

sisted of recombinant insulin (60%), sodium citrate, mannitol, glycine, and nominal amounts of sodium hydroxide (used to adjust the pH to 7.2–7.4) and was manufactured on a commercial scale spray-dryer with an inlet temperature of 181 °C and resulting outlet temperature of 87 °C [99]. With a final moisture content of <2% and the formation of a high- T_g amorphous solid, Exubera® was stable for more than 2 years at room temperature [101]. The following section reviews examples of spray-dried insulin formulations reported in the literature with particular focus on those publications which assess the effects of formulation and processing parameters on the final product characteristics.

Balducci et al. (2014) developed a spray-dried insulin formulation without excipients to maximize the insulin content and safety of the final formulation [41]. Their formulation was manufactured with a Büchi Mini Spray Dryer B-191 with an inlet temperature of 120 °C, airflow rate of 600 L/h, feed rate of 3.5 mL/min, and outlet temperature of 40–60 °C. They sprayed an acidic solution (acetic acid solution adjusted to pH 3.6 with ammonium hydroxide) of insulin, achieving an insulin content of 95%, a median particle diameter of 4 µm, and an MMAD of 2 µm. The obtained particles were “shriveled and raisin-like,” and they contained an 89.5% respirable fraction of the delivered dose, indicating that the shape and density of the particles contributed to the respirability of their formulation. Additionally, their formulation stayed within the European Pharmacopoeia requirements (<2.0% molecular masses greater than that of insulin (high molecular weight protein (HMWP)), <5% A21 desamido insulin (A21), and <6% for other related proteins (ORP)) for 3 months at 25 °C/60% RH. Following 18 months of storage, they had no content modification at 5 °C (i.e., within the European Pharmacopoeia requirements) and were just outside of specifications at room temperature with approximately 3% HMWP, 5.9% A21, and 4.3% ORP.

Bi et al. (2008) chose to use spray-freeze-drying to manufacture an aerosol formulation of insulin under the supposition that the spray-freeze-drying process produces large particles with small MMADs which would improve aerosolization and dissolution [102]. Their optimal formulation was a spray-dried liposomal formulation containing soya lecithin and cholesterol with sucrose as a lyoprotectant. Using a Büchi Mini Spray Dryer B-191, they sprayed their formulation with a two-fluid nozzle positioned 10 cm above the liquid nitrogen. Drug retention in the formulation was used to select the best excipient with results as follows: sucrose > lactose > glucose > mannitol. Also, in evaluating the spray-freeze-drying procedure, compressed air pressure (optimal=0.4 MPa) was determined to be the most critical parameter for optimizing the particle size, followed by liquid flow rate (optimal=5 mL/min) and concentration (dilution of 6% (w/v)). They found that a higher air pressure resulted in finer powders (higher FPF). Bi et al. reported that the spray-freeze-dried liposomal insulin formulations produced a prolonged hypoglycemic effect in rats after pulmonary administration.

Depreter et al. (2010) manufactured a spray-dried solid lipid formulation intended for pulmonary delivery of insulin with cholesterol/phospholipon (75/25) as the lipids [103]. After spray-drying, their best formulation achieved an FPF of 63%, an MMAD of approximately 3 µm, and a yield of 60%. Al-qadu et al. (2012) used chi-