Negative Impact on Stability

Conversely, there are cases where the lyophilization from cosolvents can produce a less stable system. An example of this occurrence is illustrated by the lyophilization of the protein, bovine pancreatic trypsin inhibitor from 1% water/DMSO (36). The data appear to support the premise that the protein dissolving DMSO denatures the protein sufficiently to reduce its enzymatic activity after reconstitution. Additionally, it is important to evaluate the impact of residual organic solvent remaining at the end of primary drying since the combination of the solvent and higher product temperatures during secondary drying may lead to undesirable chemical reactions (71). The use of cosolvents can also have a negative impact on the stability of cyclodextrin-bound stabilized drug preparations since the cosolvent may compete for the binding of the drug molecule to the cyclodextrin and lessen the percentage of bound drug at the end of freezing prior to lyophilization.

IMPACT ON RECONSTITUTION PROPERTIES FOR STERILE PRODUCTS

The ability of the freeze-dried cake to be readily reconstituted upon addition of an appropriate pharmaceutical solvent is dependent on several factors. The structure of the dried product, the degree of cake collapse or melt-back that has occurred during drying, the surface area of the cake, the presence of hydrophobic coatings, and the homogeneity of the dry matrix are all factors that can influence the reconstitution properties of the dried product. Depending on the organic cosolvent selected and processing conditions used to freeze-dry, the product may or may not readily reconstitute. Therefore, one will need to evaluate this property on a case-by-case basis. However, there are examples of freeze-drying sucrose and lactose solutions from *tert*-butanol/water solutions with the proper drying cycle where amorphous cakes with large surface areas were produced (2,76). These cakes tended to reconstitute extremely rapidly upon addition of reconstitution vehicle. Proper freeze-drying of tobramycin sulfate from *tert*-butanol/water systems produced a friable easily reconstitutable cake; however, freeze-drying the same drug with less than 10% ethanol or isopropanol produced a hard, difficult to reconstitute cake (10).

It is also important to recognize the importance of extractables from the filling line and package system (i.e., the glass vial and rubber closure or the filter and tubing) used to filter, fill, and hold the solution being lyophilized. The use of siliconized vials or stoppers can cause problems when organic cosolvents are used because the organic solvent can solubilize or extract silicone oil from the package component. This can be especially problematic when freeze-drying in syringes since they are typically siliconized to facilitate their use. This same problem can also occur if silicone tubing is used to transfer solution during filtration, filling, etc. The extracted silicone oil can impede the wetting of the affected portions of the cake, result in the cake being difficult to reconstitute, cause the reconstituted solution to become hazy, or exceed the particulate matter and/or clarity specification limits. A high organic content also requires a judicious choice of sterilizing filters. Fortunately there is now a reasonable choice of high-quality solvent-resistant filters available. However, it is recommended that the filter manufacturer be consulted on their selection and that appropriate compatibility studies be performed.