A more in-depth study was later completed evaluating the use of *tert*-butanol as a mass transfer accelerator during the freeze-drying of a 5% wt/vol sucrose solution (77,78). Again it was demonstrated that the primary drying phase (i.e., sublimation) proceeded more rapidly when 5% wt/wt *tert*-butanol was present, thereby resulting in an approximately 10-fold reduction in drying time. This subsequent decrease in sublimation time was confirmed by others studying the effect of *tert*-butanol used in freeze-drying and concluded that the drying times were comparable to what was observed with agitated vacuum contact dryers (79). This increased drying rate was caused by the formation of needle-shaped ice crystals that dramatically lowered the product resistance of the dried cake. The resulting surface area of the dried cake increased by approximately 13-fold when the 5% *tert*-butanol was used. The presence of the *tert*-butanol did not impact the collapse temperature; however, the rapid sublimation prevented the product from reaching the collapse temperature. The rationale for this was postulated to be because the water content in the partially dried layer decreased faster in the presence of the *tert*-butanol, which resulted in an increased viscosity and thereby prevented collapse. The rate of sublimation of both the water and the *tert*-butanol was impacted by the ratio of the two solvents. Water appeared to sublime faster at ratios of less than 20% wt/wt *tert*-butanol/water. *tert*-Butanol appeared to sublime faster at ratios of greater than 20% wt/wt *tert*-butanol/water. Both solvents sublimed at equal rates at 20% wt/wt *tert*-butanol/water. The latter data suggested a strong association at this concentration. This data is consistent with the sublimation of water and *tert*-butanol from the frozen matrix of CAVERJECT Sterile Powder during freeze-drying, as illustrated in Figure 4. Others noted an increased drying rate for sulfobutylether-7-β-cyclodextrin lyophilized from 5% *tert*-butanol (72). They also noted a top-down freezing mechanism for this system. It was postulated that, in addition to the large ice crystals that form in solutions of *tert*-butanol/water, the ice structure formed by the top-down freezing mechanism might help increase the sublimation rate (72). The addition of the 5% *tert*-butanol for this system reduced the T_g' by 10°C; however, it only decreased the collapse temperature by 2°C.

Mixtures of *tert*-butanol/water were also used to increase the rate of freeze-drying for solutions for a model drug, gentamicin sulfate (14). Simple freeze-drying of the gentamicin with the cosolvent system was not sufficient to produce an acceptable cake. The investigators had to apply a statistical experimental design to achieve the final formulation. All components of the formulation studied, that is, the active ingredient, *tert*-butanol/water ratio, and the amount of the maltose bulking agent were optimized to achieve a reduction in drying time by approximately 40% and yet produce a freeze-dried cake of acceptable porosity. The addition of the maltose was a key component for this particular formulation and process. It should be readily apparent that optimization of the formulation and process parameters are necessary to maximize the impact of the cosolvent system on drying rates.

IMPACT ON STABILITY OF FREEZE-DRIED PRODUCT

Positive Impact on Stability

It is noteworthy that the chemical stability of the freeze-dried product can be positively impacted by the type of solvent system from which it is lyophilized. The product, CAVERJECT Sterile Powder, is significantly more stable when it is