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Expert Review

Particle Engineering for Pulmonary Drug Delivery

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Abstract. With the rapidly growing popularity and sophistication of inhalation therapy, there is an increasing demand for tailor-made inhalable drug particles capable of affording the most efficient delivery to the lungs and the most optimal therapeutic outcomes. To cope with this formulation demand, a wide variety of novel particle technologies have emerged over the past decade. The present review is intended to provide a critical account of the current goals and technologies of particle engineering for the development of pulmonary drug delivery systems. These technologies cover traditional micronization and powder blending, controlled solvent crystallization, spray drying, spray freeze drying, particle formation from liquid dispersion systems, supercritical fluid processing and particle coating. The merits and limitations of these technologies are discussed with reference to their applications to specific drug and/or excipient materials. The regulatory requirements applicable to particulate inhalation products are also reviewed briefly.

KEY WORDS: aerosols; crystalline and amorphous solids; inhalers; micro- and nanoparticles; micronization; particle size; respiratory drug delivery; spray drying; spray freeze drying; supercritical fluids.

INTRODUCTION

Recent advances in inhalation therapy have sparked considerable biomedical interest in the development of novel particle technologies for respiratory drug formulation. Introduction of new potent medicines in various therapeutic areas such as asthma, chronic obstructive pulmonary disease (COPD) and various infectious diseases has necessitated an accurate and consistent dosing with inhalation devices. There are many emerging inhalation products with new absorption mechanisms and/or rapid onset of action for systemic therapies (e.g., for the treatment of diabetes, osteoporosis, pain, erectile dysfunction), and their effectiveness is closely related to their efficiency of delivery to the lungs. Preparation of powders suitable for inhalation and loaded with biomolecules is also of particular interest for gene therapy and vaccination. Multi-dose dry powder inhalers (DPIs) capable of delivering high dosage loads have rapidly evolved over the last decade despite the fact that they are probably the most difficult and expensive formulation system to develop. Nanoparticles have proved highly beneficial for liquid formulations, particularly for "soft-mist" inhalers. Controlled and sustained release with composite particles is another application area holding promise for both local and systemic drug deliveries. In addition to the above drug delivery advantages, an advanced particle technology can further improve the pharmaceutical manufacturing process by affording better quality control over the particulate and solid-state properties as well as ensuring better product consistency and process economics for many inhalable drugs.

The inhalation dosage technology has primarily been focused on two parallel development pathways: fabrication of novel inhaler devices with enhanced efficiency and improvement of the existing inhalation formulations (1). It is well known, for example, that DPIs of the first generation commonly exhibited a relatively low efficiency (10–15%) in terms of the fine particle fraction (FPF) and, even more seriously, inconsistency in the emitted dose (ED) (1,2). This may be explained by the sensitivity of the dose delivery from DPIs to the inhalation flow rate, but it can also be ascribed to common formulation problems such as particle adhesion and static charges, which are largely responsible for material retention in the delivery device, reduced dose metering uniformity and insufficient deaggregation of particles in the airflow. Although these problems can be partially resolved by designing more sophisticated inhalers utilizing active dispersion of respiratory powders, electronic synchronization and actuation control, such delivery devices are complex and costly, and their reliability and practicality have been questioned. On the other hand, superior delivery efficiency may be achieved more cost-effectively by developing optimized particulate formulations for use with simple and user-friendly inhalers. This alternative strategy, which is synonymous with the controlled production of drug particles in pure physical forms or with carriers as composite materials of optimized size, morphology and structure, can be broadly referred to as "particle engineering." In practice, various options for engi-

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neering particles with the desired properties are available, encompassing direct particle formation techniques, post-process particle conditioning, optimization of the milling processes and various novel formulation approaches for the inhalation systems. The main goal of particle engineering is to incorporate into the particles desirable attributes such as narrow particle size distribution, improved dispersibility, enhanced drug stability, optimized bioavailability, sustained release and/or specific targeting (3), taking into account the specifics of inhaler design and drug delivery requirements. A practical particle engineering process has to be significantly advantageous for the final drug product, consistent and economically feasible at the required industrial scale. Ideally, it should be able to reduce the manufacturing complexity and costs associated with GMP manufacturing of inhalable drugs and to provide new opportunities for continuous and environmentally benign production.

The present article is intended to provide a critical account of the current goals and technologies of particle engineering for the development of respiratory drug delivery systems. The complex nature of interparticulate interactions on the lower micron-size scale together with the extensive application of dry powder formulations and the specifics of aerodynamic behavior within the inhaler devices and respiratory system have rendered such dosage form development one of the most challenging pharmaceutics area. In what follows we commence with some theoretical discussion on the physicochemical requirements of respiratory formulations, followed by a literature review of different particle engineering techniques with special emphasis on those which have progressed from a purely conceptual state to more extensive industrial evaluation. The broad and multifaceted spectrum of references cited here reflects the enormous variety of issues and challenges that have to be addressed in respiratory particle engineering.

REQUIREMENTS OF RESPIRATORY PARTICLES

General Considerations

The overall efficiency of any inhalation system is given mathematically by the product of the fraction of emitted dose (ED), dose delivered to the lung (i.e., fine particle fraction, FPF) and lung bioavailability. Both ED and FPF are normally determined *in vitro* using a multistage cascade impactor (MSCI) (4) and predominantly governed by both the particulate properties and inhaler design. FPF is measured as the mass of particles (with reference to the ED) below a certain cut-off diameter (e.g., 4.7 μm, which is below the Andersen Cascade Impactor stage 2 (4)). The bioavailability is influenced not only by the nature of the drug, its *in vivo* molecular permeability and metabolism but also by the particle size and shape through their effects on the dissolution rate and phagocytic clearance in the lung (3).

Engineered in the lower micron-size range, solid particles for pulmonary delivery can exhibit markedly different aerosolization behaviors, depending on the complex nature of interparticulate interactions, the type of formulation and inhalation device, inhalation flow rate and breathing pattern. Table I lists the fundamental physical parameters influencing the therapeutic performance of respiratory formulations. The desirable product characteristics include high FPF and ED, high dose consistency and uniformity and, ideally, independence of the type of device and inhalation flow rate. Thus, apart from the correct aerodynamic particle size (often expressed as the mass median aerodynamic diameter, MMAD), the particles should have a relatively narrow particle size distribution (PSD) and should be readily aerosolizable at relatively low aerodynamic dispersion forces (5–7). Additionally, the requirement of physical and chemical stability implies that storage must not have a significant effect on the drug's physical form (e.g., crystallinity, polymorphism), PSD and/or the dose content uniformity. The latter usually means negligible caking in the DPI container, blister or capsule or slow sedimentation and ease of dispersion when formulated into the metered dose inhalers (MDIs) or liquid nebulizers.

Particle Aerodynamic Diameter

The aerodynamic diameter, d_A, is defined as the diameter of a sphere of unit density, which reaches the same velocity in the air stream as a non-spherical particle of arbitrary density. This diameter defines the mechanism of particle deposition in the respiratory system. A more detailed analysis and the concept of aerodynamic particle diameter

Table I. Particulate Properties and their Effects on Respiratory Drug Delivery

Particle Characteristics	Effects on Formulation
Process parameters: temperature, pressure, solvents, pH, additives, yield, recovery, manufacturing complexity	Process economics, development risks and costs
Solid state: crystallinity, polymorphism, hygroscopicity, impurities, solubility, dissolution rate	Physical and chemical stability, bioavailability, toxicity
Particle size distribution, shape, porosity/density	Aerosolisation behaviour, *in vitro* and *in vivo* deposition profiles, bioavailability
Surface morphology, energetics and electrostatics	Powder handling, inhaler filling, dose metering, storage stability, shelf-life, dose uniformity and consistency
Powder bulk density, agglomeration, cohesiveness, flow properties	Dose uniformity
Co-formulation/blending; composition/coating	Modified or extended release, toxicity
Formulation, dispersion media	Type of inhaler
	Mode of administration

and shape factor in relation to the inhalation and cascade impactor measurements are considered in our previous review (4). It has been shown that the aerodynamic diameter (d_A) generally depends on the airflow (particle Reynolds number, *Re*) as well as the particulate properties (geometric size, shape and density) and can, therefore, be calculated numerically using semi-empirical models. The well-known relationship depicted by Eq. 1 below, though strictly applicable only at the Stokes flow regime of $Re < 0.1$, can be used to estimate the aerodynamic diameter:

$$d_A(\text{Stokes}) \cong d_V\sqrt{\frac{\rho}{\chi\rho_0}} \tag{1}$$

where d_V is the *volume-equivalent diameter*, ρ_0 is the unit density (of spherical calibration spheres), ρ is the particle density and χ is the *dynamic shape factor*, defined as the ratio of the drag force on a particle to the drag force on the particle volume-equivalent sphere at the same velocity. Thus d_A can be reduced by one or more of the following manipulations:

(a) Decreasing the volume-equivalent particle diameter (d_V)
(b) Reducing the particle density (ρ)
(c) Increasing the particle dynamic shape factor (χ)

Traditionally, reduction of d_V has been effected for solid drug particles by micronization, usually by jet-milling. Decrease of both particle density and size is currently achieved by spray-drying (8–10) or more recently, by spray-freeze drying (4,6,11,12). Theoretically, a smaller d_A can also be obtained with particles of non-spherical shapes, such as platelets, rods or fibers (5,7,13,14), because the χ value for such particles can be as high as 10 (4). In terms of aerodynamic performance, changing the "ruggedness" of particle surface, as quantified by the surface fractal dimension (4,15), is analogous to a simultaneous reduction of the particle density and increase of the dynamic shape factor. However, for all these non-spherical shapes, deagglomeration may depend more on the particle packing as shown next.

Interparticulate Interactions, Surface Energetics and Particle Dispersion

In addition to the aerodynamic diameter of primary particles, the dispersibility of the particles has to be taken into consideration for defining the overall particle size distribution and deposition during inhalation (4,12). It should be noted that the magnitude of the interparticulate forces per se, which is so often stressed in the literature, may not adequately account for the dispersion phenomenon observed. This is because both the aggregate strength and aerodynamic forces generated, being dependent on the force per unit area (at contact point or particle projection), should be more appropriately defined in terms of *stress* which is also a function of the aggregate structure. Thus dispersibility of powders in the airflow is defined by the balance of the aerodynamic stress and the aggregate (agglomerate) strength. When the aerodynamic stress exceeds a certain level, the primary particles forming an aggregate can disperse simultaneously and thus penetrate deeper into the respiratory system. The aggregate strength, σ (N/m^2), consisting of uniform particles can be estimated using the following equation (16):

$$\sigma \cong 15.6\phi^4\frac{W}{d_V} \tag{2}$$

where ϕ is the packing fraction expressed as the ratio of the powder bulk density to particle density (ρ_B/ρ) and W (J/m^2) is the (non-equilibrium) specific work of cohesion between particles. It is assumed here that the mean curvature of non-spherical particles increases in proportion to the volume equivalent diameter, d_V, although in some instances, the volume-surface equivalent diameter may be a better approximation (5,7). For respiratory formulations, the strength of the aggregates is proportional to the work of cohesion (drug–drug interaction) or work of adhesion (e.g., drug–lactose interaction). Since the lactose and drug particles can differ in size by an order of magnitude, the effective interaction diameter can be taken as the harmonic mean of the drug and lactose diameters:$d_V \approx d_1d_2/(d_1 + d_2)$, according to the Hamaker approximation for van der Waals' forces (17). It has been suggested that the dispersion process in the DPIs typically occurs at the viscous turbulent stress between 1–30 N/m^2 (4,18,19). It should be noted that capillary forces associated with adsorbed moisture can generate forces comparable to or greater than van der Waals' interactions. Therefore most of the theoretical predictions and experimental measurements are only valid for dry powders at low RH.

Electrostatic charge and associated Columbian forces may also exert a significant influence on particle dispersion, and for certain materials, such interactions are comparable in strength to the van der Waals' forces (15,20). The ED is strongly influenced by the electrostatic deposition in the inhalers and on the mouthpieces, and differently charged particles may promote particle agglomeration.

Direct experimental determination of the aggregate strength is technically very difficult, and hence various theoretical approaches have been used to estimate this parameter on the basis of particle surface energy. One of the approaches is to use the data obtained by inverse gas chromatography (IGC) to calculate the relative strength of the cohesive (σ_C) or adhesive (σ_A) interaction from the total (Hildebrand) solubility parameters, δ_C and δ_A, for the respective interactions, based on the following relationships (21):

$$\sigma_C = 0.25\delta_C^2 \tag{3a}$$

$$\sigma_A = 0.25\theta\delta_C\delta_A \tag{3b}$$

where θ is the interaction parameter, which can also be determined by IGC (21). The total (Hildebrand) solubility parameters can be computed from the Hansen component parameters for dispersive forces, polar interactions and hydrogen bonding by multiple linear regression analysis as described previously by Tong *et al.* (22,23). The work of cohesion or adhesion, W_C or W_A, can be assumed to be directly proportional to the strengths of the cohesive (σ_C) and adhesive (σ_A) interactions, respectively (5). The follow-

ing conclusions can be generated from the above theoretical analysis:

(a) The aggregate strength decreases with increased d_V.
(b) Low powder bulk density, ρ_B, affords loose and weak aggregates.
(c) Decreased particle surface energy (expressed through the parameters σ_C or σ_A) promotes dispersion.
(d) Particles with an irregular surface have a smaller aggregate strength than a smooth particle of the same d_V, because of reduced contact area and reduced interparticulate forces.

The first effect is well known for porous or hollow particles which have a relatively large d_V value compared with their d_A. The low powder bulk density has been observed for some non-spherical irregular particles produced by supercritical fluid (SCF) precipitation (5) and this may partially explain their enhanced performance in the cascade impactor tests (24). The favorable influence of low surface energetics on the dispersion of respiratory formulations has also been widely discussed in the literature. For pure drug crystals, reduction in surface energy was observed with some SCF-processed powders (5,22–25). For formulations, a number of strategies have been successfully developed to enhance particle dispersion with additives capable of lowering the particle surface energy. For example, reduced particle agglomeration was achieved by co-formulation with either force-controlled additives, FCA (26–28) or fine lactose particles and low-density additives such as L-leucine (28,29). As an alternative carrier to lactose, different forms of trehalose, mannitol, menthol and materials that are endogenous to the lungs such as albumin and dipalmitoylphosphatidylcholine (DPPC) have also been considered (30,31). It has also been shown that irregular particle morphology can significantly lower the interparticulate interactions and increase the FPF for solid corrugated particles produced by spray-drying (32) as well as for carrier particles (33). The same effect may be mimicked by micron-sized particles coated by a layer of low-adhesion nanoparticles (26). Similar principles can be applied to powders intended for formulation into suspensions for pMDIs. In such formulations, the production of particles with enhanced surface properties is critical for preventing aggregation and sedimentation of suspensions in the pressurized devices, as most of the widely used surfactants have poor solubility in the alternative hydrofluoroalkane (HFA) propellants.

Based on the above considerations, it is apparent that particle dispersion is governed by multiple interrelated parameters such as powder and particle density, particle size and aggregate structure, particle shape factor, surface morphology and surface energy, in addition to the nature of the aerodynamic dispersion forces, which also vary with the type of inhaler used. It is often difficult to pinpoint which of these factors exerts the most dominant impact on the dispersion process, as it is not always possible to resolve or quantify them. For example, surface energetics of some materials, notably amorphous and composite particles, may be difficult to assess using IGC because of the complex nature of the dispersive and polar interactions measured by this technique (28,34). The work by Schiewe and Zierenberg (35) showed that even employing a combination of analytical approaches such IGC, atomic force microscopy (AFM) and powder density measurements may afford no predictive capability for ranking the micronized drugs according to their FPF with the Handihaler® device, although many other studies appear to suggest otherwise. It has been pointed out by Chow *et al.* (36) that a typical IGC analysis, based on infinite dilution of liquid probes, may not give an adequate or complete picture of the energy distribution of the whole particle surface. In addition, the contribution of the entropy to the total surface free energy is substantial and can only be taken into account when a series of measurements are taken at different temperatures (22). Thus it has been concluded that particle dispersion is a very complex phenomenon and, in order to properly assess the impact of each contributing factor, the particulate properties have to be tightly controlled, leaving the property of interest the sole or most dominant independent variable in the study (28).

The intimate link between particle dispersion and FPF is probably one of the major reasons why cascade impactor measurements remain the primary technique of choice for both the development and QA/QC testing of commercial inhaler products (4). Since the FPF measured by such devices is a function of both the aerodynamic particle diameter, d_A, and particle dispersion characteristics, it would be a logical approach to plot FPF *versus* d_A as a measure of particle dispersion for different formulations. However this would require additional time-of-flight (TOF) measurements, which are not readily available (4). Fortunately, the geometric volume particle diameter, d_V, is frequently reported in the literature together with FPF. Figure 1 presents a plot of FPF as a function of d_V for particles prepared by different technologies. High FPF is characteristic of porous particles with relatively large d_V produced by spray-drying and spray-freeze drying. The best results are seen for small solid particles (1–2 μm size range) obtained by surface modification techniques and for corrugated/porous particles. Particles prepared by supercritical antisolvent (SAS) precipitation have better dispersion characteristics than micronized materials but often cannot be produced at the optimum size (i.e., between 1 and 2 μm). Apparently, the large deviation of data in Fig. 1 is a result of the different types of formulations, inhalers and cascade impactor techniques used.

Particle Deposition, Uptake and Dissolution

The particle size and morphology have a pronounced effect on all aspects of drug delivery to the lungs, including deposition, dissolution and clearance mechanism. Particles below 5 μm can be distributed deep into the smaller airways and this penetration correlates well with good clinical response for local treatment (2). The particle fraction with d_A in the 1–2 μm range is probably the most efficient for deposition into the capillary-rich alveolar airspaces. This is the target for the systemic delivery of drugs which are less efficient or less convenient when delivered by other routes. For this size range, the other main mechanisms of particle deposition—diffusion and sedimentation—become more important due to very low air velocity in this part of the lungs (4). Submicron particles ($d_A < 0.5$ μm) can be exhaled, if they are not aggregated and/or if insufficient time is available for their migration to the lung walls. Therefore slow deep breathing and breath holding aid deposition of such small

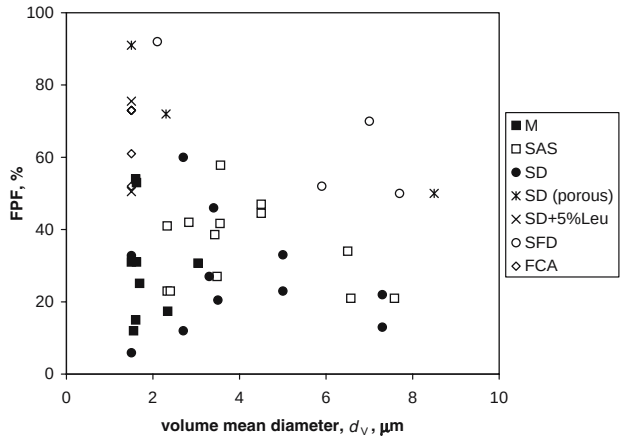

Fig. 1. Compiled data showing fine particle fraction, *FPF*, *versus* the volume mean particle diameter, d_V, for different materials: *M*, micronized (5,12,26,224,227,230), *SAS*, produced by supercritical antisolvent precipitation (5,12,26,224,227,230), *SD*, solid spray-dried (28,167,188,252), *SD* (*porous*), porous spray-dried (120,121). *SD + 5% Leu*, spray dried with 5% leucine additive (28), *SFD*, spray-freeze dried (188; Shekunov, unpublished data), and *FCA*, micronized particles modified with force-controlled additives (26). The d_V, values were typically obtained using laser diffraction analysis or from SEM image analysis. Although different inhaler devices and airflow rates were used, most cited research dealt with comparison of two or more formulations under the same measurement conditions.

particles. It has been suggested that particles of acicular shapes (fibers) can be more efficiently deposited on the wall because of the particle interception i.e. physical entanglement of long particles by the wall even if the particle center of mass moves with the air stream (37). Computational models have also shown that electrostatic properties of aerosols can contribute to the deposition via electrostatic attraction between the particle and opposing induced charge on the walls (15). Such interactions naturally depend on the particle hydrophobicity and relative humidity (RH) although the exact mechanisms involved are unclear (15).

Fine micron particles deposited in the conducting airways are normally cleared by mucociliary escalator within several hours. Particles that penetrate the lower respiratory tract but are not solubilized immediately may adhere to the epithelial lining and be cleared more slowly. However, the shortened drug action associated with the relatively rapid clearance represents a significant challenge to drug delivery to the lungs (3). Particles of large volume diameter such as porous particles usually show a better bioavailability than solid particles of the same volume diameter either because of their improved dissolution rate (larger specific surface area; see below) which is advantageous for immediate release, or because of their size-related delaying effect on the phagocytic clearance, which can afford sustained action up to several days (3). Compared with micron particles, nanoparticles are deposited in much greater number concentration and, therefore, their phagocytic clearance can be delayed (38). In addition, nanoparticles of poorly water-soluble drugs have higher overall dissolution rate. These two factors in combination may lead to enhanced bioavailability for drug particles engineered in the nanosize range. A specific case can be made for ultrafine nanoparticles (<150 nm), which exhibit different interactions with both the trachea-bronchial and alveolar epithelia. Specifically, such particles showed delayed lung clearance, increased interaction/binding with certain proteins and enhanced translocation from the epithelium into circulation and subsequent target organs (38). Although these properties may pose safety hazards for water-insoluble substances, they are worthy of further investigation for potential application in targeted drug delivery.

Different particle shapes are also cleared at different rates, as well exemplified by certain fibers which can be entrained into epithelia and which are also more difficult to engulf by the macrophages, especially for fibers longer than 5 µm (39). Particles of the "rugged" morphology (particularly those with ruggedness comparable to the particle dimensions) as well as particles engrafted with long polymer chains, such as PEG, cannot be efficiently cleared due to their increased equivalent volume diameter, and such surface characteristics may be exploitable in sustained release formulations.

Finally, particle dissolution is governed by several factors which can be described by the following modified form of the Noyes–Whitney kinetic equation (40):

$$\frac{dm}{mdt} = \frac{k_d k_s}{k_d + k_s} s(c_0 - c) \tag{4}$$

where $dm/(mdt)$ is the fraction of mass dissolved per unit time, s is the specific surface area, c is the concentration of the drug in the bulk and c_0 is the equilibrium concentration of the drug in solution (i.e., solubility). The total mass-transfer coefficient for dissolution is defined by both the diffusion (k_d) and surface kinetic (k_s) coefficients. It has been shown that for the poorly soluble drugs, k_d is much larger than k_s and k_s is approximately equal to 10^{-4} ms^{-1}, which is further reduced for polymer-drug particles by at least two orders of magnitude (41). Thus, it can be inferred that the dissolution process for poorly soluble particles and sustained release formulations is mainly governed by the surface dissolution kinetics and the specific surface area (or particle size). For highly water-soluble drugs, the effect of diffusion becomes more important and for submicron particles, both the surface curvature and surface energy come into play (40).

Solid-State Form and Structure

The physical stability and solid-state structure of particles need to be considered in conjunction with their aerodynamic performance and dissolution behavior. As a rule, pure solid drug particles used in different DPIs and MDIs formulations are required to be crystalline and in the most stable form to avoid any potential changes associated with solid-state transitions. Crystalline particles are typically non-spherical, have low-energy surfaces and are stable thermodynamically; however, they have a relatively high particle density and tend to pack more tightly with a high tapped bulk density. For ensuring the therapeutic effectiveness of the inhaled particles, consideration may be given to an amorphous form for the purposes of achieving rapid dissolution and absorption, stabilizing biological molecules

and/or formulating drugs into sustained-release biodegradable polymeric microspheres or microcapsules. Some drugs, notably therapeutic proteins, cannot be prepared in crystalline forms. Large porous particles that are highly advantageous for respiratory drug delivery are normally amorphous. Many composite particles containing active ingredients as well as stabilizing and/or absorption enhancement excipients are also amorphous or partly crystalline. It should be noted that the current list of excipients approved by regulatory agencies for respiratory drug delivery is very limited, and in the United States, the choices are confined to lactose, lecithin, mannitol, and polysorbate (Tween). Other substances not in the list have to undergo stringent toxicity assessment, which would add uncertainty to the drug product development.

Following from the above discussions, an advanced respiratory formulation should possess the following optimal characteristics for efficient pulmonary delivery—narrow aerodynamic particle size range, low surface energy and charge, non-spherical morphology, low density or high porosity as well as high physical and chemical stability. However, it would be extremely difficult, if at all possible, for a particulate formulation to acquire all of these properties concurrently. Nevertheless, these attributes have formed the basis of the numerous formulation strategies utilizing a combination of particle technologies and excipients to develop the most desirable inhaled dosage forms, as discussed next. The typical product forms, major advantages and challenges of key particle technologies for formulating inhalation products are summarized in Table II.

Table II. Comparison Between Different Particle Formation Techniques

Method	Typical Product Forms	Major Advantages for Respiratory Drug Delivery	Challenges
Micronization and blending	Dense, irregularly shaped, crystalline particles	Established, proven	Cohesiveness, amorphous domains, poor powder dispersion due to electrostatic charges
Spray-drying (SD)	Solid or low-density composite amorphous particles	Developed, simple	Thermal degradation, protein aggregation, solid-state instabilities
Spray-freeze drying (SFD)	Low-density composite amorphous particles with high specific surface area	Processing of heat-sensitive compounds (biomaterials), dissolution rate enhancement	High processing cost, underdevelopment
Emulsion-based	Solid composite particles, drug particles with narrow particle size distribution	Production of controlled release formulations, micro- and nanosuspensions	Manufacturing complexity, slow production rate, large waste streams, residual solvent removal
Supercritical antisolvent (SAS)	Low-powder density crystalline particles	Pure, stable, non-cohesive powders	Particle size control, material-specific

DRUG MICRONIZATION AND POWDER BLENDING

Milling Techniques

The majority of currently marketed inhalation products such as DPIs, MDIs and suspension nebulizers consist of micronized drug in either agglomerated or blended form. Such particles are normally produced by batch crystallization, followed by filtering, drying and micronization. The particle size reduction can be achieved by pressure, friction, attrition, impact, or shear. Vibration milling, ball milling and, in particular, jet-milling (fluid energy) are well-established and well-validated techniques used to manufacture dry powders for inhalation. Although milling can be carried out on a dry or wet basis, dry grinding is more commonly employed, as it is less labor-intensive. In the jet-milling process, the starting material undergoes many impact events before a significant quantity of the required particle size fraction is achieved and separated from the larger particles by inertial impaction. This classification ensures that the particles size required for respiratory delivery is eventually obtained. The characteristic particle shape is either tabular or rounded (i.e., particle sphericity close to 1). However, this milling process can be quite time-consuming and inefficient for soft ductile organic pharmaceuticals and can adversely alter the surface and solid-state properties.

Micronization is also notorious for inducing electrostatic charges and generating amorphous domains on the particle surface, which render the ground material both cohesive and adhesive. In extreme cases, the whole material bulk may turn

amorphous. Being thermodynamically unstable, such amorphous domains will undergo recrystallization leading to crystal growth on the milled particle surface and formation of solid bridges between the particles. The material is also prone to chemical decomposition and water sorption. All these physical and chemical changes are highly undesirable, and can adversely affect the *in vitro* and *in vivo* performance of the respiratory formulations (42,43). Only in a few exceptional cases can sufficient conditioning at defined temperatures and relative humidities ensure the complete conversion of the amorphous domains to the stable, crystalline state (44). Since micronization may generate local hot spots in pharmaceutical materials and reduce their stability, special modification of the technique is necessary for circumventing this problem, particularly for thermolabile biopharmaceuticals such as proteins and peptides. For instance, micronisation of decapeptide cetrorelix can be conducted by suspending the material in a fluid propellant inside a pearl mill coupled with a cryostat operating at temperatures down to −70°C, followed by evaporation of the fluid propellant to recover the micronized material (45). This milling technique was considered effective and mild for the peptide, and probably better than spray drying because of the higher respirable fraction of the milled material (45).

In summary, although micronization is a well-developed and convenient technique for size reduction of highly crystalline small-molecule drugs and can, to a certain extent, be adapted for biopharmaceuticals, it is by nature a disruptive process and can only provide limited opportunity to manipulate and control the particle characteristics. It is generally not suitable for fragile molecules and more complex engineered structures, such as porous/hollow particles, nonspherical particles, composites, nano-aggregates as well as surface-modified, coated or encapsulated materials.

Blending and Formulation with Lactose

Most current dry powder inhalation products are formulated with a drug carrier, commonly lactose, which also serves as a bulking agent. The formulation usually involves simple blending of the drug of interest in micronized form (1–5 μm) with coarse lactose (30–60 μm). Purely micronized form of lactose can also be used as a carrier for inhalable drugs. Granulation of the materials is required for more efficient pulmonary delivery. Pellets of micronized lactose monohydrate with one or more active ingredients can be prepared by dry or wet granulation procedure (46). In addition, fine lactose particles (<5 μm) produced by jet milling can be agglomerated into spherical granules with uniform diameter and weak deaggregation strength using pressure swing granulation, a binderless granulation process involving cyclic fluidization and compaction by reciprocal upward and downward airflows (47).

The crystallinity of lactose carrier also plays an important role in the aerosol performance of DPI formulation. Having high-energy surfaces, amorphous lactose exhibits strong adhesive interactions with drug particles, leading to low inhalation efficiency (48). Compared with conventional crystalline α-lactose monohydrate, spray-dried amorphous lactose showed no improvement in aerosol performance (49–51), and in fact, its dispersion performance was poorer than those of the spray-dried crystalline lactose prepared with different polyethylene glycols (52). The major limitation with amorphous carrier is its strong tendency to undergo spontaneous recrystallization at ambient conditions (48) or higher RHs (51). Consequently current strategies in carrier engineering are targeted at reducing the amorphous content or increasing the crystallinity of the lactose carrier. Among various crystalline lactose materials available commercially, α-lactose monohydrate is the crystal form most commonly employed as drug carrier in DPI formulation although other physical forms, e.g. anhydrous β-lactose, have also been used (49). Compared with α-lactose monohydrate and spray-dried amorphous lactose, roller-dried anhydrous β-lactose may yield consistently better and more reproducible *in vitro* deposition results (49). Different crystalline forms of lactose carrier can be engineered by spray drying using different solvent compositions (53) or by a one-step crystallization process (54). Engineered samples exhibiting more acicular morphology and higher crystallinity tended to afford considerably better aerosol performance than commercial materials (54). Similar effects have been observed with recrystallized α-lactose monohydrate materials having different particle morphologies but similar particle sizes. Here, the recrystallized elongated particles were superior to micronized lactose in improving salbutamol sulfate aerosolization (55,56). However, it must be noted that the acicular morphology may adversely impact the flowability of the carrier and the drug content uniformity in the powder mix (57).

Surface roughness of the carrier particles (as opposed to the surface roughness of much smaller inhalable drug particles; see above) may also contribute to poor aerosol performance of some DPI formulations. The problem may be manifested as asperities introduced on carrier surfaces by mechanical milling. Such asperities may entrap drug particles, which, coupled with the involvement of mechanical interlocking, may seriously resist detachment of drug particles from the lactose carrier during inhalation (58,59). In view of these deleterious effects of surface asperities on aerosol performance, various techniques have been applied to smooth carrier particle surfaces, encompassing dry coating with hydrophobic lubricants, e.g., sucrose tristearate (60) and magnesium stearate (61), wet coating with hydrophilic polymers, e.g., hydroxypropylmethylcellulose (62), surface dissolution with organic solvents, e.g., 70% ethanol (63) or a combination of these techniques (64–66). While the above approaches appear to hold promise, the safety of the hydrophobic excipients (magnesium stearate and sucrose tristearate) for use in the lungs has yet to be established, as their clearance mechanisms from the lungs are not well understood.

As substantiated by previous studies, the presence of a small amount of adhered fines (<5 μm) on coarse lactose carrier is critical for facilitating particle deaggregation in the air turbulence generated by inhalation (29,67–69). Thus it is possible to control the surface properties and related aerosol performance of lactose carrier by immobilizing the fines on their surfaces (70). This can be accomplished by fluidized bed coating of micronized lactose particles with dissolved lactose in spray solution (70).

Although lactose is extensively employed in DPI formulation, it is not a universal drug carrier, as it can react chemically with certain drugs such as formoterol, peptides or

proteins (71). In the search for alternative drug carriers that are relatively free from this limitation, mannitol has emerged as a promising carrier (71), being able to demonstrate a higher respirable fraction with budesonide compared with standard lactose carrier (72).

Nanoparticles and Nanosuspensions

Suspensions of water-insoluble drugs become increasingly important for miniaturized liquid nebulizers (soft-mist inhalers). For both topical and systemic administration through the lungs, nanoparticulate formulations (typical size between 100 and 700 nm) offer several important advantages over the more traditional microsuspensions (size between 1 and 5 μm). As discussed earlier, nanoparticles can afford higher bioavailability, which is attributable to more efficient drug delivery, more rapid dissolution or increased residence time in the lung (73). The statistical homogeneity of nanosuspensions is also superior to that of microparticulate suspensions leading to significantly higher delivered dose and better dose uniformity (74,75). The small particle size also bestows on nanosuspensions a solution-like rheology that facilitates the dispersion of sprays into smaller and more uniform droplets, particularly in the case of jet-nebulizers and perforated membrane inhalers (76).

The most developed techniques for the production of nanoparticles are probably wet micronization by ball-milling and high-pressure homogenization (73). In both cases, particles are composed of a predominantly crystalline drug, with surfactants or stabilizing agents such as phosphatidylcholines, polyvinyl alcohol (PVA) or Pluronics, although for respiratory formulations the choice of excipients is limited. The surfactants are required to prevent crystal growth during size reduction and to stabilize the suspension against aggregation by forming a thin coating on the crystal surfaces. Typically 20–30% w/w of the surfactant is required to stabilize the nanosuspensions with mean sizes between 120 and 300 nm. This amount is directly proportional to the specific surface area or inversely proportional to the surface-volume mean particle diameter (77). Both micronization techniques have been scaled-up and commercially tested on several compounds, mostly for oral and injectable dosage forms but with suitable surfactants can also be used for inhalable compounds. However, they are not without drawbacks. The potential problems are the difficulty to reduce the size below certain limits for very ductile materials, potential contamination with grinding media and/or adverse effects of the high shear and temperature on the chemical stability. These problems may be minimized or overcome by utilizing direct nanoparticle formation techniques, including direct solution precipitation with stabilizers (78), supercritical fluid extraction of emulsions (40) and some other emulsion-based particle formation processes (79) as discussed below.

DIRECT CONTROLLED CRYSTALLIZATION

Controlled crystallization of hydrophobic drugs in the respirable size range can be attained by an antisolvent precipitation technique using growth-retarding stabilizing additives such as hydroxylpropylmethylcellulose (HPMC) (80–82). Higher additive concentrations usually yield smaller particles. The precipitated drug crystals (e.g., budesonide, predonsiolone, fluticasone and disodium cromoglycate) have been shown to exhibit a higher FPF than jet-milled samples (80,83,84). The amorphous content of such particles is lower than that of the mechanically treated micronized materials, thus affording better physical stability.

Zinc-free insulin crystals in the inhalation size range of 0.2–5 μm have also been prepared by the solvent change (antisolvent precipitation) method (85). The precipitated insulin crystals were shown to be more stable than those powders of essentially the same composition prepared by spray drying, freeze drying, vacuum drying or oven drying (85). As an alternative to the solvent change method, insulin microcrystals can be prepared by the seed zone method involving pH adjustment of the crystallization medium (86). In contrast to the rapid onset and short duration of action with spray-dried amorphous insulin (see below), the crystalline insulin particles produced by the seed zone method persistently reduced the blood glucose level in diabetic rats for over 7 h (86).

Characteristic morphologies associated with different crystalline polymorphs have also been exploited in improving deep lung delivery. Solid-state transformation from one polymorph to another can be induced by agitating the powdered material in a liquid medium. For instance, the α-form (mean diameter = 2.2 μm) of the steroid KSR-592 can be converted to the acicular β-form (1.8×41 μm) by agitation in hexane/ethanol (95:5) mixture, followed by hexane washing, oven drying and deaggregation by blender (87). The resulting particles show substantial aerosolization improvement because of the increased aerodynamic shape factor. In addition, controlled hydration or dehydration of a crystalline material under defined conditions can be utilized to improve the delivery of dry powder formulation. For example, conversion of nedocromil sodium trihydrate to the heptahemihydrate at 86% RH significantly reduced the deaggregation performance in an *in vitro* aerosolization model while storage at 12–76% RH showed no significant effect on the aerosol performance of the trihydrate form (88).

Direct crystallization of spherical agglomerates has been utilized in pulmonary formulations. This technique involves antisolvent precipitation of drug solution in a water-miscible organic solvent, followed by addition of a bridging solvent, which is immiscible or partially miscible with water. For example, introduction of ethyl acetate into the water/acetone crystallization medium resulted in formation of spherical agglomerates (200–300 μm) composed of primary crystals in the respirable range ($d_{50} = 1.3$–2.7 μm) (89,90). The agglomerated crystals could deagglomerate readily into primary particles upon mixing with lactose carrier for 2 min or more, and the adhered primary crystals were easily detached from the lactose during inhalation with substantial enhancement in inhalation efficiency, i.e., two to three times higher FPF compared with micronized materials (89–92). Spherical crystallization can also be achieved for certain drug materials by quenching of a hot organic or aqueous organic solution of the drug with a cold organic or aqueous organic solvent. The quench solvent should be miscible with the drug solvent. For instance, spherical accretions of microcrystals of salmeterol xinafoate, a long-acting anti-asthmatic agent, can be readily

produced by adding a hot solution of the drug in 2-propanol to a chilled quench solvent (93). The resulting agglomerates are free-flowing, friable and readily micronizable to a material suitable for inhalation delivery.

The challenge of particle size control in all crystallization methods is that most small molecules tend to form relatively large crystals. This is due a competition between the nucleation and growth mechanisms, which normally yields particles within the 10–100 μm size range, even under ideal mixing conditions (94). Different types of mixing between the drug solution and non-solvent can be employed, including fast agitation (43), high-velocity mixing jets in coaxial or impinging configurations, which is a natural choice for particle production in a continuous manner (78,94), and also precipitation with ultrasound (95). A more exotic mixing technique involves the use of high gravity in rotating packed bed (96). In the ultrasonic crystallization method, the particle size can be altered not only by the sonic-induced mixing but also by the influence of cavitation on supersaturation and nucleation, which renders the particles more uniform. In order to decrease the mean particle size, high concentrations of growth-retarding or stabilizing excipients are usually required. These growth inhibitors are compound-specific in terms of their interaction with the crystal surfaces. Furthermore, the use of tailor-made additives, molecularly designed to inhibit crystal growth, can be highly restrictive due to stringent purity control and toxicity issues. Finally, it should be noted that, although the possibility to obtain well-defined, crystalline particles with narrow size distribution is quite feasible with controlled liquid crystallization, a major drawback of such a process is the necessity to remove all the additives and to dry the material completely. The latter processing steps are not at all straightforward and may result in powder caking, impure sample and reduced powder dispersibility.

SPRAY DRYING (SD)

Process Parameters and Control

Spray drying (SD) technology has been widely applied since the early 1940s in the processing of food, biochemical, and pharmaceutical materials in industry. The popularity of the technology lends itself to its relative simplicity, availability of large-scale equipment, ease of operation and ability to produce composite materials. However, particle production for inhalation using this technology is a relatively new field with only a single marketed (Exubera®—mannitol-stabilized insulin) and several late-stage development products currently reported. One major reason for this is that production of particles in the 1–5 μm range is at the very limit of the size reduction capability of this method and, therefore, an intense process engineering optimization is required at both drying and collection stages. In addition, there is a common concern regarding the physical instability and thermal degradation of the products. Nevertheless the range of applications with this powder production method is rapidly expanding as the technology becomes more optimized and new formulations approaches are developed.

A typical SD process consists of four steps (97): (a) atomization of feed solution into a spray; (b) spray-air contact involving flow and mixing; (c) drying of sprayed droplets at elevated temperatures; and (d) separation of dried product from the air. For each of these operating steps, a wide variety of process designs are available, depending on specific needs or applications. For feed atomizers, selection can be made from rotary atomizer, pressure nozzle or two-fluid nozzle while air/product flow inside the drying chamber can be co-current, counter-current or mixed flow type. More recently, four-fluid nozzles with in-line mixing have been developed for production of composite particles (98). The SD process can also be operated in different modes such as open-cycle, closed-cycle, semi-closed cycle, with or without aseptic control (97). The system can be further modified for better product recovery and larger production scale, particularly for thermolabile materials such as proteins and peptides. For instance, by replacing the bag-filter unit with a vacuum system, the drying airflow resistance can be reduced, thus allowing the protein product to be dried at a lower inlet air temperature (99). Design of high-efficiency cyclone separation is also essential for this technology to be economically acceptable on an industrial scale.

To modify or optimize the particulate product characteristics, advantages can be taken of the operating parameters of the SD process such as atomization pressure, feed properties, feed rate, airflow and drying temperature (inlet or outlet) (97). For particle size control, plain-jet air-blast atomizers offers the advantage of generating smaller initial droplet size over ultrasonic atomizer, thus yielding particles within the respirable size range (100). Larger particles can be prepared by using a larger nozzle orifice, smaller atomization airflow and a higher feed concentration (101,102). Control of particle shape/morphology can be gained by varying the feed solvent (103) or adjusting the outlet drying temperature (104). Both feed concentration and atomization rate can be concomitantly manipulated to generate particles with different degrees of surface corrugation (32,105). Common excipients such as lactose and polysorbate 20 (Tween 20) can also be added to the feed solution to yield particles with rougher surfaces (104). The SD process can be rendered more versatile by suitable modification to meet specific needs. For example, the system can be adapted to aseptic processing of heat-sensitive materials by ultrasonic atomization of feed solution into an atmosphere under reduced pressure to aid removal of the solvent at a much lower temperature. Such modified drying technique has been successfully applied to encapsulation of protein powder in poly(lactic-co-glycolic acid) microspheres (106). Recently, the availability of in-line jet mill in conventional SD system has made possible the elimination of aseptic transfer between these two processing steps when being operated separately, thus minimizing production cost and processing time (107). In certain cases, proper humidity control of the drying gas can afford particles with the desirable densities or aerodynamic diameters for pulmonary administration, and the production conditions can be optimized at dew points ranging from 0 to −40°C (108). Drying gas with too high or too low moisture content tends to yield particles with higher tapped densities and MMAD as well as lower volume median geometric diameters (108).

A special variation of SD technique utilizes CO_2-assisted nebulization with bubble-drying (CAN-BD) (109). CAN-BD utilizes the solubility of supercritical or compressed CO_2 in

aqueous or organic solvents to generate small droplets. It was suggested that such nebulization leads to decreased shear forces, increased atomization efficiency and reduced drying temperature.

Processing of Biologicals

SD has attracted the most attention in the area of respiratory drug delivery because of its potential application to the formulation of therapeutic proteins and peptides for systemic delivery via the lungs, an attractive alternative to parenteral administration. There have been a growing number of studies demonstrating the feasibility to prepare protein particles with the desired physical characteristics for inhalation. Typically, the MMAD of the particles generated is in the 1.5–4.0 μm range, as observed for insulin, parathyroid hormone, human calcitonin, α-1 antitrypsin, β-interferon (8,110,111), influenza vaccine (112) as well as nucleic acid derived drugs (e.g., bare nuclei acid molecules), DNA/lipid vector, viral vector and vesicle structures (113,114).

However, the SD process is potentially hazardous to biomolecules and can cause conformational changes and even denaturation of proteins. The thermal stress is always significant, though reducible by the "wet bulb" effect (i.e., smaller droplet temperature compared to the drying gas temperature during the initial stages of solvent evaporation). The shear stress induced by feed atomization may result in preferential adsorption of the protein at the air–liquid interface of the spray droplets, causing protein aggregation and further activity loss (115). In addition, SD is a very rapid solidification process, which may be accompanied by phase separation (or recrystallization) and can cause damage to the proteins, depending on the production conditions. Consequently, a good number of strategies have been attempted to formulate stable inhalable proteins, including process optimization using multivariate analysis (116) and addition of protein stabilizers (117–119). Simple sugars, such as sucrose, mannitol, lactose, raffinose, trehalose, and surfactants such as Tween 80 have been widely used to preserve protein activity during SD (115,117–119). The physical state of these sugar stabilizers has an important bearing on both the stability and aerosol performance of the formulated proteins. Thus, agents capable of retarding mannitol crystallization, e.g., sodium phosphate, can drastically lower the rate of solid-state aggregation of proteins (117). Concentration of sucrose has also been found to be critical for protein stabilization, the optimum sucrose-to-protein ratio being about 1:1 (118). Higher sucrose concentration leads to less effective protein stabilization, indicative of undesirable excluded volume effects. Surfactants (e.g., Tween 80), which adsorb preferentially at the air–liquid interface of the atomized droplets, can displace the protein from the surface and thus preserve its activity (115).

Porous/Hollow Particles

As explained earlier (see Eq. 1), particles of low density (ρ) are advantageous for aerosol drug delivery because of their relatively large volume diameter (d_V) and small aerodynamic diameter (d_A). Low ρ coupled with small d_A lead to better dispersibility and more efficient deep lung delivery, with FPF reaching 65–95% (9,110) (Fig. 1). In addition, large porous particles allow for escape from the natural phagocytic clearance in the lungs and bring about an increase in bioavailability (120). Such low density particles are currently produced by the PulmoSphere™ process, involving spraying an emulsion of fluorocarbon in water stabilized by phospholipid, where the drug is dissolved or dispersed in the external aqueous phase which also contains excipients. The fluorocarbon serves as a blowing agent at high temperature to produce porous or hollow structures with a powder tapped density below 0.1 g/cm^3 (121,122). Alternatively, porous particles can be prepared by co-spray drying of drugs, e.g., insulin (123), albuterol (124,125) and estradiol (126) dissolved in an ethanolic solution, with simple sugars and/or polysaccharides (e.g. lactose) and additives such as human serum albumin and dipalmitoyl phosphatidylcholine (DPPC), an endogenous surfactant present in abundance in the lungs (10,123). During spray drying, such mixtures may produce walled hollow particles, which collapse into "crumpled-paper" structure. DPPC plays a key role in this process, probably due to its surface activity and tendency to adsorb on the droplet surface. The size, density and morphology of the resulting particles can all be controlled by varying the concentrations of DPPC and lactose (124). With increasing DPPC concentration, there is an increase of the volume diameter and decrease in density.

Albumin has also been used as a carrier for spray-dried therapeutic proteins, such as interferon (127). Control of electrical charges of albumin by varying the pH of the feed solution may also be utilized to generate particles of different sizes and shapes (124). Attempts have also been made to employ other excipients in combination for achieving the desired particle characteristics, including spray drying from a colloidal solution composed of a carboxylic acid, phospholipids and a divalent salt in an aqueous-organic solvent (128) or from an emulsion with lipid-based liquefied propellant, surfactants and bulking agents (129). In certain cases, inclusion of a water-immiscible volatile propellant alone in the aqueous feed solution can also produce porous matrix with faster dissolution rate (130). For sustained release formulation, a wall-forming polymer can be dissolved in the volatile liquid and mixed with water at an appropriate ratio in the feed to produce hollow or porous microspheres (131).

Surface Modification

Effective inhalation delivery requires the overcoming of particle aggregation associated with electrostatic, van der Waals and capillary interactions between particles (28). Such interactions can be regulated using excipients capable of preferential adsorption at the particle surface. A well-known surface-active additive serving this purpose is DPPC (see also "Porous/Hollow Particles"), whose predominant presence at the particle surface has been confirmed by XPS analysis (132). Similar finding has been obtained for a spray-dried liposomal protein formulation containing DPPC and sucrose, in which the protein is well surrounded and protected by DPPC and sucrose (133). Simple amino acids, particularly the hydrophobic or water-insoluble ones, can be co-spray dried with drugs to produce powder with improved dispersibility (28,134,135). Of all the amino acids tested, leucine appears to show the most promising dispersion enhancing effect for a

number of spray-dried pulmonary formulations, such as disodium cromoglycate (DSCG) (28,136) and nucleic acid based drugs (137). In the case of DSCG, the relatively strong interparticulate interactions characteristic of the pure material resulted in a strong dependence of FPF on the inhalers type and the airflow rate (28). Decrease of interparticulate interactions for leucine-containing powders led to a significant increase in FPF and a reduction of FPF dependence on the flow rate and inhaler type (see also Fig. 1). It was proposed that this effect can be correlated with the strength of intermolecular interactions between DSCG and leucine at the particle surface, which may be expressed by the difference in their component Hansen solubility parameters measured by IGC (28). However, no direct relationship was observed between the dispersive or polar component of surface free energy determined by IGC and the ED or FPF.

Absorption Enhancement

An additional issue that has to be addressed for protein formulations is the limited protein absorption through the lung mucosa. To promote lung adsorption, numerous attempts have been made to incorporate penetration enhancers, mostly surfactants (e.g., glycoholate, deoxycholate and taurocholate), into the protein particles during SD. However, safety has been a concern with the use of such surface-active agents because of their potential damaging effect on the epithelial blood barrier (138). In terms of safety, endogenous surfactants such as DPPC and albumin are some appropriate choices for pulmonary protein formulation. DPPC has been shown to enhance the permeation (absorption) of parathyroid hormone (1–34) in rat lungs (139). Furthermore, spray-dried powders containing human growth hormone, lactose and DPPC in ratio of 20:20:60 by weight display earlier t_{max} and higher absolute bioavailability than those of simple solution when administered via the pulmonary route (140). However, the inclusion of albumin in the DPI formulation of parathyroid hormone (1–34) has been observed to decrease the systemic bioavailability of the hormone by 1.6 fold, possibly because binding to albumin prolongs the presence of the hormone in the alveolar space, thereby subjecting it to further inactivation by local enzymes and/or other degradation processes (141).

Citric acid, a safe additive and a common component of buffer salts (110), has also been used to enhance pulmonary absorption of spray-dried insulin (142). Such citric acid-treated insulin also exhibits improved stability without loss of hypoglycemic activity (143). Other additives that are considered safe for use as pulmonary absorption enhancers with spray-dried particles include hydroxypropylcellulose and dimethyl-β-cyclodextrin (144,145). As a mucoadhesive, hydroxylpropylcellulose increases pulmonary absorption by retarding the mucociliary clearance of the particles (144). Dimethyl-β-cyclodextrin is capable of increasing the transfection efficiency of spray-dried lipid-polycation-pDNA vector by improving its dispersibility and absorption (145).

Aggregates of Microcrystals and Nanoparticles

The material preparation is a two-step process in which suspensions of micronized drug crystals and different nanoparticles are spray-dried to form particulate aggregates, usually with excipients. The main goal here is to produce inhalable particles of water-insoluble drugs and/or porous or hollow particles to improve the particle aerodynamic properties. The aggregates obtained usually consist of crystals dispersed in a matrix of amorphous excipients. However, different degrees of crystallinity can be obtained for both the drugs and excipients, depending on the method used to engineer the particles in the suspensions and on the SD conditions. Examples of materials studied by this technique include corticosteroid (80,83), disodium cromoglycate (84), ECU-R2 (43,80), and nanoparticles prepared from chitosan (146) or from gelatin and polycyanoacrylate (147). Porous aggregates consisting of budesonide (9) and albuterol sulfate (148) were prepared using the PulmoSphere™ process. *in vitro* assessment showed that these particles have improved physical stability, content uniformity, aerosolization efficiency, and are superior to conventional micronized materials in terms of delivery from passive DPIs (9,121) or MDIs (148) (see also Fig. 1). The systemic efficacy of these particles for delivery via the inhalation route has been substantiated by clinical assessment (148). Homogeneous amorphous solid dispersions of poorly soluble drugs in a wide variety of polymers were also prepared by conventional and modified SD processes (149). Drug particles can also be co-spray dried with nanospheres of hydrophilic polymers (e.g., hydroxypropylmethylcellulose phthalate) to modify the particle surface and to enhance dispersion performance (150).

Sustained/Controlled Release Formulations

The challenges in this area are mostly related to finding suitable, non-toxic excipients which can produce a desired drug loading and release profile and which also have a sufficiently low solution viscosity to be sprayed as micro-droplets. SD involving the use of organic solvents presents significant challenges with regard to the process development as well as the safety and toxicity issues with residual solvents. Therefore aqueous solutions or dispersed systems are preferred.

Chitosan, hyaluronic acid and starch are some natural polymers of choice for pulmonary sustained-release formulations. Thus betamethasone-loaded chitosan microparticles have been produced within the respirable size range (151,152). Incorporating 50% w/w gelatin into these particles results in prolonged drug release for 12 h (151). However, initial burst release with this formulation was significant, with more than 40% of the encapsulated drug released within the first 30 min (152). Solid dispersion of theophylline in chitosan matrix has also been prepared (153). The spray-dried theophylline-chitosan particles had an MMAD of 4.5–5.0 μm, and displayed a sustained release profile at pH 6.8, possibly due to the strong hydrogen bonding between the carbonyl group of theophylline and the amino group of chitosan (153). Employing a similar approach, hyaluronic acid can be co-spray dried with insulin to yield a dry powder suitable for inhalation (154). Compared with spray-dried pure insulin, the incorporation of excess zinc or hydroxylpropyl cellulose into the hyaluronic acid-based dry powder enables controlled release of insulin in the lungs of male Beagle dogs, as evidenced by improvement in the mean residence time, AUC/dose and t_{max} of the insulin (154).

Soluble starch, whose degree of swelling can be controlled by the ratio between the starch and the cross-linking agent, epichlorohydrin, used, may also serve as a sustained release matrix material for the formulation of pulmonary microsphere (5 μm) (155).

Trehalose oligosaccharide ester derivatives (OED) represent another group of synthetic polymers with potential application in sustained-release pulmonary drug formulation. The material can be co-spray dried with insulin to form amorphous insulin microparticles (156). Insulin release from such microparticles is governed by the crystallization of the matrix upon contact with water (156). OEDs have also been employed to prepare spray-dried leuprolide acetate particles via hydrophobic ion pairing with sodium docusate (157). Pulmonary administration of such leuprolide microspheres shows controlled release of the drug with limited initial burst, which may be explained by the high glass transition temperature of OEDs (157). However, the safety profiles of OEDs for use in pulmonary drug delivery have yet to be established. A new category of biodegradable ether-anhydride polymers has also become available recently for the development of microparticles capable of inhalation as a dry powder and controlled drug release (158). The polymers are synthesized using various ratios of sebacic acid (SA) and poly(ethylene glycol) (PEG). The SA serves to render the polymer water-insoluble while the PEG can reduce particle clearance by macrophages and improve aerosolization. Safety is less likely a concern with these polymers, as they are composed entirely of FDA-approved monomers (158,159). In addition, the surface and bulk properties of these microparticles can be optimized by varying the percentage of PEG in the polymer backbone to achieve a high FPF and controlled release (158,159).

Sustained-release rifampicin poly-(DL-lactide) microspheres for direct lung targeting have been prepared by SD (160,161). Molecular weight and hydrophilicity of the polymers as well as temperature are important factors affecting the rifampicin release rate from these spray-dried microspheres (160). Another common approach for sustained release inhalation formulation is to disperse a water-soluble, hydrophilic, ionized drug within the hydrophobic (polymer or lipid) matrix of microspheres. Such formulation can be accomplished using a multi-step process in which nanoparticles or microparticles are suspended in a polymer solution and then spray-dried. For example, the drug is first emulsified into an organic phase with up to 10% surfactant, and the resulting w/o emulsion is frozen with liquid nitrogen, followed by freeze-drying (162). The nanoparticles produced are then dispersed into a non-solvent of the drug containing hydrophobic excipients, such as glyceryl behenate, tripalmitin and hydrogenated palm oil. Subsequent spray drying produces nanoparticles-loaded microspheres exhibiting not only favorable aerosol properties (FPF = 46.5%; MMAD = 3.93 μm) but also sustained release for over 180 min in both phosphate buffer and simulated lung fluids and with no significant initial burst release (162). Similarly, PLGA polymer was used in the SD process to coat particles of a model protein (β-glucuronidase, previously co-spray dried with mannitol or lactose) to develop a tuberculosis vaccine formulation (163).

Another approach to preparation of composite particles for sustained release utilizes liposomal formulations. The drug-loaded liposomes are prepared using a thin film technique followed by high-pressure homogenization and co-spray drying with an excipient (lactose, sucrose or mannitol) and anti-adherent (e.g., glycine) (164). It has been shown that such formulations can attain high FPFs (55–70%) and different release times, depending on the excipient used. This work also compared the performance between spray-dried and lyophilized products and showed that the spray-dried materials have superior aerosolization efficiency and longer sustained-release duration associated with their higher dense particle content.

Apart from the use of biomaterials, biopolymers or specific excipients, sustained delivery via the inhalation route may be attained in certain cases by simply controlling the crystallinity of the drug material or the size of the delivered particles. With regard to crystallinity control, insulin is a well-known example, for which it has been shown that high crystallinity is associated with a slow dissolution rate and prolonged hypoglycemic action in diabetic rats (86). Long-acting inhaled insulin can be produced by complexation with protamine and zinc chloride or co-spray drying with hydrophilic excipients (e.g., lactose, albumin, etc.) (123). The latter spray-dried formulation in the form of porous particles has a bioavailability of 80.5% relative to subcutaneous injection of the same insulin, and provides a sustained insulin plasma level for half a day (123). As discussed before, phagocytic clearance in the pulmonary region is slower with larger particles, which can, therefore, be utilized to provide low-dose, long-acting inhalation drug therapy. For instance, large porous estradiol particles ($d_V = 10.1 \pm 5.6\,\mu m$; $\rho_b = 0.08$ g cm^{-3}) are 1.5–4.7 times more bioavailable than small dense particles ($d_V = 3.1 \pm 1.8\,\mu m$; $\rho_b = 0.48$ g cm^{-3}) when delivered via the inhalation route, with elevated systemic estradiol concentrations lasting for 96 and 24 h for the respective formulations (126).

Amorphous Forms and Stability

As alluded to earlier, SD is a rapid solidification process and generally yields amorphous materials. The utility of amorphous forms in inhalation formulations is conceivably limited by their inherent instability. Being thermodynamically unstable, amorphous solids are more prone to chemical degradation than their crystalline counterparts and tend to revert back to the stable forms via recrystallization. Atmospheric moisture will likely mediate such physical and chemical changes, and can adversely influence both the stability and aerosol performance of the formulation. For instance, moisture can induce crystallization of amorphous mannitol in spray-dried salmon calcitonin/mannitol mixture at RHs above 50%, resulting in aggregation of the calcitonin (165). Low environmental RH (<50%) during storage is critical for maintaining the aerosol performance of spray-dried human monoclonal antibody (anti-IgE) and recombinant human deoxyribonuclease (166). In general, drier powders show better preservation of protein monomers with reduced aggregation (166). All these observations suggest that a tighter control on the relative humidity during storage is crucial for preserving the structural integrity of spray-dried proteins.

In some cases, however, SD can be employed to prepare crystalline substances (167). The crystallinity of spray-dried materials can be regulated by varying the solvent or excipient

content of the feed solutions, as demonstrated for cromolyn sodium (103) and recombinant human deoxyribonuclease (168). Production of different polymorphic forms is also possible by spray drying drug solution at temperatures above or below the transition points, as shown for phenylbutazone (169) and tolbutamide (polymorph IV) (170). Other SD parameters that are considered critical for crystal form control include the nature of solvent (171) and acidity of the feed solution (172) for particular materials.

SPRAY FREEZE DRYING (SFD)

SFD Process

A typical SFD technique involves the atomization of an aqueous drug solution via a two-fluid or an ultrasonic nozzle into a spray chamber filled with a cryogenic liquid (liquid nitrogen) or halocarbon refrigerant such as chlorofluorocarbon or fluorocarbon (173). The spraying process can be performed beneath (spray-freezing into liquid) or above the surface of the cryogenic liquid, depending on the position of nozzle (174). It is also possible to use a nozzle arrangement for introducing liquid nitrogen directly into the spraying solution (175) although the application of such a method for inhaled particles has not been discussed. Since the level of the cryogenic liquid will inevitably drop due to evaporation, continuous addition of fresh cryogenic liquid is required, especially when a lengthy atomization process or a large spray volume is used. Upon contact with the cryogenic medium, the liquid droplets solidify rapidly (in milliseconds time scale) because of the high heat-transfer rate (176). Stirring of cryogenic liquid may be required to prevent the possible aggregation of newly formed frozen particles. Once the spraying process is completed, the whole content can be lyophilized, as with conventional freeze-drying. As tray lyophilization is expensive and not readily amenable to scaling up, atmospheric freeze-drying involving sublimation of the spray-frozen solvent has also been developed (177,178). This involves drying of the frozen particles by a stream of dry cold air inside an insulated stainless steel gas vessel (178). Without interrupting the drying process, changes of moisture content in the product can be monitored continuously by numerical evaluation of the dew-point temperatures of both inlet and outlet air based on the Mollier-h,x-diagram (177).

Spray freeze-dried particles can be engineered to the desired respiratory size range—below 5 μm (179–181) or even down to nano-scale (7,181–184). The most significant operating parameter governing particle size is the mass flow ratio of atomized nitrogen to liquid feed (185). A decrease in particle size can be achieved by an increase in mass flow ratio (185,186) while the addition of excipients (e.g., trehalose, ammonium sulfate) may lead to an increase in particle size (187).

Further modification of the spray-freezing process has been proposed; instead of spraying the drug solution into the cryogenic medium, the drug solution is atomized and frozen simultaneously by mixing with a liquefied gas or supercritical fluid, such as supercritical CO_2 (SFD-CO_2 method) (6,7,12). The liquid droplets are first dispersed with a static mixer within the supercritical CO_2 and then frozen within due to the Joule Thomson's expansion cooling, the freezing being accomplished within 10–100 μs time scale as shown by theoretical modeling and computational fluid dynamics (CFD) (7). It has also been shown using the CFD that supercritical conditions before expansion are crucial for achieving smaller particle size and more uniform or narrower PSD. After spray freezing, the frozen solvent is removed, as in the case of freezing with cryogenic liquids, by vacuum or atmospheric freeze-drying. The large surface area of the frozen powder and loose porous structure of the powder bed allow relatively fast and homogeneous drying compared with a standard lyophilization process (6).

SFD methods are not as well established and extensively utilized as SD due to their higher complexity, more tedious scale-up and higher costs. However, with the introduction of new large-scale spraying techniques and accelerated drying cycle, SFD has become a viable economical alternative to SD, which also provides a superior product in many cases. The applications of SFD are also not limited to aqueous solutions. Most volatile organic solvents can be processed by freezing with liquid nitrogen. Other solvents, notably tributyl alcohol (TBA) and TBA–water mixtures, have sufficiently high freezing point and high vapor pressure to be processed under conditions close to those for standard lyophilization or CFD-CO_2, without the need to go into extreme cryogenic temperatures and specific equipment design.

SFD Material Properties and Applications

SFD has become increasingly popular for processing of biologicals such as therapeutic proteins, monoclonal antibodies and vaccines because of its ability to produce porous particles with high FPF at sub-ambient temperatures with or without excipients. The large porous particles (>6 μm) produced showed significantly better aerosol performance than the small dense particles (~3 μm) generated by a typical SD process because of their more favorable aerodynamic properties as well as reduced interparticulate interactions (176,188,189) (see also Fig. 1). As revealed by Z-contrast scanning transmission electron microscopy, these large porous particles are composed of nanoparticles interconnected by narrow bridges (190), which likely accounts for their friable nature and vulnerability to fragmentation under certain processing conditions (185). However, using SFD-CO_2 for processing insulin, Shekunov *et al.* (7) have demonstrated that by varying the operating parameters such as the feed solution concentration and flow rate, the products can be modified from relatively cohesive aggregates of nanoparticles (with primary particle diameter of 100–300 nm) at concentrations below 1% w/w, through platelet shapes to well-defined and easily dispersible spherical microparticles at concentrations above 5% w/w. Leucine and other excipients such as lactose imparted additional porosity to the insulin particles and improved their dispersion.

Further downstream processing of spray-freeze dried products is possible; the friable particles can be reduced to submicron size by a secondary process such as milling, homogenization or fluidization (176,191,192), or encapsulated into poly(D,L-lactide-co-glycolide) microspheres (193). However, care should be taken to avoid the formation of excessively porous and fragile particles, since such particles

will not be able to withstand subsequent handling and processing involved in the DPI lactose formulations. Small fragments from broken particles may also adhere tenaciously to the carrier, resulting in an apparent reduction in FPF (180). While porous particles are advantageous for improving the aerosol performance of protein drugs, the associated increase in specific surface area may destabilize the protein and may also cause initial burst release of encapsulated protein drug from polymeric [e.g., poly(lactide-*co*-glycolide)] microspheres (185). However, for low-molecular-weight synthetic drugs, particularly hydrophobic and poorly water-soluble compounds (e.g., danazol and carbamazepine), such porous particles with a large specific surface area possess the advantage of being readily wetted and dissolved when formulated with or without the aid of hydrophilic excipients (e.g., poloxamer 407 and PVP K-15) (182,194,195).

As with SD, SFD has also been successfully employed for the production of particles for controlled release. For instance, protein drugs can be encapsulated into biodegradable polymers for formulating sustained or controlled release microspheres that are less prone to an initial burst release, a common problem with this type of formulation in depot drug delivery (184,186). Liposomal formulations can also be used to produce respirable dry powders by SFD although they have been traditionally used in pulmonary delivery in the form of MDIs and liquid formulations. Drugs are typically entrapped within liposomes using, for example, lecithin and cholesterol together with a suitable cryoprotectant (e.g., sucrose) and then freeze-dried (164,196). The ability of liposomes to encapsulate drugs and preserve them in dehydrated form using cryoprotectants offers a number of advantages over the liquid formulations including more prolonged release and improved physicochemical stability. This is an example of how nano-aggregates are utilized for respiratory dry-powder formulation. In addition, polymeric (doxorubicin-loaded butylcyanoacrylate) nanoparticles generated using an emulsion method were spray freeze-dried with lactose (197). The same work also reported a liposomal (lipoplex) formulation prepared by the same drying technology. The MMADs of particles produced in the two formulations were 1.7 and 3.4 μm, respectively, both with a volume mean diameter of about 400 nm after reconstitution.

It is worth noting that the application of SFD is not limited to the production of porous materials; the technique is equally capable of producing high-density particles (with tapped density ≥ 0.5 g cm^{-3}). This can be achieved by increasing the solid content of the spray solution or by using additives (e.g., ternary mixture of trehalose/mannitol/dextran for protein drugs) to induce particle shrinkage (6,12,198). In terms of the solid-state structure, the particles produced by SFD are typically amorphous and homogeneous (199). This fact can be explained by the very rapid rate of solid phase separation during the freezing stage, forming solid supercooled solutions ("freeze concentrate") intermittently with small crystalline or amorphous regions of relatively pure ice or other solvent. During drying, the pure solvent sublimes first (primary drying) followed by sublimation of the relatively low, more bonded solvent fraction in the freeze concentrate (secondary drying). The glassy/amorphous structure may account for the observed increase in wetting and dissolution rate (182,194,200).

Despite its higher cost, SFD carries certain advantages which cannot be matched by SD. Unlike SD, SFD is conducted at sub-ambient temperature, and has, therefore, been used to formulate a significant number of thermolabile and highly potent therapeutic proteins/peptides into dry powder inhalation products, including recombinant-derived humanized anti-IgE monoclonal antibody (188), recombinant human deoxyribonucleases (188), insulin (7,174), cetrorelix acetate (180) and plasmid DNA pSG5*lac*Z (201). However, instability associated with protein aggregation is still a concern (185,187,202,203). Various approaches have been employed to circumvent this problem, encompassing complexation with zinc (187,203) and addition of sugars, such as trehalose (185,202,204) and mannitol (204) as well as addition of surface-active ingredients such as Tween 80 (6,24). Consideration has also been given to spraying beneath the cryogenic liquid surface, which can minimize protein denaturation and aggregation by eliminating the liquid–air interface (174) and decreasing the droplet residence time before freezing (6,24).

In summary, a great variety of engineered structures consisting of pure drugs as well as composite materials and nano-formulations have been successfully prepared by SFD. While most of the products obtained by SFD appear to have better quality and fewer formulation problems than SD, SD is nevertheless a simpler technique with the option of a larger production scale. Indeed, there have been cases reported where SD is not only comparable but also superior to SFD for drug encapsulation (164,205,206).

PARTICLE FORMATION FROM LIQUID DISPERSED SYSTEMS

Emulsion-Based Methods

These methods have been traditionally applied to the preparation of sustained and controlled release injectable forms. However, a significant amount of research effort is now dedicated to the respiratory formulations. The technique involves preparation of double (o/w) or triple (w/o/w) emulsions with subsequent removal of the oil phase (a volatile organic solvent) through evaporation, non-solvent (antisolvent, solvent exchange) extraction or solvent dilution (77). Suspensions of solid drug particles in the internal organic phase can also be employed for microencapsulation. Among a wide variety of biodegradable polymers that have been investigated as carrier or encapsulation materials, poly(L-lactic acid) (PLA), poly(glycolic) acid (PGA), and poly(lactide-co-glycolide) acid (PLGA) have received special attention. Prepared by the polymerization of lactide and/or glycolide monomers via polyester linkage, these polymers can be readily hydrolyzed across their ester backbone to yield non-toxic products with excellent safety profiles (207). Numerous examples of sustained-release microspheres for pulmonary delivery are documented in the literature, e.g., isoproterenol PLGA microspheres (208), nedocromil sodium/beclomethasone dipropionate PLA microspheres, etc. (209). These microspheres were produced to a suitable size for aerosolization (209) and were successfully tested for sustained release/action *in vitro* and/or *in vivo* (208).

An area of particular therapeutic interest is the sustained delivery of anti-infectious drugs. For example, pulmonary tuberculosis requires prolonged oral anti-tuberculosis pharmacotherapy to eradicate mycobacterial infection, and hence, sustained release of anti-tuberculosis drugs (e.g., isoniazid, rifampicin) via the inhalation route provides an attractive alternative therapeutic approach. In addition to the SD and SCF methods (see below), preparations of anti-tuberculosis drugs such as isoniazid and rifampicin poly-(DL-lactic acid) microspheres in the respirable size range (0.5–3 μm) have been prepared by the solvent evaporation method (210). The microspheres showed sustained drug release over a period of 4 weeks although initial burst release (25–30%) was still a problem (210). In contrast to the shriveled rifampicin microspheres produced by SD, the particles generated by the solvent evaporation method are spherical (211). To ensure efficient pulmonary delivery, surface treatment of the drug-loaded poly(DL-lactide-co-glycolide) microspheres can be attempted by suspending the microspheres with polylysine and polyglutamic acid in isopropanol, followed by rinsing and vacuum-drying (212). Such surface-treated microspheres show smaller MMAD and better dispersion (more than two fold increase) than untreated samples, probably due to their higher net surface charges (212).

It should be noted that despite the demonstrated utility of poly(lactide)- and/or poly(glycolide)-based polymers in sustained-release pulmonary formulations, potential adverse immunological response to these polymeric materials in the lungs still remains a concern (213). However there are many other biodegradable biomaterials with a better safety profile available for pulmonary drug formulation. Thus albumin has been used for formulating sustained-release microspheres. Such inhalable microspheres are capable of reaching the alveolar region, and coating with surfactants not only can decrease the interaction of the microspheres with mucus layer but can also increase their deposition in the lower airways (207). The albumin microspheres can be prepared by the solvent evaporation method and have been used to deliver tetrandrine by the pulmonary route for the treatment of silicosis (214). Ciprofloxacin is another drug candidate that can be loaded in albumin microspheres to provide sustained release for over 12 h in the lungs (215). Doxorubicin can be similarly incorporated into albumin microparticles and engineered to the required size (2.6 μm) for aerosol delivery to the lungs (216).

The drawbacks of emulsion-based precipitation techniques are mostly related to their manufacturing complexity. The emulsion evaporation process usually proceeds at a very slow rate in a batch process, with possible adverse effects on the emulsion stability and uniformity, which have to be carefully monitored and controlled. Extraction of emulsions with other organic solvents leads to large waste streams, increased costs and various formulation problems. Moreover, the process operation is complicated by a number of additional steps, including separation of stabilizers/surfactants, filtration and drying to obtain dry respiratory powders. Another major problem is the difficulty to completely remove all residual organic solvents from the polymer matrix. These residual solvents, particularly the commonly used chlorinated hydrocarbons, can lead to reduced efficacy, increased toxicity and other complications that would create additional regulatory hurdles in the product development process. These problems can be addressed using a novel method of supercritical fluid extraction of emulsions discussed below.

Coacervation

Coacervation is a phenomenon of phase separation in a solution between two liquid phases (differing only in composition of solute species, e.g., polymer-rich and solvent-rich) induced by a change of temperature, solution composition or pH for some thermodynamic systems, usually involving macromolecules. A more complex coacervation may involve deposition of a shell material around the core of drug to be encapsulated. Coacervation typically follows by hardening of the dispersed phase to yield solid particles. In the area of respiratory drug delivery, this technique has been employed for the production of insulin (217) and alpha-1-antitrypsin (AAT) (218) in DPI and MDI formulations. The technology (PROMAXX™) utilized a temperature controlled coacervation process in the presence of PEG. The dry powders were produced by subsequent dialysis against an aqueous solution, centrifugation for PEG removal and then lyophilization. Both products were composed of solid homogeneous spheres within 1–3 μm range, with MMADs of about 3.2 μm (MDI) and 2.7–2.9 μm, as determined with Cyclohaler and Sisphaler devices, respectively, using an Andersen cascade impactor. For AAT microspheres, an FPF of 73% and ED of 73% were observed. In both formulations, the activity of the protein was retained, as verified, respectively, by *in vivo* comparison with subcutaneous insulin injection and *in vitro* biostability analysis. The special advantage of such a process is the utilization of an aqueous system for the production of relatively uniform protein spheres in the respirable size range. The process is reported to be scalable (218), although it does require a multi-step particle separation. The physical chemistry of any coacervation process is complex and has several critical parameters. Further investigation into its applicability to small molecules and formulations (e.g., proteins with stabilizing excipients) is certainly worthwhile and can be challenging.

Protein/Peptide Coating of Crystals

This category of technology utilizes surface interactions between crystalline materials of small molecules and biological molecules to obtain stabilized aggregates suitable for respiratory delivery. This is essentially a direct precipitation technique, involving specifically coating of crystals by a layer of proteins or other biomolecules. For instance, Technosphere® technology (219), which is based on pH-induced precipitation of fumaryl diketopiperazine (FDKP), forms aggregates of platelets with high surface area, high internal porosity (60–80%) and low MMAD (2.5 μm). These particles, which were employed as a substrate for co-precipitation of insulin adsorbed on the surfaces in monomeric form, showed very rapid pharmacokinetics when delivered using a DPI. Other therapeutic proteins used include salmon calcitonin (SCT) and parathyroid hormone (PTH) for the treatment of osteoporosis (220). Another patented technology (http://www.XstalBio.com) utilizes a

different process to obtain protein-coated micro-crystals (PCMC), which are water-soluble micron-sized particles consisting of a core crystalline material, such as an amino acid, sugar or salt. PCMC are prepared in a single-step process that simultaneously precipitates the protein and carrier materials from aqueous media using a water-miscible organic solvent such as ethanol, resulting in the immobilisation of the protein on the surface of the carrier. It has been reported that the particle morphology, protein payload and particle size can all be manipulated by adjustment of precipitation conditions. After formation, the PCMC can be filtered and dried. Protein powders produced thus exhibit good flow characteristics, minimal loss of bioactivity and very low level of aggregation under temperature and humidity stress conditions (221). It is apparent that for these techniques, the maximum drug loading is defined by the specific surface area of the carrier particles and the maximum retainable thickness of the adsorbed drug layer.

Solid Lipid Particles

The use of polymeric colloidal drug carriers in pulmonary formulations is often limited by the unknown toxicity of the carrier in the lungs, and even biodegradable polymers have not yet undergone any rigorous toxicity testing for ensuring safe delivery via the lungs. It has been suggested that lipids have a faster biodegradation rate and higher tolerability in the lungs compared to particles made from certain polymeric materials (222). It is feasible that aqueous suspensions and perhaps dry powder formulations of solid lipid particles can be used for pulmonary administration of drugs. Examples include lipid carriers such as liposomes, lipid emulsions, lipid complexes and solid lipid micro- and nanoparticles (SLN) (223). One of the methods commonly used for preparing SLN is high-pressure homogenization (223). The drug is dissolved in a molten lipid and then homogenized in aqueous media into particles in the 200–500 nm size range followed by solidification. This method follows the same processing steps as the preparation of lipid emulsions, which is a well-established pharmaceutical manufacturing technique and can be easily scaled-up. The major drawback, however, is the limited drug solubility in the molten lipid and in the solidified lipid phase. Alternatively, SLN can be prepared by precipitation from oil-in-water (o/w) emulsions (77), which may afford a higher drug loading and smaller particle size, and which can also be accomplished as a continuous process using supercritical fluid extraction method as detailed below.

SUPERCRITICAL FLUID TECHNOLOGIES

Use of Supercritical CO_2 in Particle Engineering

Supercritical fluids (SCFs) are defined as compressed gases or liquids above their critical pressures and temperatures, which possess several fundamental advantages as solvents (or non-solvents) for pharmaceutical manufacturing (12,94). For pharmaceutical applications, SCF is almost synonymous with supercritical CO_2 (SC CO_2) because of its low critical temperature (31.1°C) and moderate pressure (73.8 bar), non-toxic inert nature and low cost. Despite the fact that SCF technology is often associated with supercritical antisolvent precipitation (SAS; see below), there exist several variants of the technology differing in physical principles, material applicability and products generated. One of the most important physical attributes of SC CO_2 processing is efficient extraction and separation of organic solvents, which often enables production of the particles in a pure dry form or as pure aqueous suspensions and also facilitates a clean and recyclable precipitation process at low temperatures. The high diffusivity of SCFs can be utilized for plasticization of polymers and its high compressibility for promoting efficient atomization of solutions or melts (expansion of SC CO_2 with solutions has been discussed earlier with reference to the CAN-BD spray drying and SFD-CO_2 spray-freeze drying processes). All these properties have been utilized for direct production of pure and composite particles for respiratory delivery, with the added advantages of selective precipitation, impurity separation and control of crystalline forms. In certain applications, such as particle engineering of high-value, high potency and sensitive drugs, SC CO_2 can reduce manufacturing complexity, energy and solvent requirements and, generally can afford a more environment-friendly and benign process than the more conventional particle formation techniques.

Precipitation of Small Molecules with Supercritical Antisolvent (SAS)

In all SAS processes, the fundamental mechanism is based on rapid precipitation when a drug solution is brought into contact with an SC CO_2 (94). It should be noted that the mechanism of SAS changes under different pressure and temperature conditions, and also depends on the solvent composition, known as the mixture's critical point (94). In the higher pressure, lower temperature phase region, the solvents are completely miscible and the SAS proceeds as a typical precipitation process. In the lower pressure, higher temperature region, however, the SAS shifts towards a spraying–extraction mechanism, resembling spray drying in its extreme. Different SAS modifications, used with different acronyms, are distinguished by mixing between the solution and SC CO_2 feeds (12). For example, Solution Enhanced Dispersion with Supercritical Fluids (SEDS™) (224) utilizes high-velocity mixing in a multi-component nozzle.

Because most of the drugs have very limited or no solubility in CO_2, SAS processes have attracted much attention in recent years because they offer a direct means for production of micron-sized dry powders (Fig. 1). Most of the studies to date have focused on small-molecule anti-asthmatic drugs. These agents are currently the most important class of inhalation medicines and conveniently, their commercial inhaler devices and formulations with micronized materials are available for bench-mark comparison. For instance, production of such particles has been demonstrated for eight steroid compounds including budesonide and fluticasone (225,226). A number of pure and coated (with lecithin) particulate products that are suitable for formulation into pMDIs can be obtained with this technology. Coated particles produced with SAS showed a significant increase in FPF when compared with jet-milled products. Production of dry powders of salmeterol xinafoate, albuterol

sulphate, terbutaline sulfate and fenoterol hydrobromide has been investigated and compared with micronized powders by Shekunov *et al.* (227).

It has been shown that SAS-produced powders normally exhibit non-spherical (typically platelet) particle morphology and have lower bulk density and smaller cohesive–adhesive interactions than micronized materials. Although the SC CO_2-processed particles generally display larger geometric and aerodynamic diameters than the micronized materials (see Fig. 1), they have a significantly higher FPF (typically by a factor of two), consistent with their enhanced dispersibility at low airflow rates. Analysis of hydrocortisone particles using a multistage liquid impinger (228) showed that the delivered dose increased by about 30–40% for the SAS-processed materials relative to the micronized particles. The improved discharge of the SAS-processed particles from the inhaler device can again be explained by the weak surface adhesion of these particles to the inhaler reservoir. However, subsequent work with salbutamol sulphate (229) showed that the SEDS™-produced powders afforded a more consistent delivery but with a lower FPF in most cases and the delivery is relatively independent of the flow rate. It has been similarly observed that SEDS™-processed materials generally tend to be non-adhesive and readily dispersible, and can enhance blend uniformity for DPIs and suspension stability for pMDIs, thus affording higher emitted doses (224). However the results of the cascade impactor tests for the SEDS materials were mixed and did not always show higher FPFs. Although no specific reasons for such inconsistent behavior have been given (224), the data analysis in this and previous reports (12,227,228) suggests that such a problem with SEDS (and SAS in general) is probably attributable to the relatively large MMADs of the powders produced (between 4 and 7 μm), compared to an MMAD (measured using Andersen cascade impactor) of about 3 μm for the micronized powders. When the MMAD of the SAS-produced powders is comparable to or only slightly larger than that of the micronized materials, a significantly better overall *in vitro* aerodynamic performance ensues (5,6,12,229) (Fig. 1).

It is also evident from Fig. 1 that the potential of SAS-produced powders for pulmonary drug delivery has not been fully realized due to the limit on their smallest attainable MMAD (~3 μm). However, decrease of the MMAD below this level would certainly improve their performance further. The size reduction process in SAS needs to be optimized to obtain particles in the respirable range and with the required shape (12). For such optimization, nozzles may suffer from the disadvantages of inefficient macro-mixing and periodic blockage, both of which can result in broadening of the PSD. To address some of these problems, an SCF technology utilizing turbulent-shear mixing has been developed recently (227).

SAS processes possess a very important advantage of being able to control the physical form of drug powders. Controlled production of different polymorphic forms, including new forms, has been demonstrated with this technology by varying the working conditions of temperature, pressure or solution flow rate (5,224,230–232). The materials produced are usually crystalline and have a low residual solvent content (25,84,230,233). Engineering of hydrates, solvates and amorphous solids by SAS processing has also been reported (36,230).

Precipitation of Biological and Composite Materials Using SAS

For processing of biological materials, SAS methods are operated at near-ambient temperatures and relatively low atomization rates to minimize potential damage to the delicate materials. Cost effectiveness, possible sterilizing properties of SC CO_2 and feasibility for scale-up are some important considerations in the application of this technology. However, since water and CO_2 are poorly miscible, any precipitation with CO_2 of aqueous solutions requires addition of an organic solvent. This may be damaging to the biomolecules, even though SC CO_2 may dilute the solvent and reduce denaturation. The effect of CO_2 itself has been shown to be neutral or even beneficial to the recovery of the secondary structure of protein molecules (12). There are two main methods used to prepare dry protein powders; the first method involves preparation of protein solution in a polar organic solvent such as DMSO or halogenated alcohol (234,235) while the second approach utilizes a modified (e.g., CO_2-ethanol) antisolvent capable of removing water from the protein aqueous solution (234,236). Water-in-oil emulsions have also been used to produce particles of respirable size (237). The particle morphology produced varies from nanoparticulate aggregates to solid microspheres. It is usually possible to maintain the water content in the SAS precipitation within the range of 3–7%, which is comparable to the stable form of lyophilized powders.

Addition of stabilizing excipients (e.g., disaccharides, surfactants or buffers) is often necessary to preserve the protein structure. These excipients and the precipitation regime need to be carefully selected to avoid potential solid-phase separation between the drug and excipient molecules with consequent loss of intimate molecular bonding. Such co-precipitation is likely to improve both the processability and stability of the resulting material (238). Chitosan–plasmid DNA complex powders were obtained with mannitol as a carrier using SAS (238). The chitosan complexation not only suppressed the degradation of the bioactive pCMV-Luc during the SCF precipitation, but also increased the yield and the luciferase activity in the mouse lungs compared to pCMV-Luc without chitosan or pCMV-Luc solutions with or without chitosan.

Finally, it is worth noting that SAS is a single-step process that offers the options of co-formulation of drugs with certain excipients and blending of different drugs (36). Formation of composite microparticles using the SAS technique is likely to succeed for structurally similar compounds or other molecules with affinity to each other which can form ordered solid solutions, molecular dispersions, coatings or amorphous mixtures by strong hydrogen bonding or complexation (12,36). In the event of solid phase separation or re-crystallization, a non-homogeneous drug dispersion or partial coating could occur, leading to a characteristic "burst" drug release in dissolution studies. An example of successful co-precipitation is microencapsulation of budesonide into PLA in an amorphous form (239). Gentamicin and naltrexone were also co-precipitated with PLA using the hydrophobic ion pairing (HIP) approach (240). This approach was also used to obtain prodrug of isoniazid for subsequent encapsulation into microspheres for

anti-tuberculosis inhalation therapy (241). Similarly, PLA microspheres for pulmonary drug delivery, noted for their high dispersibility and low aggregation, were obtained by Cheng *et al*. (242).

Particle Formation Using Supercritical Fluid Extraction of Emulsions (SFEE)

While the SAS techniques are capable of producing pure drug particles in the respiratory size range, it should be noted that the control of particle size here is limited by the fundamental nucleation and crystal growth parameters (94). The precipitation mechanism in SAS may result in phase separation of different materials in the solid phase (36) as well as particle aggregation. In addition, plasticization of amorphous and partly crystalline excipients, such as most biodegradable polymers, lipids and waxes, with SC CO_2 leads to agglomeration such that production of composite particles becomes very difficult (227). Consequently, development of alternative SCF processing techniques that can tackle some of these challenges is warranted.

SFEE is a novel process which is based on extraction of the organic phase in oil-in-water or multiple emulsions using SC CO_2 (6,40,41) This process combines the flexibility of particle engineering using different emulsion systems (see above) with the efficiency of large-scale, continuous extraction with SC CO_2 widely used in the nutraceutical and food industries. Each emulsion droplet serves as a micro-reactor, which enables localized precipitation, encapsulation or blending, thereby yielding particles of more uniform size and morphology. Such particles are typically stabilized in aqueous media and therefore do not aggregate even when excipients with low glass transition temperatures are used. In addition, the precipitation occurs relatively slowly providing the opportunity to obtain thermodynamically stable solid structures with complete removal of organic solvent. SFEE is a truly continuous SCF process and normally produces materials in a form of aqueous suspensions with a solid content between 0.5 and 10% w/w and with the surfactant (emulsifier) retained in the aqueous phase.

For respiratory formulations, SFEE can provide uniform crystalline drug particles, composite particles such as microspheres or microcapsules including porous polymer and lipid materials as well as nanosuspensions (40,41). For instance, easily dispersible budesonide crystals with MMAD between 1 and 2 μm were obtained for dry powder formulations (Shekunov, unpublished data). In recent works (76,77), SFEE was employed for the preparation of drug-encapsulated SLN formulations with particle size less than 50 nm. It was shown that emulsion droplet size and the nature of the emulsion are the major particle size control parameters, although the drug, solvent and emulsifier concentration used may also influence the resulting particle size. The model drugs used in these studies were shown to remain in a stable molecularly dispersed state within the SLN with up to 10 and 20% w/w of drug loading in tripalmitin and Gelucire 50/13, respectively, well above their saturation limits in these lipids in the molten state. Both aerosolization efficiency and PSDs of the nanosuspensions produced were found optimal for delivery to the lung for either local or systemic action using the Aradigm Inc AERx Single Dose Platform or the AERx Essence system. The PSD of the aerosol was consistent with that required for minimal oropharyngeal deposition and maximal delivery to the peripheral lung for uptake by the systemic circulation.

Other SCF Techniques

The method proposed by Koushik and Kompella (3) involves exposure of microparticles prepared by an emulsion solvent evaporation to SC CO_2, leading essentially to the same type of particles as that prepared by SFEE, with the option of manipulating particle porosity through adjusting the suspension de-pressurization rate. Deslorelin, a non-apeptide with potent luteinizing hormone releasing hormone agonistic activity, was prepared with PLGA using this method to produce large porous particles. The volume particle size after SC CO_2 treatment increased from 2.2 to 13.8 μm with the bulk density reduced to 0.082 g/cm^3. Mass spectroscopy and circular dichroism indicated the peptide structure was not significantly affected. In addition, SC CO_2 enabled removal of residual solvent from 4,500 ppm down to less than 25 ppm. Such particles afforded sustained peptide release in rat lungs for over 7 days possibly because of their reduced uptake by the respiratory clearance system (3). This point has been substantiated by *in vitro* studies which indicated a significant decrease of uptake of deslorelin from these particles into the respiratory epithelial cells (Calu-3 and A549) compared to the non-porous PLGA particles.

Rapid Expansion of Supercritical Solution (RESS) (243), the oldest SCF process known, is based on precipitation of particles by expansion of a solution in SCF, and hence its application is limited to those compounds which have a significant solubility in SCF. When a compound is soluble in supercritical CO_2 at concentrations of about 10^{-4} mole fraction, this is the technique of choice because it provides simple, direct, solvent-free and continuous production of dry respiratory powders. RESS can be optimized to achieve a relatively narrow PSD and can also be used for the coating of micron-sized particles with CO_2-soluble polymers or waxes. Addition of an organic solvent miscible with CO_2 can improve the solubility of the drug; however, efficient removal of this solvent is required after expansion.

Particle formation from Gas-Saturated Solutions (PGSS) (244,245) utilizes the high solubility of CO_2 in certain materials such as polymers, which result in plasticization, reduced viscosity, and depressed melting and glass-transition points. This is beneficial to blending, coating and encapsulation, which occur without the use of organic solvents. Furthermore, the reduced temperature (typically below 60°C) is important for the physical and chemical stability of many bioactive materials. For example, studies with ribonuclease demonstrated that activity of this protein was preserved after PGSS and that a constant release rate of the protein from PLA polymer could be obtained (244). The expansion of melts under reduced pressure may produce micron-sized particles, often with a porous structure. The biggest challenge of PGSS is, however, the particle size control because the high melt viscosity may suppress the formation of fine particles. Therefore, this technique may be utilized for co-formulation coating of respirable particles with lipids (see Fig. 1) or low-molecular-weight biodegradable polymers.

Respiratory particles of very high porosity and surface area can also be produced from some preformed materials such as aerogels using SC CO_2 as the drying agent (246). The aerogels are prepared from modified organic carriers such as derivatized mannitol and trehalose using a gel method. The matrices are then saturated with a therapeutic agent, dried with SC CO_2 and micronized using a jet-mill. The density of the aerogel can be as low as 0.003 g/cm^3. The respiratory particles produced have the benefit of a relatively large volume diameter and may show reduced interparticulate interactions and better aerosolization than solid particles.

Table III summarizes the required solubility characteristics of processed materials (drugs and excipients), typical product forms and major applications of various SCF technologies for inhalation formulations. It should be emphasized that the list of potential SCF techniques is not limited to the processes just described. The different and unique solvent properties of SCF, combined with different processing schemes, offer many additional particle engineering possibilities, particularly in the areas of composite and porous particles; processing of liposomes, emulsions and bioactive materials; manipulation of the solid-state structure; and co-formulation of different drugs and excipients for enhancing the pulmonary deposition or therapeutic efficiency.

PARTICLE COATING

Coating can be distinguished from encapsulation by the maximum drug loading of the coated particles, which is above 50% w/w, preferably above 90% w/w. Such high loading means that the particles have a core-shell structure. For pulmonary drug delivery with sustained release, or in the case where the drug is simply protected from degradation by a layer of coating materials such as polymers or lipids, the high drug loading can be important to avoid possible accumulation of the water-insoluble excipients in the lungs and/or to increase the therapeutic dose delivered. The small size of respiratory particle precludes the use of traditional coating techniques such as fluidized bed or rotating-pan coating. In such systems, the coating of micron-sized particles cannot be adequately controlled and thus quickly leads to particle agglomeration. To circumvent this problem, special methods need to be adopted. Coacervation and emulsion techniques, in particular the SFEE technique described above, are capable of generating microcapsules by dispersing drug particles in the internal organic solution of a coating material.

Production of ultra-thin coatings (20–30 nm) can be achieved by a pulsed laser deposition method (247), which employs a high-intensity laser to vaporize a flux of a polymer substrate such as PLGA inside a vacuum chamber and then allows it to deposit on the drug powder placed in a fluidization device. This technique has been used to coat drugs for treating asthma such as glucocorticoids. Preliminary studies suggested that the coated particles had longer retention time (significantly longer half-life) and slower release rate than the uncoated drug. Another method reported for coating from the vapor phase is condensation coating (248). Aqueous disodium fluorescein and pentamidine aerosols were dried, concentrated, and condensation

Table III. Comparison of Different SCF Techniques for Production of Inhalable Particles

SCF Method	Solutes	Typical Product Forms	Major Applications
Supercritical antisolvent (SAS)	Drugs and excipients insoluble in CO_2 but soluble in organic solvents	Dry, crystalline powders formed by loosely packed, regularly shaped crystalline particles	Micronization for pure drugs, purification and modification of the drug crystal form
Rapid expansion of supercritical solutions (RESS)	Drugs and excipients soluble in CO_2	Dry powders or aqueous suspensions	Liposomes and lipid-coated particles
Particles from gas-saturated solutions (PGSS)	Drugs mixed with excipients which are plasticized by dissolved CO_2	Porous particles, aggregates or fibers	Sustained release materials, lipid formulations, polymer purification
Supercritical fluid extraction of emulsion (SFEE)	Water-insoluble drugs, composite materials: polymer or lipid with small or biological molecules	Aqueous suspensions or dry stabilized powders of crystalline or composite particles	Preparation of drug micro- and nanoparticles, also solid or porous composite particles for controlled release

coated with paraffin wax. The apparent MMADs of the coated fluorescein particles were 2.8–4.0 μm and the wax-to-fluorescein ratios were 0.38–1.05. The dissolution half-life increased by over three-fold when the aerosols were coated with paraffin wax. Wax-coated aerosols generated from fluorescein mixed with ^{99m}Tc-labeled iron oxide colloid delivered to the canine lungs demonstrated a 3.4-fold increase in the absorption half-life. No change in pulmonary function on inhalation of these wax-coated aerosols was observed.

Gas-phase coating of functional nanoparticles (leucine) on the surface of microparticles of salbutamol sulphate has been achieved using a modified SD process (249). In this method, the starting solution containing the drug and leucine was atomized and fed into laminar flow reactor at high temperature (150–180°C). Under these conditions, leucine had a sufficiently high vapor pressure to be vaporized and then precipitated as nanoparticles on the drug surface. Such particles, in the form of nanoflakes, increased the flowability and dispersion of these materials. It should be noted, however, that all the techniques involving particle coating from a gas phase are still in their infancy and therefore it would be difficult to make any solid conclusions regarding their efficiency and scalability. Nevertheless they represent another development tool for engineering coated and composite particles.

PRODUCT QUALITY, PAT AND PARTICLE ENGINEERING

Particle engineering for pulmonary delivery can be regarded as consisting of two integral parts: (a) design of better and more consistent dosage forms; and (b) development of innovative, advanced and scientifically driven manufacturing processes. From a regulatory perspective, this forms a part of the new Pharmaceutical Quality Assessment System (PQAS) and the Quality by Design (QbD) concept, being propagated by the new FDA guidelines (250), in which the basic science and engineering principles are taken to design, develop and manufacture a safe and effective drug product of intended quality and performance consistently, reliably, efficiently and economically (250). The QbD elements include at least the following (in addition to the drug product efficacy):

(a) A physically and chemically stable formulation lasting at least through the intended shelf-life
(b) Consistent delivery of the optimal/target dose to the intended lung sites
(c) Inert and robust container closure system (inhaler) which accurately meters and delivers the target dose through the proposed shelf-life of the drug product

These quality elements will define:

(1) The selection of the dosage form and formulation such as inhalation spray, solution or suspension, pMDI, DPI (pre- or device-metered)
(2) Inhaler design with maximum mechanical robustness
(3) Inertness (minimal impurities)
(4) Target dose reliability
(5) Manufacturability

It is generally recognized that the specific critical quality attributes for the pulmonary drug delivery include the PSD and delivered dose uniformity/dose content uniformity. Therefore, special attention is normally given to the design and development of the manufacturing process. One of the main goals of particle engineering is to minimize all possible sources of the product variability, such as wide PSD, changes of the solid-state form and particle cohesiveness, which may lead to the dependence of inhaler performance on the airflow rate. The technical foundation of the PQAS can be traced to the concept of the Process Analytical Technology (PAT, FDA) which is defined as "a system of designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality." It has been pointed out that this definition means more than just applying on-line sensors (251). Essentially, it is focused on building quality into the process and products with a view to be able to guaranteed their compliance with the typical end-product testing requirements that are currently employed. This also applies a holistic approach to the process design from the very beginning of the drug development process, optimization and scale-up to understand the key factors affecting the product quality and variability, including the physicochemical attributes of the drug substance, excipients, formulation and device as well as the manufacturing process. Therefore it is clear that particle engineering should be considered within the PAT framework for inhalation products.

Following the same basic principles (251), many examples in this review enable tracing of the manufacturing principles of certain formulations from the biopharmaceutical *in vivo* data and physicochemical attributes of a specific particulate system. For example, as demonstrated by Koushik and Kompella (3) the relatively large size of porous PLGA particles loaded with deslorelin (about 10 μm) correlated with sustained peptide release in rat lungs for over 7 days, likely due to their reduced uptake by the respiratory clearance system (3). Because of their reduced density (<0.1 g/cm^3), the aerodynamic diameter of such particle is below 3 μm, corresponding to deep deposition into the respiratory system. Therefore, knowing the critical process parameters (e.g., MMAD, volume mean diameter, particle density and drug loading), one can design a drug product that has maximal safety and efficacy for such a sustained release formulation. The product design that follows may include selection of a suitable inhaler design, which allows complete dispersion and dosing of such particles. Once the product design is established, the development work can focus on achieving the design goals and end points in laboratory and pilot scale studies, and then on process optimization through to commercial manufacturing process. Design of experiments (DoE) is a typical path for optimization in the pharmaceutical industry, although analytical chemical engineering science can be used to direct the studies based on process mechanism. Using emulsion and supercritical fluid technology as an example for illustration, the critical process parameters can be the size of the emulsion droplets and the time required for expansion of supercritical CO_2 to produce the required porosity. Simultaneously, a number of in-line sensors can be employed to control the droplet and particle size and control feedback systems can be

used to maintain the required particle size within the specified limits. Thus the PAT in this example may involve development of both novel formulations and novel manufacturing processes.

CONCLUSIONS

The present review has highlighted the current status as well as the major merits and limitations of both existing particle technologies and those that are being developed to meet the ever-changing needs of the inhalation therapy. The potential and possibilities of particle engineering for optimal drug delivery via the pulmonary route are enormous although the multifarious regulatory hurdles involved in taking them through rigorous assessment to eventual application are conceivably difficult to surmount. These hurdles are largely related to the issues dealing with the validation, scale-up and optimization of the manufacturing process, design of inhaler device and its dosing accuracy and reproducibility as well as the potential toxicity and adverse effects of the excipients used in the formulation. It can be envisaged that as more of the newly developed particle production technologies become mature through extensive evaluation, a more diverse range of powder inhalation products with particular therapeutic advantages (e.g., controlled/sustained release, direct targeting) or for specific therapeutic indications (e.g., diabetes) will become available.

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GLOSSARY

AAT	Alpha-1-antitrypsin
AFM	Atomic force microscopy
AUC	Area under the curve
CAN-BD	CO_2-assisted nebulization with bubble-drying
CFD	Computational fluid dynamics
COPD	Chronic obstructive pulmonary disease
DoE	Design of experiments
DPI	Dry powder inhaler
DPPC	Dipalmitoylphosphatidylcholine
DSCG	Disodium cromoglycate
ED	Emitted dose
FCA	Force-controlled additives
FDKP	Fumaryl diketopiperazine
FPF	Fine particle fraction
HFA	Hydrofluoroalkane
HIP	Hydrophobic ion pairing
HPMC	Hydroxylpropylmethylcellulose
IGC	Inverse gas chromatography
MDI	Metered dose inhaler
MMAD	Mass median aerodynamic diameter
MSCI	Multistage cascade impactor
QbD	Quality by design
OED	Oligosaccharide ester derivatives
PAT	Process analytical technology
PSD	Particle size distribution
PCMC	Protein-coated micro-crystals
PEG	Poly(ethylene glycol)
PGA	Poly(glycolic) acid
PGSS	Particle formation from gas-saturated solutions
PLA	Poly(L-lactic acid)
PLGA	Poly(lactide-co-glycolide) acid
PQAS	Pharmaceutical quality assessment system
PVA	Polyvinyl alcohol
PTH	Parathyroid hormone
RESS	Rapid expansion of supercritical solution
RH	Relative humidity
SA	Sebacic acid
SAS	Supercritical antisolvent
SCF	Supercritical fluid
SCT	Salmon calcitonin
SD	Spray drying
SEDS	Solution enhanced dispersion with supercritical fluids
SFEE	Supercritical fluid extraction of emulsions
SFD	Spray freeze drying
SLN	Solid lipid nanoparticles
TBA	Tributyl alcohol
TOF	Time-of-flight
XPS	X-ray photoelectron spectroscopy

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