presence of tobramycin sulfate than in the presence of tobramycin base (67). Thermal analysis studies (via differential scanning calorimetry and freeze-dry microscopy) have been used to evaluate the various stable and metastable states that form for *tert*-butanol/water systems during freezing (68). The authors were able to apply various annealing techniques to eliminate the metastable states and were able to construct the true phase diagram. Although this phase diagram agreed well with other *tert*-butanol/water phase diagrams reported in the literature (69,70), it was claimed that the slight differences could be explained by the presence of metastable events that thermal treatments eliminated. These data suggested that *tert*-butanol levels in the range of 3% to 19% caused the ice to form needle-shaped crystals. As these large needle-shaped crystals sublimed, they created a more porous, less resistant matrix, which facilitates drying. Other solvents such as acetic acid, formic acid, or dimethyl carbonate also appear to freeze under production freeze-dryer conditions and can be adequately lyophilized. However, most of the organic solvents investigated (56) such as methanol, ethanol, *n*-propanol, *n*-butanol, acetonitrile, methyl ethyl ketone, dichloromethane, and methyl isobutyl ketone do not freeze in typical commercial freeze-dryers but remain as liquid residues within the frozen matrix. The following appears to occur when using conventional freeze-dry equipment: (*i*) solutions containing 8% ethyl acetate, 10% dimethyl carbonate, or 10% *n*-butanol appeared to dry rapidly; (*ii*) solutions containing 10% ethanol, 10% *n*-propanol, or 10% methanol appeared to dry slowly; and (*iii*) solutions containing up to 20% ethanol experienced collapsed cakes and were near impossible to dry [56]. However, other investigators stated that mannitol, in ethanol concentrations up to 30%, may be freeze-dried and produce an elegant cake appearance (65). The ability to achieve this acceptable cake would be a function of various parameters such as ethanol ratio, cycle design, mannitol concentration, and characteristics of other excipients present. Some of these more hydrophilic solvents such as ethanol and methanol retained significant amounts of associated water that only partially froze as the temperature decreased. Samples dried with organic solvents that do not completely freeze may produce a product that is heterogeneous with respect to residual solvent. Use of appreciable levels of solvents, which do not freeze, usually result in unacceptable cake appearance. However, in those products that produce a resistant surface skin during the drying process, a small level of unfrozen organic can cause discontinuities in the skin sufficiently to potentially facilitate the removal of the frozen water vapor (71).

In those systems that completely froze (e.g., *tert*-butanol), the ice and frozen solvent grew upward until reaching the solid surface and formed a eutectic skin. However, other investigators noted that solutions of sulfobutylether 7-β-cyclodextrin in 5% *tert*-butanol froze by having the ice crystals nucleate, grow from the vial bottom, float to the top, and result in fast top-down freezing (72). Hydrophilic solvents that retained large volumes of water formed thick liquid skins containing ice whereas less hydrophilic solvents containing less water formed thinner skins with less ice.

It should also be noted that the time between filling the cosolvent solution and the freezing of this solution should be carefully controlled. The volatility of the organic portion of the solution can be such that a significant portion of the organic solvent can be lost due to evaporation. The loss of solvent may affect content uniformity among different vials. One should be aware of the potential