

more stability data become available; while formulation changes prove expensive, if these result in extension of the shelf life, it is almost always a good investment.

Proteins are most stable in solid form and show less impact of storage temperature (though they still need to be kept at a cool temperature). The liquid formulations are more advanced formulations that are generally stabilized and must be stored at controlled temperature throughout the use chain. As the bulk manufacturing of proteins results in a concentrated solution state, this must be processed to concentrate and eventually solidify it through such processes as cryopreservation, cryogranulation, spray-drying, undercooling, and lyophilization.

9.9.2 Cryopreservation

Freezing can extend the shelf life of unstable products and improve containment if the freeze–thaw process is consistent. Frozen products can be transported safely for final formulation elsewhere and stockpiled to optimize the fill and finish process, which can reduce the processing costs. Generally, freeze–thaw cycles result in a significant loss of activity, and many believe that proteins cannot be frozen and thawed without damage, because no practical methods exist for doing so on a large scale. The usual method, which is both slow and nonreproducible, involves small volumes in bags, bottles, or vials freezing at -0°C or below. A slow freeze alters the physical properties (pH, diffusion, and reaction rates) of the aqueous solvent medium or mixture, which can denature proteins, particularly over an extended time. The solution is then thawed at room temperature, with some components thawing before others. Ice recrystallization in the thawing process creates mechanical stress.

9.9.2.1 Cryogranulation

It is a frequently used technique for small-molecule drugs, but cryogranulation of proteins using liquid nitrogen has not been very successful.

9.9.2.2 Spray Drying

It is a dehydration process that uses heat from a hot-air stream to evaporate dispersed droplets created by atomization of a continuous liquid feed. Products dry within a few seconds into fine particles (powders). It is similar to freeze-drying. Important data for formulators working with any type of freezing process will be the glass transition temperature (T_g) of each component and the solution. At this temperature, ice crystal formation decreases to undetectable levels, and the freeze is an amorphous glass from which water will sublime. Spray drying offers some advantages over freeze drying: shorter process times, lower capital investment in equipment, and lower energy input to the solution, which can lessen the chances for protein denaturation. Disadvantages include the brief but high air-temperature exposure during the rapid-drying step (around 100°C) and shear stresses caused by spraying a formulation through a nozzle. The product temperature reaches about 80°C but only for a fraction of a second. Particle characteristics and size distribution can be closely controlled in spray drying by changing process variables, such as solution composition and feed rate, atomizing gas pressure, air flow rate, and the inlet and outlet gas temperatures.