cooling gas to increase the cooling rate of the particles and by spraying smaller droplets. The final size of the lipid particles following spray-congealing is a direct reflection of the atomizer's ability to shear the feed stream into small droplets, and the particle size can be reduced by heating the feed stream to lower its viscosity and by increasing the force of aspiration. The most important difference in particle properties for spray-drying versus spray-freeze-drying is the size and porosity. Spray-freeze-drying results in large, highly porous, fragile particles [46]. The temperature at which the droplets are dried can also change the morphology of the particles. If the drying temperature is above the T_g of the solutes, the particles may not maintain the spherical shape of the original droplets (i.e., becoming collapsed or shrunken), which will affect other properties such as the density of the particles [47].

Lyophilization Versus Spray-Drying

Freeze-drying, or lyophilization, is a well-established pharmaceutical manufacturing procedure, encompassing approximately 50% of currently marketed biopharmaceutical products [48]. The predominant role of freeze-drying is to improve the long-term stability of labile biopharmaceuticals, by inhibiting or sufficiently decelerating chemical and physical degradation [49]. Additionally, solid state, lyophilized formulations are easier to handle, ship, and store [50]. Formulation by spray-drying seeks these same characteristics. Choosing between these two drying methods is ultimately dependent on the final desired storage conditions and formulation characteristics, as well as consideration of the specific tolerable stresses (physical and/or chemical) of the biopharmaceutical in question. However, several overarching advantages and disadvantages remain true regardless of the nature of the biopharmaceutical. First, specific to the manufacturing process, spray-drying is more easily scaled to the industrial production level and has lower initial investment costs [3]. The processing time is much shorter for spray-drying, which is on the order of hours, than for freeze-drying which can take days [51]. Spray-drying is a one-step process, whereas freeze-drying may require another milling procedure to form particles. However, spray-drying requires a secondary bottling or packaging step for the final product, whereas freeze-drying can dry and cap samples aseptically in one step if milling is not required. Freeze-drying is limited to a batch process as opposed to continuous processing with spray-drying. Both drying methods can achieve low residual moisture levels [7, 52], which is important because high residual moisture content negatively affects chemical and physical stability [53]. Spray-drying offers the flexibility to tailor particle properties to suit varied purposes (e.g., controlled release, optimal size and morphology, etc.) as outlined in section "Basics of Spray Drying," while freeze-drying offers few options for particle property manipulation. However, spray-drying subjects the biologic to added shear and temperature stresses that are not present in freeze-drying. Biopharmaceuticals sensitive to high temperatures may not be suited for spray-drying, but those biologics particularly vulnerable to freezing temperatures are not suitable for freeze-drying.