of two different proteins (deoxyribonuclease (rhDNase) and anti-immunoglobulin E (IgE) monoclonal antibody) had smaller particle sizes than those produced by spray-freeze-drying (3 vs. 7–8 µm) but had poorer FPFs (30–50 vs. 50–70 %) [83]. Additionally, the spray-freeze-dried formulations had significantly better dispersibility of particles less than 3 µm (53 vs. 15 % for rhDNase and 20 vs. 11 % for anti-IgE antibody) [83]. Even with a tenfold difference in geometric particle diameters, spray-dried (1–2 µm) and spray-freeze-dried (approximately 10 µm) DNA/peptide/mannitol particles had similar FPFs (about 50 %); however, the spray-dried particles had a significantly higher cell transfection efficiency [46]. Comparing the two methods, spray-freeze drying is more appropriate for temperature-sensitive biopharmaceuticals but is less easily scaled to the industrial level and is more expensive. Spray-drying has poor yield (typically 20–50 % but may exceed 70 % with a Büchi high-performance cyclone [33]), but spray-freeze-drying can achieve much higher efficiencies, typically > 80 % yield. Mohri et al. (2010) achieved 83–85 % yield for spray-freeze-dried pDNA for gene therapy [84]. However, spray-freeze-dried particles are very fragile and may be adversely affected by handling and shipping. Another challenge for both spray-dried and spray-freeze-dried inhaled formulations is the high excipient content. For example, of the studies referenced above, several have stabilizer concentrations in excess of 95 % of the formulation [46, 78, 84]. Special attention must be paid to the pulmonary safety of the excipients. Spray-drying and spray-freeze-drying are the most common production methods for dry powder aerosols of biological macromolecules [46, 73, 83], and the list of biological macromolecules developed for pulmonary delivery is extensive [70]. We discuss two indications of biopharmaceuticals which can greatly benefit from pulmonary delivery—disease prevention through vaccination and the treatment of diabetes mellitus.

Spray-Drying for Vaccine Stability and Delivery

Spray-drying research with vaccine candidates covers the gamut of possible types of biopharmaceuticals which can benefit from preparation as a spray-dried powder—live, attenuated vaccines which are whole, live pathogens; inactivated/killed vaccines which are dead pathogens; subunit vaccines which are generally pathogenic proteins; toxoid vaccines which are inactivated toxins from bacteria; conjugate vaccines which combine subunit or toxoid vaccines with the polysaccharide outer coat from bacteria; DNA or RNA vaccines; and recombinant vector vaccines which combine microbial DNA with a virus or bacterium as a carrier [85]. Indeed, many lyophilized vaccine products are commercially available in the USA, including M-M-R®II (measles, mumps, and rubella virus vaccine live, Merck & Co., Inc.), Hiberix® (haemophilus b conjugate vaccine (tetanus toxoid conjugate vaccine), GlaxoSmithKline), Varivax® (varicella virus vaccine live (chickenpox), Merck & Co., Inc.), and Rotarix® (rotavirus vaccine, live, oral, GlaxoSmithKline), to name a few. Researchers seek spray-dried vaccine formulations for the same reasons