optimal outcome. The amorphous content of the micronised particle produced was reduced by at least 50% and showed superior physical stability [89]. Furthermore, addition of one or more solvent vapours with condition gas has been shown to be useful in eliminating the amorphous content. The choice of solvent vapour depends on the nature of the micronised particles. If a hydrophilic substance is used, then a water miscible organic solvent may be utilised.

In recent years, new production techniques aim to stabilise the amorphous state or speed up recrystallisation by the addition of excipients [73]. Several studies have investigated the physical stabilisation of unstable amorphous form by utilising hydrophilic excipient such as PVP [81]. Alternatively, co-milling with crystalline excipient such as adipic acid, lactose and magnesium stearate was found to be effective in reducing amorphisation [73]. The crystalline excipient acts as a crystal seed inducing recrystallisation of the amorphous particles. Since jet mill can induce instability, the introduction of conditioning step, in-process conditioning and co-milling are novel solutions to resolve the current limitations.

3.2. Spray Drying

Spray drying is an established, one-step process that is both scalable and economical [5, 81]. Briefly, the technique involves atomising the feedstock liquid into fine droplets that are rapidly evaporated in a current of warm air to form dry particles, and the particles are separated and collected (Fig. **3**).

Since the early 1990s, spray drying has been an attractive approach to formulate biopharmaceuticals such as proteins and peptides [93, 94]. The advantage is that particles of uniform size and shape can be obtained with physical diameters in the range suitable for inhalation. One of the challenges associated with spray drying is that most spray-dried materials are amorphous, which may cause a stability issue. However, process and formulation parameters can be controlled to facilitate desirable crystallisation during particle formation [95, 96] or to stabilise the amorphous form. For example, high outlet temperatures achieved using an insulated drying chamber setup significantly increased lactose crystallinity [97]. On the other hand, the amorphous particles produced could be deamorphorised via spray-blending. Spray-blending involves blending two types of spray dried particles [98]. The first type of spray dried particles are produced by spray drying solution containing APIs and hydrophobic excipient, whereas the second spray-dried particles are produced from the hydrophobic excipient only. Spray blending was shown to limit the degree of amorphous content in the final

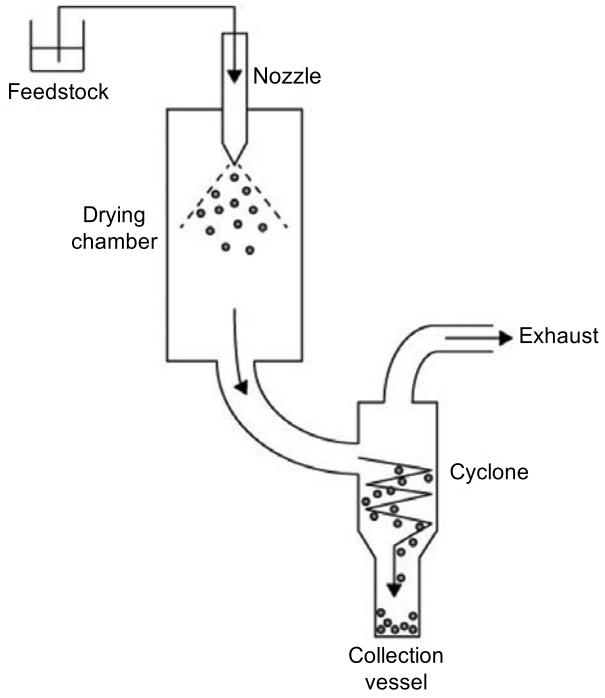

Fig. (3). Schematic of the spray drying process. Diagram not drawn to scale.

spray-fried formulation. Other potential limitations for processing of biotherapeutics by spray drying include degradation from thermal stress during droplet drying, high shear stress during atomisation and possible peptide/protein denaturation due to adsorption at the greatly expanded liquid-air interface of the fine droplets. However, although the drying air temperature can be relatively high (> 100 ºC), the actual temperature of the evaporating droplets could be significantly lower due to evaporative cooling. In practice, the outlet temperature could be optimised with the aim to minimise thermal degradation. Furthermore, the relatively short timescale of the drying process (in the order of milliseconds) may not lead to thermal degradation. A low-temperature spray-drying process (an inlet temperature of 75°C and outlet temperature of 40°C–45°C) was applied to produce powder aerosols of heat-sensitive bacteriophage with trehalose and casein sodium salt as protective agents [99]. Excipients may also be used to minimise instability [100, 101] and many biotherapeutics have been reported to maintain integrity and bioactivity through the optimised process, with or without excipients [102-104]. The aseptic spray drying [105] is now commercially available and gaining popularity to manufacture injectable-grade products such as vaccines, under truly aseptic conditions.

While a review of the numerous spray dryer designs and process parameters have been described elsewhere [95], novel multi-fluid nozzles and the nano-spray dryer are discussed here. Multi-fluid nozzles, coupled to spray drying, include multi 3- and 4- fluid constructions, as well as the more unique 2-solution mixing nozzle that has customisable configurations. The 3-fluid nozzle has two concentric channels that allow the core-forming fluid (containing the drug) to flow through the inner stream and the coat-forming fluid (containing a polymer) to flow through the outer stream [106]. This design is suitable for microencapsulation of drugs in polymeric materials such as Chitosan [107] or PLGA [108, 109] due to the formation of multilayered droplets [107, 110]. Similarly, the 4-fluid nozzle consists of two liquids and two atomising gas channels that can spray dry two feedstocks separately. The acceleration zone is at the tip of the nozzle edge where the two liquid channels collide and mix. The 4-fluid nozzle has been proved to be useful to produce composite microparticles [111-119], though it was unclear whether sufficient mixing occurred. As a result, a customisable 2-solution mixing nozzle was developed to ensure enhanced mixing [119, 120]. Another advance in spray drying technology is the development of the Nano Spray Dryer B-90, which enables direct spray drying and collection of nanoparticle by incorporating a vibration mesh droplet generation system and an electrostatic precipitator. This new type of spray dryer makes it possible to produce particles down to the submicron size range (300 nm), with a narrow size distribution and a high yield greater than 70% [121, 122]. The novel aspects and limitations of the instrument have been further evaluated by Heng *et al.* [122]. To date, this technology has been successfully utilised for excipients [121], model drugs [121, 123-125], proteins [122, 126] and enzymes [126]. Overall, the timely arrival of multi-fluid nozzles and the nano-spray dryer will no doubt contribute to the next wave of developing solid biopharmaceutical fomulations in the new decade and beyond.

In addition, the past decade has seen intensified efforts to understand and control particle formation processes [127-129]. Hence, the design of fine particles for pulmonary drug delivery has seen a shift from empirical and experimentally driven to an engineering approach based on better understanding of inter-related processes and formulation parameters in spray drying [130, 131]. As an example, when a drug solution of concentration C is atomised into droplets of diameter D, the geometric diameter of the spray-dried particle d with density ρ is governed by a simple mass balance:

$$d = \sqrt[3]{\frac{C}{\rho}} D \tag{2}$$

This equation shows that particle size can be directly affected by changes in the concentration of the feedstock, as well as effectively controlled by the atomisation process which determines the diameter of the droplets, D. With regards to particle formation in spray drying, several authors emphasise the usefulness of the ratio between droplet evaporation rate κ and diffusional motion of the solutes D_i (also known as the dimensionless Peclet number, P_e) [130, 132]:

$$Pe_i = \frac{k}{8D_i} \tag{3}$$

Small Peclet numbers (< 1) result in solid particles with a density close to the true density of the dry components. In this case, the diffusional motion of the solutes is fast compared to the velocity of the receding droplet surface during evaporation. On the other hand, high Peclet numbers (> 1) leads to particles with a range of different morphologies. These may include solid hollow spheres, if the shell becomes rigid quickly and does not buckle or fold, as well as dimpled or wrinkled particles. Large Peclet numbers suggest that the receding surface moves faster than the motion of the solutes and, depending on the nature of the formulation, different solidification mechanisms are triggered.

There has also been a movement of dry powder formulations towards combination therapy, particularly with the use of antibiotics for chronic and multi-drug resistant infections. The benefit to patients is clear – one inhaler containing all the respiratory medicines can enhance adherence and minimise the risk of incorrect device use. Adi *et al*. [133] co-spray-dried mannitol-ciprofloxacin to produce a combination that had potential to simultaneously promote mucus clearance in the respiratory tracts and treat local chronic infection in cystic fibrosis patients. Zhou *et al*. developed dry powders containing colistin and rifampicin [134] or colistin and rifapentine [134] that exhibited synergistic antibacterial activity, as well as high aerosol efficiency and protection from moisture. Chan *et al*. [135] further reported a dry powder combination containing three first-line anti-tubercular drugs that could be used to treat drug-susceptible tuberculosis by inhalation. Other combination formulations include triple antibiotics (ciprofloxacin hydrochloride, gatifloxacin hydrochloride, and lysozyme) [136], antibiotics (ciprofloxa-

acin hydrochloride) plus steroid (beclomethasone dipropionate) [137] and antibiotics (ciprofloxacin hydrochloride and gatifloxacin hydrochloride) plus secretolytic agent (ambroxol hydrochloride) [137]. Hoe *et al*., have applied a set of theoretical models including Particle Formation Model, Mass Balance Calculation and Lung Simulation Model to design the target formulations of multi-components (D-amino acid: D-Leucine, D-Methionine, D-Tryptophan, and D-Tyrosine; and trehalose) with optimal aerosol performance [138].

Spray drying can also be used together with other particle engineering techniques such as spray drying emulsions to produce porous particles (Table **1**). Pulmosphere™ technology has employed a unique combined emulsification-spray drying process to produce highly porous drug particles that have showed improved flow and dispersion [22]. Such improved aerosolisation is translated to improved lung delivery efficiency, where the reformulation of tobramycin from nebulisation into a DPI significantly reduced the administered dose from 300 mg twice a day to 112 mg twice a day [139]. The TOBI®Podhaler™ encompasses the notable advantages of DPIs that include markedly reduced administration time (from about 20 mins for nebulisation to under 6 mins for DPI), ease of portability, and improved treatment satisfaction [140]. Other approved DPI products manufactured by spray drying include insulin (Exubera®, Pfizer) and mannitol (Aridol® and Bronchitol®, Pharmaxis Ltd.). Therefore, spray drying is becoming a popular powder production and particle engineering strategy to provide alternative therapeutic options for patients.

3.3. Spray Freeze Drying

Freeze drying or lyophilisation has been the gold standard method for drying biotherapeutics, such as the recently debuted Afrezza® DPI insulin produced using the Technosphere® technology [141, 142]. On the other hand, spray freeze drying presents as an alternative drying method to spray drying for the heat labile therapeutics [143]. It is a two-step technique that involves atomising the feedstock into a freezing medium (commonly liquid nitrogen), which turns the fine spray into frozen droplets, and the cryogenic liquid may be stirred to prevent possible aggregation of the frozen droplets [143-146]. This is followed by lyophilisation to remove the ice via sublimation, thereby leaving behind a powder (Fig. **4**). The setup can be altered to atomise the feed below the surface of cryogenic liquids (such as nitrogen, argon, or hydrofluroethers) [147] or compressed liquids such as CO_2 [148], to minimise exposure of biotherapeutics to the liquid-air interface during atomisation. Since conventional freeze drying is expensive and not readily scalable, atmospheric spray freeze drying has been invented to enable commercialisation of the spray-freeze drying process. In general, this involves drying the frozen particles by a stream of dry cold air inside an insulated stainless steel gas vessel. Mumenthaler and Leuenberger [149] were among the first to report the feasibility of spray freeze drying under atmospheric pressure in 1991. Later studies improved the setup to enable commercial viability [150-152], and the development of atmospheric freeze drying has been reviewed by Claussen *et al.* [153].

Spray freeze drying has the advantages of preserving integrity of biotherapeutics [154, 155], as well as high production yield (could be as high as near 100%) [146] (Table **2**). Due to the phase separation of solids from the ice crystals during freezing, the removal of ice by lyophilisation produces light and porous particles [156] that appear to have enhanced aerosol performance by reducing the particle density [145, 146, 157, 158]. As a result, spray freeze drying has been successfully applied to produce insulin [159], bovine serum albumin [154], trypsinogen [148] as liposomal ciprofloxacin [160] microparticles as well and an influenza vaccine powder suitable for inhalation [161, 162]. Following pulmonary administration to mice, this influenza vaccine induced a potent, systemic immune response which was more enhanced than the conventional intramuscular administration [163]. This demonstrated the good prospects for the implementation of inhalable vaccines as an alternative to current immunisation strategies.

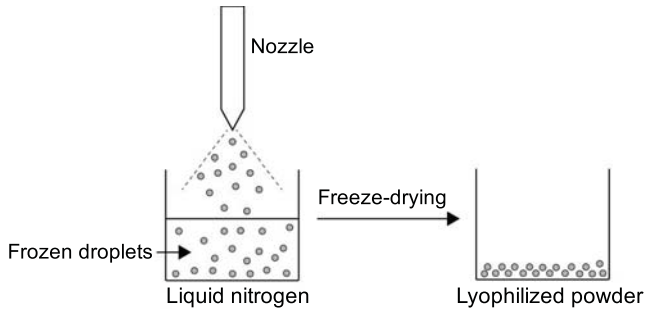

Fig. (4). Schematic of the spray freeze drying process. Diagram not drawn to scale.

3.4. Supercritical Fluid Technology

Supercritical fluid (SCF) technology is a relatively new powder production method that is currently under development. Krukonis [164] was one of the first scientists to apply the SCF to particle engineering [79]. Since then, many different forms of SCF have been utilised in the pharmaceutical industry. The most common and simple one is the Rapid Expansion of Supercritical Solution (RESS) [79] which involves an extractor to solubilise drug particles in a SCF (Fig. **5**). The drug containing SCF is then passed through a nozzle allowing for precipitation of the drug through rapid expansion of SCF in the expansion vessel. In RESS, the most common SCF is CO_2, as it has a very low supercritical pressure (7.4kPa) and temperature (31.2^{o}C) [79]. RESS possesses several advantages over other production methods [165], these advantages are: (1) no organic solvent is required during the process and hence, no organic residual left in the final product; and (2) it's ability to produce particle of narrow size distribution suitable for inhalation. Despite this, the major limitation of RESS relates to the poor solubility of most APIs in supercritical CO_2 [87]. Consequently, this has motivated the development of other supercritical techniques.

Gallagher *et al*. pioneered the work to develop supercritical anti-solvent as a way to overcome poor drug solubility in SCF [166]. This is achieved by dissolving drug in a solvent that is miscible with the SCF (Fig. **5**). Variations of supercritical anti-solvent exist, these consist of solution enhanced dispersion by supercritical fluids, gaseous anti-solvent and aerosol solvent extraction system (ASES) [167]. The particle characteristics are strongly dependent on the flow rate of SCF, temperature and pressure [79, 168, 169].

Other SCF-related inventions include the carbon dioxide assisted nebulisation with a bubble dryer® (CAN-BD), supercritical carbon dioxide assisted spray drying and supercritical fluid-assisted atomisation (SAA) [79, 87, 169, 170]. The main drawback of SCF technologies is that scale up from the laboratory to an industrial level is a challenge [171]. Over the last decade, significant progress has been made with a purpose to achieve the reasonable scale-up for manufacturing of commercial products [172].

SCF is gaining popularity for production of DPIs as it offers more flexibility with respect to the control of particle characteristics, which enables the generation of particles with more uniform shape, size distribution, morphology and crystallinity compared to conventional crystallisation (Table **2**) SCF-produced particles show improved flowability and dispersibility [83], which led to higher $FPF_{(total\ dose)}$ when compared to micronised particles [173]. SCF technology has been successfully applied to several inhaled APIs that consisted of ipratropium [86], steroids such as budesonide [82, 168, 174], salbutamol [84], salmeterol [83], terbutaline [173] and

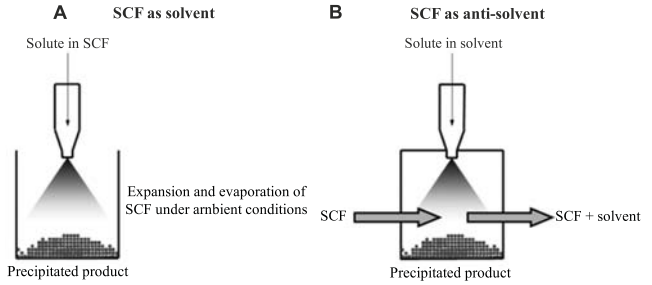

Fig. (5). Schematic of the supercritical fluid process, (**A**) using SCF as the solvent and (**B**) using SCF as the anti-solvent. Diagram not drawn to scale. Reproduced from [206] with permission from Elsevier.

sodium cromoglycate [85]. The addition of excipients, such as albumin, may further enhance aerosol performance. For example, formulations incorporating albumin into SCF-produced terbutaline sulfate and ipratropium bromide exhibited better aerosolisation than formulations without albumin. This enhancement was attributed to reduced agglomeration as a result of the addition of albumin [175].

3.5. Particle Surface Coating

Particle surface coating has been shown to improve the flow, fluidisation and aerosolisation of cohesive particles by reducing cohesive and adhesive forces. The most commonly used force control agents for oral dosage forms are lubricants or glidants. However, traditional glidants such as colloidal silica are unsuitable for inhalation because of the safety concerns, leaving lubricants as the potential candidates. Leucine and magnesium stearate have been extensively examined to coat cohesive inhalable particles through spray drying or other coating techniques (i.e. dry coating). Leucine has been widely examined in research studies but has not been approved for inhalation products to date. Magnesium stearate is recognised as safe for inhalation and approved for aerosol products including Pulmicort® CFC-free metered dose inhaler and Foradil® Certihaler® [176]. Other coating materials of lipids [177] and polymers (ethyl cellulose and PVP) [178] have also shown their capability in reducing agglomeration tendency and improving aerosolisation.

3.5.1. Solvent-based coating

Spray drying is the most commonly used surface coating method for inhalable drug particles. Typically, the coating material has a hydrophobic nature, allowing the coating material to dominate the surface of the spray dried particles. For instance, co-spray drying hygroscopic colistin with hydrophobic rifampicin produced a composite particle with synergistic antimicrobial activities and protection from moisture [179]. The hydrophobic rifampicin dominated the particle surface and controlled the aerosolisation of the composite particles at the elevated humidity, which was confirmed by the advanced surface analytical techniques of X-ray Photoelectron Spectroscopy (XPS) and Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS) [179].

Lately, the development of a newly designed nozzle (3-fluid nozzle) and co-axial ultrasonic atomiser open up a new dimension for dry powder surface coating. 3-fluid nozzle enables the feeding of two separate streams of solution: the core-forming fluid (containing an API) and the coat-forming fluid (containing a polymer) allowing the formation of particles with two distinct layers. Likewise, Pabari *et al*. [110] have successfully applied 3-fluid nozzle spray drying technology to produce diclofenac sodium particles coated with a hydrophobic polymer, ethyl cellulose. Similar to 3-fluid nozzle, co-axial ultrasonic atomisation involves feeding two concentrated liquids at the same time and is typically use for microencapsulation [180]. Alternatively, the second concentrated solution

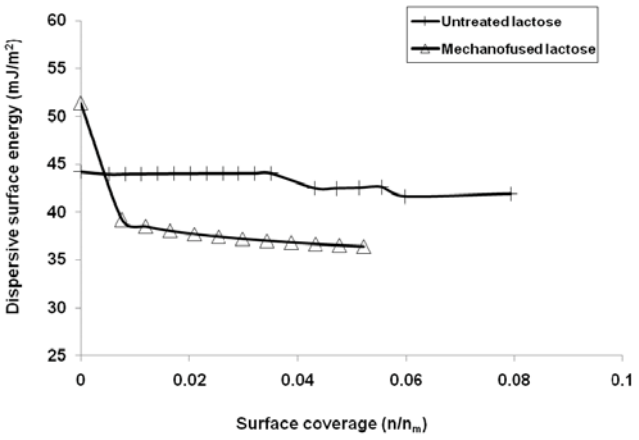

Fig. (6). Dispersive surface energy distribution of dry-coated (*via* mechanofusion) lactose powder determined by inverse gas chromatography at finite dilution. Reprint from [207] with permission by John Wiley and Sons.

(one without APIs) could be replaced by coating material, to form particles coated with desirable coating materials. Undoubtedly, the invention of 3-fluid nozzle and co-axial ultrasonic atomiser will play an important role in the future of particle surface coating. Other solvent-based coating techniques include the aerosol flow reactor method [181, 182], fluid-bed coating [66, 183] and spray freeze drying [143]. Most studies have focused on modification of surface chemistry and only a few attempted to alter physical properties including surface roughness [66].

3.5.2. Dry Coating

Dry coating has attracted interest in modifying surface properties of cohesive particles. Compared to solvent-based coating, dry coating is quicker, safer, cheaper and more environmentally-friendly [184]. There are several dry coating devices available including Mechanofusion®, Hybridiser®, Magnetically Assisted Impaction Coater (MAIC)® and Theta-composer®. While configurations may vary, the principles are similar: intensive mechanical forces are applied to distribute and coat smaller or softer guest particles of coating material onto the surface of host particles. The coating is achieved through high-shear and high-energy interactions between the guest and host particles, which can be either physical and/or chemical bonding, but the true mechanism is unclear [185]. Despite the complex particulate interactions, the operation is simple, straightforward and quick (approximately 5-15 min depending on the material and device) [186].

Magnesium stearate is the most favourable coating material attributable to its capability to form a thin coating film with the thickness down to the nanoscale. This coating film provides extraordinary anti-cohesive or anti-adhesive properties between coated particles or between particle and inhaler device [186]. Dry coating of micronised lactose powder with 2% (w/w) of magnesium stearate, significantly improve the flowability, fluidisation and deagglomeration which contributed to reduced device retention and better dispersion through a Monohaler® device [187]. Furthermore, dry coating of triamcinolone acetonide, salbutamol sulfate and salmeterol xinafoate with 5% (w/w) of magnesium stearate also showed up to approximately a fold increase in FPF [188].

The improvement in aerosolisation after dry coating is believed to be related to the decreased surface free energy. Surprisingly, earlier study showed an increase in surface dispersive energy for the lactose particles coated with magnesium stearate, measured by the infinite dilution method of inverse gas chromatography (IGC) [189]. These observations did not agree with the measured

Table 1. Summary of various production methods utilised in producing porous/hollow particles.

Method of Production	System	Ingredient	Pore Forming Agent	Morphology	Degree of Porosity	References
Double emulsion method	Water/Oil/Water (W/OW) emulsion	Poly(lactic-co-glycolic acid)	Hydrogen peroxide Ammonium bicarbonate Pluronic F127 Sulfobutyl ether β cyclodextrin sodium salt	Porous particles	Porosity could be varied by altering the concentration of pore forming agent.	[191-195]
Spray drying	PulmoSphere™ Disperision stabiliser: Phospholipid (Distearoylphosphatidylcholine, DSPC) Surface modifier: Calcium chloride	Tobramycin, ciprofloxacin, amphotericin B, indacaterol, budesonide and leuprolide	PFOB	Small porous particles with MMAD between 1 and 5 μm	Porosity is controlled by the ratio of PFOB/DSPC	[22, 23]
Spray drying	Air® pulmonary delivery system Dipalmitoylphosphatidylcholine (DPPC) with albumin and saccharides using ethanol/water co-solvent system	Levodopa, salbutamol sulfate, and insulin	DPPC and albumin are responsible for the spokge-like shape of the particles.	Porous particles		[18-21]
Spray drying	Simple solution	Hydroxyapatite	Ammonium bicarbonate	Spherical, hollow particles		[196]
Spray drying	Solvent and anti-solvent (Ethanol: Water or Methanol: Water)	Bendroflumethiazide	Ammonium carbonate	Porous particles		[28]
Spray drying	Solvent and anti-solvent (Ethanol: Water)	Budesonide and ambroxol HCl (mucolytic)	Ammonium carbonate	Hollow or porous, with rough surfaces	Hollow particles were produced when the ammonium carbonate concentration exceeded 35% w/w.	[197]
Spray drying	Solvent and anti-solvent (Methanol: n-butyl acetate with or without water)	Sodium cromoglycate	None	Spherical or non-spherical porous particles	Spherical porous particles were produced via spray drying with methanol:n-butyl acetate: water. Different solvent combinations resulted in particles of different shape and porosity.	[198]
Spray drying	Solvent and anti-solvent (Methanol: Water)	Budesonide	Ammonium carbonate	Porous particles		[199]
Spray drying	Solvent and anti-solvent (Ethanol: Water)	Budesonide	With or without ammonium carbonate	Porous particles		[199]

(Table 1) Contd….

Method of Production	System	Ingredient	Pore Forming Agent	Morphology	Degree of Porosity	References
Spray drying	Solvent and anti-solvent (Methanol: n-butyl acetate)	Raffinose or trehalose	None	Nanoparticles aggregated in cluster to form large particles with pores		[200, 201]
Spray drying	Suspension	Hyaluronic acid	Polystyene latex (PSL)	Spherical, porous particles with well-defined pore sizes.	The size of the pore and the porosity could be easily altered by changing the concentration and size of the PSL particles.	[202]
Spray drying	Solvent and anti-solvent (Methanol: n-butyl acetate: Water)	Trypsin	None	Porous particles		[203]
Spray freeze drying	Water	Mannitol, lysozyme, bovine serum albumin or budesonide	None		The porosity is controlled by the concentration of the active ingredient.	[204, 205]

Table 2. Advantages and disadvantages of various powder production approaches.

Powder production approach	Advantages	Disadvantages
Jet milling	- Established method.	- Particles have poor flowability and dispersibility as well as high surface charges. - Excess energy induces surface amorphisation, which contributes to chemical and physical instability.
Spray drying	- One-step process that is scalable and economical. - Produces particles with physical diameters in the inhalable range. - Versatile process that can control particle size, morphology, and surface composition to optimise aerosol performance.	- Many materials undergo amorphisation, which may cause stability issues (In practise, it is possible to control the physical form by controlling the spray drying conditions and adding additives) - May not be suitable for therapeutics that cannot withstand thermal stress, shear stress during atomisation. However, the process may be optimised to overcome the issues.
Spray freeze drying	- Alternative to spray drying for therapeutics that are heat-labile. - Offers potentially the best preservation of integrity for biotherapeutics that are not sensitive to cryogenic stress. - Often produces light and porous particles. - High production yield.	- May not be suitable for therapeutics that cannot withstand cryogenic stress and shear stress during atomisation. - Porous particle may be fragile - Long processing timescale
Supercritical fluid	- Stable and pure particles without any solvent residues. - Able to produce micronised particles with narrow size distribution suitable for inhalation. - Relatively simple to use, a single step process. - Green technology, the supercritical fluid is recyclable.	- Difficulty in scale-up. - Difficulty in predictive control of particle size and morphology.

increases in FPF and improvement in flowability. Zhou *et al*. proposed dry coating process creates a small area of high surface energy, while the majority of the surface has a low free energy [186]. The infinite dilution method of IGC only measures very small area of surface with the highest surface energy, therefore the high value of surface energy measured by the infinite dilution of IGC does not represent the whole surface. In contrast, finite dilution method of IGC is able to measure the distribution and heterogeneity of surface energy. When finite dilution method of IGC was utilised, only very small area of surface (< 1%) of dry coated particles with magnesium stearate exhibited high dispersive surface energy (Fig. **6**) [186]. Once the measured area was increased to 1% of the total surface, dispersive surface energy dropped sharply and was much lower than that of unprocessed lactose particles [186].

Co-jet milling of drug particles with the coating material may also provide surface coating to achieve low surface energy. Stank and Steckel have demonstrated the dispersive surface energy of micronised salbutamol sulfate was lowered after co-jet milling with magnesium stearate and the energy distribution was more homogenous [190].

CONCLUSION

Novel technologies have been explored to engineer inhalable particles with an aim to accommodate the requirements of new emerging DPI therapies such as high-dose antibiotics and high-value biopharmaceuticals, as evidenced by the TOBI® Podhaler™ (tobramycin DPI) manufactured by the Pulmosphere™ technology and the Afrezza® (insulin DPI) produced by the Technosphere® technology. It is expected that the next decade will see more successes in transferring innovation to commercially-available products, which will become the next generation of inhaled therapies with safer and more effective therapeutic profiles.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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