the diffusion coefficient of the volatile organic to the diffusion coefficient of water decreases. This ratio becomes so small for low water/organic concentrations in dry amorphous carbohydrates that the system is only permeable to water (100,101).

The impact of formulation and process variables on residual solvent levels for formulations that were freeze-dried from *tert*-butanol/water cosolvent systems has been critically evaluated (102). The physical state of the solute (i.e., amorphous vs. crystalline), the initial *tert*-butanol concentration, freezing rate, cake thickness, and temperature during secondary drying were examined. It was noted that when a crystalline matrix was used (e.g., glycine), the residual *tert*-butanol was very low (0.01–0.03%), regardless of freezing rate or initial *tert*-butanol concentration. Freeze-drying of SarCNU from neat *tert*-butanol produced crystalline SarCNU, which was very low in residual *tert*-butanol (0.001%) (49). Interestingly, the residual *tert*-butanol data when a D-mannitol matrix was used was reported to be approximately 0.8% (6). Although the authors claimed to have produced crystalline mannitol via annealing at $-20^{\circ}C$, it is possible that the thermal treatment was only annealing some unfrozen *tert*-butanol hydrate and that part of the mannitol remained uncrystallized. This may explain the higher than expected residual *tert*-butanol levels for a totally crystalline matrix. Considerably higher residual *tert*-butanol levels were noted when freeze-drying an amorphous sugar such as sucrose from *tert*-butanol/water systems. However, processing conditions had a profound impact on the residual solvent level present at the end of drying. Low levels of *tert*-butanol/water (1–2% wt/wt) resulted in high levels of *tert*-butanol residuals in the dried sucrose amorphous cake ($\approx$10–18%). Higher levels of *tert*-butanol (3–5% wt/wt of an aqueous solution) resulted in lower residual *tert*-butanol levels in the dried amorphous cake ($\approx$2%). Freeze-drying tobramycin sulfate from various levels of *tert*-butanol (5–9%) produced residual solvent levels ranging from 0.6% to 1.0% (67). Similar results (1–2% residual levels) were obtained when freeze-drying lactose solutions from 20% vol/vol *tert*-butanol/water mixtures (2). This latter matrix would also be expected to produce an amorphous cake. It was postulated that, when using *tert*-butanol levels above the threshold concentration required for eutectic crystallization of the solvent, lower residual *tert*-butanol levels in the freeze-dried cake are obtained. The reverse is true when the starting *tert*-butanol concentration is below this threshold. Freezing rate appeared to impact the residual *tert*-butanol level for amorphous systems in that fast freezing (e.g., with liquid nitrogen) produced cakes with higher residual *tert*-butanol. Examples of the latter observation were supported by the higher residual alcohol levels when flash freezing *tert*-butanol solutions of tobramycin sulfate or sucrose (10,102) or liquid nitrogen freezing of aqueous solutions of *n*-butanol (99). These data appeared to contradict the data reported for isopropanol retention in freeze-dried maltose or dextran (98) and other *n*-alcohols in maltodextrin (100). It also contradicts data for residual *tert*-butanol retention in freeze-dried lactose. It would, therefore, appear that the impact of freezing rate on residual solvent content requires evaluation on a case-by-case basis.

Evaluation of the factors that influenced the residual *tert*-butanol in cyclodextrin complexes freeze-dried from *tert*-butanol/water revealed that the initial *tert*-butanol concentration should be higher than the crystal formation concentration, the appropriate cyclodextrin should be selected, and one should employ an annealing technique (103). Increases in both time and temperature for