degradation rate constant for this product is related to the reciprocal of the dried cake surface area. Since the degradation kinetics of the active ingredient, alprostadil, appear to fit an apparent second-order mechanism with respect to the alprostadil concentration (i.e., the rate of formation of the major degradation product, PGA_1, increases by the square of the alprostadil concentration), the improved chemical stability is consistent with a larger cake surface area, which might increase the distance between the alprostadil molecules.

Another example of improved chemical stability for the lyophilized product includes the use of isopropyl alcohol in the freeze-drying of cefazolin sodium (26). The presence of the isopropyl alcohol helped induce crystallization of the amorphous cefazolin sodium during the freezing phase. The presence of the isopropyl alcohol decreased the glass transition temperature of the system and lowered the temperature of crystallization (80). Use of the isopropyl alcohol with a thermal treatment phase enabled a freeze-dried crystalline form of the drug to be produced, which possessed superior stability (26). Use of this cosolvent system also enabled the product to be more effectively processed with shorter lyophilization times and fewer instances of cake collapse. However, when mannitol was added to the system, the presence of the mannitol prevented the crystallization of the cefazolin sodium even with a thermal treatment (80). Other short chain alcohols, for example, methanol, ethanol, and *n*-propanol or acetone are also claimed to provide similar improvements to freeze-drying of cefazolin sodium (27). Crystalline lyophiles of cefazolin sodium could be obtained using a *tert*-butanol/water cosolvent system (25). A thermal treatment with high initial concentration of cefazolin sodium was necessary to induce crystallization.

Freeze-drying of sucrose solutions with isopropanol has been shown to produce a cohesive cake, which is more physically stable at higher temperatures (81). Heating of the dried amorphous sucrose under the right conditions can induce the sucrose to become crystalline as the residual alcohol evaporates.

A very unique technique was employed in stabilizing tobramycin sulfate by use of freeze-drying from a 20% *tert*-butanol/water system (10). Initially the product was freeze-dried using this cosolvent system. The resulting cakes contained amorphous tobramycin sulfate. However, prior to unloading the dryer, humidified nitrogen was pumped into the freeze-dry chamber. The increasing moisture level caused the glass transition temperature of the tobramycin sulfate to sufficiently decrease and allow crystallization to occur. This was followed by rapid release of the residual *tert*-butanol. The resulting product was an in situ crystallized form of tobramycin sulfate with very low level of residual *tert*-butanol (0.008%).

Spray freeze-drying of Δ^9-tetrahydrocannabinol in inulin from a *tert*-butanol/water cosolvent system was shown to help stabilize the labile drug (82). It was noted that spray freeze-drying of above produced more stable product than simple freeze-drying in a vial. It was postulated that the spray freeze-drying enables faster freezing and hence less time for phase separation to occur. It was recommended to use spray freeze-drying for the production of solid dispersions.

Freeze-drying of plasmid DNA from 20% vol/vol *tert*-butanol/water with calcium chloride produced a condensed shear resistant form of DNA with improved stability (83).