of spray-drying for pulmonary delivery is immediately apparent when taken with the fact that particle size, density, and shape are the most important design variables for aerosol formulations [73]—all properties which can be precisely controlled by spray-drying. For efficient deep lung penetration, particles must have an aerodynamic diameter between 1 and 5 μm [74]. Thus, aerodynamic particle size is the key determiner of aerosol performance for an inhaled formulation [72, 74]. The aerodynamic particle diameter takes into account the size, density, and shape of the particle and is usually expressed as the mass median aerodynamic diameter (MMAD). To fit within the 1–5-μm range, the aerodynamic diameter of a particle can be decreased three ways: decreasing the particle size, reducing the particle density, or increasing the dynamic shape factor of the particle (i.e., the ratio of the actual drag force experienced by the particle to the resistance force experienced by a sphere of the same volume) [73, 75]. For particles larger than 5 μm, they must have a low-density, nonspherical geometric shape, or surface features which compensate for the larger particle size. For instance, Chew et al. (2005) found that moderate increases in surface corrugation or roughness of spray-dried protein particles improved aerosol performance, as evidenced by an increase in fine particle fraction (FPF) from only 26 % for smooth particles to 40 % for slightly wrinkled ones [76]. In addition to the particle size requirements, an aerosol product should ideally have a high FPF, high dose, good dose consistency and uniformity, narrow particle size distribution, suitable properties for chosen inhaler device, contain excipients safe for lung tissue, and retain the biological activity of the active compound [75, 77].

Many studies have demonstrated the feasibility of spray-drying for the production of inhaled biopharmaceutical formulations with the desired aerodynamic properties. Inhaled formulations prepared by spray-drying have already been attempted with many proteins, peptides, and other biopharmaceuticals, including insulin which will be discussed further in the section "Applications of Spray-Dried Biopharmaceuticals." Spray-dried particles containing plasmid DNA (pDNA) have been produced with a particle size of 3–5 μm and 44–60 % yield, and spray-drying did not compromise the transfection efficiency of the pDNA [78]. Spray-dried rhGH particles with dimethyl-β-cyclodextrin (DMβCD) as a pulmonary absorption enhancer and stabilizer resulted in particles with an FPF as high as 53 % [79]. Spray-dried small interfering RNA/poly(lactic-co-glycolic acid) (siRNA/PLGA) particles with different stabilizers, mannitol, trehalose, and lactose produced particles with an MMAD between 2 and 5 μm, yields ranging from 20 to 60 %, and preservation of siRNA biological activity [80]. Compared to lyophilized powders, spray-drying of liposomal DNA produced smooth, spherical, 4 μm particles with better gene transfer in cell culture than either fresh solution or lyophilized formulations [81]. An inhaled human parathyroid hormone (PTH) formulation (4.5 μm particle diameter, MMAD 3.9–5.9 μm, 90 % emitted dose, and 61 % FPF) had 186 % bioavailability relative to subcutaneous administration in rats and resulted in no acute lung inflammation after 48 h [82].

Spray-freeze-drying is emerging as an exciting option for inhaled formulation because it produces porous particles with high FPF which may have better aerosol performance than those produced by conventional spray-drying. Spray-dried powders