the evaporation of the solvent from the surface of the droplet, the crystallization of the solute material in the droplet, and the diffusion of the solvent from the interior to the surface of the particle. This chapter covers the general principles which apply to most formulations, but Nandiyanto and Okuyama (2011) review the latest research regarding the correlations between spray-drying parameters and particle morphology [38]. As with yield efficiency, the interplay between the processing parameters, the different types of spray-drying equipment, and the diversity of biopharmaceuticals make the optimization of spray-dried particle morphology very specific to the biologic and its intended application. Regarding particle size and morphology, the type of atomizer, feed composition, and feed concentration are the most influential processing parameters [39]. The drying rate may be considered a significant factor only because a slow drying rate may lead to agglomeration of the particles. For atomization, smaller nozzles and higher shear lead to smaller droplets, translating into smaller dried particles. As the concentration of solids in the feed stream decreases, so will the size of the dried particles. The effect of feed composition is more complicated because both the solvent and solutes can affect the particle size but often affect the morphology of the particles as well. Specifically, the solvent evaporation rate affects the porosity of the particles, and feed composition and temperature mainly impact the morphology of the particles. If the evaporation rate is high (e.g., high drying temperatures for a volatile solvent), surface enrichment is enhanced leading to hollow shells and complex structures. Multiple solvents with different evaporation rates enhance the possibility of obtaining particles with complex interior pores with discrete domains. In addition, the use of solute materials with vastly different solubilities, mass transport properties, and heat transport properties enhance the likelihood of obtaining complex particles [40].

Finally, product stability is always an important consideration for biopharmaceuticals. The main factors that influence the stability and activity of biopharmaceuticals during spray-drying are inlet temperature, oxygen environment, and inclusion of stabilizing excipients. Vaccines and proteins can be successfully spray-dried with little physical or chemical damage [37, 41, 42] and will be discussed further in section “Challenges Specific to Spray-Dried Biopharmaceuticals.” Excipients such as amino acids, sugars, and polymers may be incorporated in the formulation to stabilize biopharmaceuticals during the spray-drying process and for long-term storage following spray-drying [43, 44]. Most spray-dryers are equipped to operate within a nitrogen atmosphere, and, therefore, they can be used for spray-drying biopharmaceuticals that are oxygen-sensitive and require processing in an inert atmosphere. Once again, only broad generalizations can be drawn since the type of stabilizing excipient and the most likely source of degradation is highly dependent on the biopharmaceutical in question.

The optimization discussion to this point has focused on the optimization of conventional spray-drying, but spray-congealing and spray-freeze-drying have additional operational parameters which impact yield, particle morphology, and biological stability. Generally, the yield from spray-congealing is high [45] but, like conventional spray-drying, is affected by adherence of particles to the walls of the drying chamber. This loss can be minimized by lowering the temperature of the