Suspended impurities in the solution or imperfections in the walls of the container initiate heterogeneous nucleation during freezing. This event almost always involves supercooling where upon crystallization occurs below the equilibrium freezing point of the solution. Consequently, when freezing does occur, crystal growth tends to be rapid and results in a complex mixture of crystalline, amorphous, and metastable materials. The impact of the presence of organic solvents on the various phases of freeze-drying has been discussed in detail (52–56). Not surprisingly, the type and concentration of the organic solvent present affects the freezing characteristics of the solution prior to initiation of drying. The resulting frozen or semi-frozen solution significantly impacts the crystal habit of the ice, the drying rates, the collapse temperatures, the appearance of the dried cake, the surface area of the dried cake, and reconstitution properties, etc. The choice of solvent can also affect the degree of crystallinity of the drug. It has been demonstrated that incorporation of isopropyl alcohol readily results in highly crystalline cefazolin sodium (26). Scaling up this process required incorporation of a heat treatment step to insure complete crystallization of the drug. Use of cosolvents can sometimes have deleterious effects during freezing. The use of volatile organic solvents has been reported to result in drug precipitation in the latter parts of freezing due to solvent evaporation. This can lead to an increase in drug concentration above its saturation level (55). Care should be taken to select excipient concentrations such as buffer salts so that they do not exceed their saturation solubility. This is particularly important for phosphate buffers since they have very low solubility products with certain cations such as aluminum, calcium, or iron (57–60). As a result, salt precipitation can produce a haze upon reconstitution. Additionally, the preferential precipitation of one of the forms of phosphate can also cause a significant pH shift for the frozen solution. Therefore, it is critical to select buffer components that can maintain pH in both the solution and frozen state. These precipitation problems can be exacerbated in cosolvent systems due to the decreased solubility and higher association constants for such systems.

The size and shape of the ice crystals has been found to vary with different organic solvents. Trace impurities of isobutyl alcohol have been shown to significantly alter the crystal habit of ice crystals (61). The presence of small levels of organic solvents (e.g., DMSO, ethanol, dichloromethane, or acetone) in an aqueous solution has been shown to influence the nucleation of ice crystals and their subsequent growth (62). These organic impurities can also potentially reduce the collapse temperature for the frozen solution (63,64). The presence of ethanol was shown to cause the inhibition of crystallization of solutions of mannitol during freeze-drying unless an annealing step was utilized (65). The presence of high melting point solvents, such as *tert*-butanol, results in solvent crystallizing between the ice matrix as the temperature is decreased. The presence of the *tert*-butanol altered the crystal habit of the ice as it formed. The size of the ice crystals (i.e., large vs. fine) changed depending on the quantity of *tert*-butanol present in the system. The other materials present with the *tert*-butanol/water system can influence the freezing behavior of the alcohol. It has been reported that crystallization of *tert*-butanol hydrate was inhibited by the presence of excipients such as sodium bicarbonate or mannitol (7). Sucrose can also influence the crystallization of *tert*-butanol during cooling such that as the ratio of *tert*-butanol to sucrose was less than 0.2 the *tert*-butanol does not crystallize (66). Investigators demonstrated that *tert*-butanol crystallizes more readily in the