higher IgG titers and a more balanced type 1 T helper cells/type 2 T helper cells (Th1/Th2) immune response than the liquid antigen.

In addition to pulmonary delivery, another alternative route of administration is through the skin but as a needle-free ballistic administration rather than an intramuscular injection. For example, Maa et al. (2004) formulated two influenza vaccines (split-virion vaccine and subunit vaccine) by spray-freeze-drying [95]. The excipients considered were dextran, mannitol, trehalose, arginine glutamate, and Pluronic F-68P. Spray-freeze-drying produced yields ranging from 82 to 89% (higher yields than from most spray-drying processes) and large particles with a median size range of 35–56 μm. A final optimized formulation consisted of trehalose, mannitol, and dextran at a 3:3:4 ratio with antigen purity identified as the most critical factor for a successful formulation and with a stability of 1 year at room temperature. Chen et al. (2010) also evaluated the formulation of two different types of vaccine antigens—a subunit vaccine with an aluminum-salt for hepatitis B virus and a polysaccharide–protein conjugate vaccine for meningitis A [96]. In contrast to spray-freeze-drying with Maa et al., Chen et al. studied the production of conventional spray-dried formulations. They used a Mobile Minor™ pilot plant (GEA Niro) to manufacture these preliminary formulation and had similar results with 2+ years of stability at 37 °C and with 90%+ yield for their HepB vaccine. Choice of type of spray-drying is not defined by the type of vaccine but rather by the processing parameters and excipients therein.

Spray-Drying for the Formulation of Inhaled Insulin

Insulin is a good candidate for pulmonary delivery, and the challenges faced by researchers in pursuit of an inhalable form of insulin accurately represent the spray-drying formulation process and the critical need for methodologies which allow fine-tuning of particle properties. Insulin is known to have a high permeability through the alveolar membrane and is a good candidate specifically for spray-drying because it can tolerate a large range of temperatures and maintain its bioactivity following spray-drying. Patel et al. (2001) confirmed that insulin can retain its activity following spray-drying with air inlet temperatures ranging from 110 to 170 °C, only losing activity at 200 °C [97]. Insulin's robust range of tolerable temperatures means that co-sprayed stabilizers can be selected from a larger pool of excipients, although its indication, diabetes mellitus, limits the use of some sugars as stabilizers.

Spray-drying insulin is a popular line of research within the spray-dried pharmaceutical industry, spurred forward by the approval of Exubera® (Pfizer) by the Food and Drug Administration (FDA) in early 2006, and making insulin the first and only approved systemic protein administered through the lungs [98, 99]. In clinical trials, patients receiving Exubera® reached peak insulin concentrations faster than those injected with insulin [100]. However, the product was discontinued in October of 2007 with Pfizer citing poor sales as the reason for discontinuation. Exubera® con-