producing small aqueous droplets. However, instead of removing the water with heated gas, heat alone is removed from the droplets leaving the solute in a matrix of ice. Subsequently, the water is removed by lyophilization. Two major approaches are used to remove the heat from the droplets. In the first, the feed is sprayed directly into liquid nitrogen, sometimes called spray-freezing into liquid (Fig. 4a). The nitrogen is then removed, and the frozen product is freeze-dried [24, 25]. In the second approach, referred to as atmospheric spray-freeze-drying, the sample is sprayed into a chilled chamber (sometimes as low as −90 °C), collected on a filter, and then dried with a stream of cold, desiccated gas (below the eutectic temperature of the target material; Fig. 4b). This approach to spray-freeze-drying was patented in 2008 [26] and has been employed for the development of pharmaceutical formulations [27, 28]. While the atomization is similar to spray-drying, spray-freeze-drying has the additional necessity of liquid nitrogen or other super cooling methods which require specialized drying chambers. Because the feed is sprayed into liquid nitrogen or onto a filter, spray-freeze-drying does not require a collection cyclone. The sample, however, must be either transferred to a freeze-dryer or freeze-dried in place. While much of the spray-freeze-drying research is conducted with in-laboratory produced equipment, there are a few manufacturers of laboratory and production scale equipment. One such company is PowderPro AB (Goteborg,

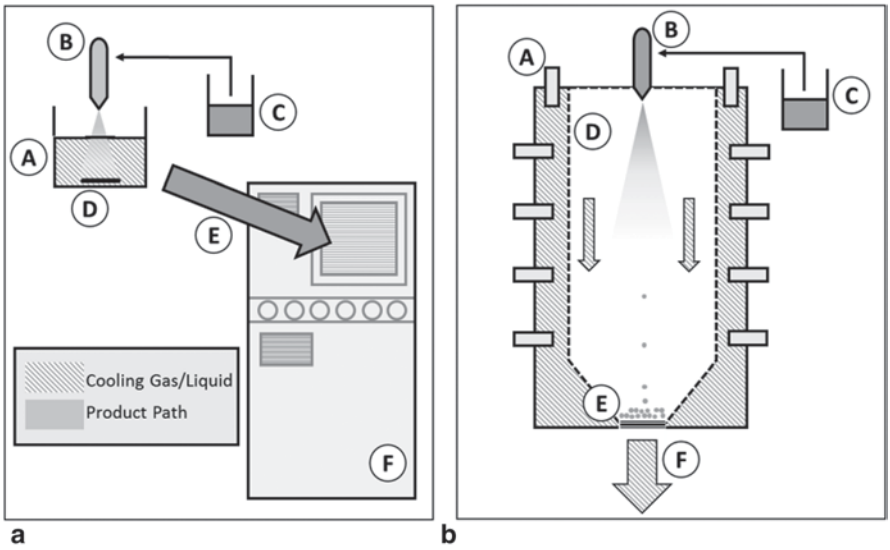

Fig. 4 Different types of spray-freeze-drying. **a** Diagram of spray-freeze-drying into liquid with (*A*) liquid nitrogen; (*B*) spray nozzle; (*C*) liquid feed; (*D*) stirrer; (*E*) transfer of frozen droplets to freeze-dryer after sublimation of liquid nitrogen; and (F) freeze-dryer. **b** Diagram of atmospheric spray-drying with (*A*) nozzles circulating coolant in outer chamber; (*B*) spray nozzle; (*C*) liquid feed; (*D*) drying chamber with porous walls; (*E*) collection filter for dry product; and (*F*) gas outlet to refrigerated condenser. This atmospheric spray-freeze-drying diagram is adapted from one configuration described by [26], but other cooling gas configurations also exist