

Physical characteristics of the final product (size, morphology, surface area, and density of particles), biochemical characteristics (purity, potency, solubility, and stability of the formulation), and process yields may be manipulated. The goal is a dry, free-flowing powder with well-defined particle characteristics and consistent purity and presentation and an active, stable, and acceptable dissolution profile, all obtained by as simple a process as possible.

9.9.2.3 Undercooling

It is another process wherein under certain conditions, a liquid can be cooled to temperatures below its freezing point (supercooling or undercooling). If a solution is separated into droplets, as in a mist or a water-in-oil emulsion, then only those drops with particles in them will freeze if cooled, rather than catalyzing a chain reaction of freezing throughout the solution. For protein formulations, the product in aqueous solution can be dispersed as microparticles through an oil-phase carrier (liquid at the mixing temperature and solid if stored at -20°C), so that the drops are locked in as liquid. Reconstitution is easier than with a lyophilized or spray-dried product, as the product is warmed up at the point of use until the phases separate. This undercooling process may be used for even high-concentration protein formulations, requiring no additives like glycerol, which must be filtered out before the product can be used. Undercooling may be a particularly good choice for products that are susceptible to freeze damage.

9.9.2.4 Lyophilization

This technique produces stress conditions that may cause certain stresses on proteins that can result in unfolding (though generally completely refolded when reconstituted); so, specific conditions must be determined, and stabilizing additives must be appropriate for use during both the freezing and drying stages to allow at least 2 years of shelf life, with stable cake morphology, dispersibility, and dissolution. The presence of solutes lowers the freezing temperature of an aqueous solution, making the solution more viscous at even below water's freezing temperature, when the solute becomes supersaturated and releases latent heat; this point is known as the eutectic point, T_e ; when the physical state changes from elastic liquid to brittle but amorphous solid glass, this is called glass transition temperature or T_g , at which point ice formation ceases. For pure water, T_g is -134°C . The T_g for solutes is generally higher, and for solutions, it is somewhere in between. The T_g is an important temperature, as below this temperature, the mobility of a solution is greatly reduced, and all degradation reactions slow down, except reactions such as oxidation. The presence of some moisture reduces T_g , and the presence of components such as sugar raises it substantially.

Freezing forms an amorphous solid of the protein and excipients with associated water in crystalline form. Annealing, an optional step, increases ice-crystal size and allows crystallization of bulking agents (such as glycine or mannitol), removing them from the amorphous portion and increasing T_g . Primary drying sublimates water ice at temperatures lower than T_g (to avoid collapse of the cake). The higher the T_g , the higher can be the mixture's temperature and sublimation rate. Increasing the protein to the excipient ratio will increase T_g . Secondary drying removes water from the amorphous phase by an increase in the sample temperature, which still may not exceed T_g .