chamber shelves are lowered after completion of the lyophilization cycle, the stopper must be able to be pushed into the vial and fit snuggly. The stopper cannot be pulled out because of tackiness nor can it pop out of the vial because of inappropriate interference fit between the stopper and the glass or because of overlubriciousness. A common mistake is applying too much silicone oil to lyophilization closures to assure they would not stick to the chamber shelves. This may cause a pop-out problem during stopper insertion because of the excessive lubricity provided by the silicone oil. Issues with lyophilization and siliconization will be discussed to a greater depth later in this chapter.

Chemical Properties

The chemical properties of any drug primary container/closure system are very important. These properties bear a direct relationship to compatibility, stability, and leachables in the final dosage form.

Chemical properties are an important consideration when choosing a primary closure. Each lyophilization cycle and drug product will have its own characteristics and processes, so understanding the closure formulation that will be used for each independent application is critical.

Extractables/Leachables

In the Guidance for Industry entitled "Container Closure Systems for Packaging Human Drugs and Biologics," released by the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) divisions of the U.S. Food and Drug Administration (FDA), there is information to help the manufacturer better prepare for New Drug Application (NDA) submissions. One of the newer areas of interest discussed in the guidance is extractables and leachables. Extractables are species that can extract from the packaging component under stressed conditions with various solvents. Leachables are the container/closure extractables that are found in the drug product. There is concern with liquid drug products that the potential to extract is greater because of direct solvent-vehicle interaction and refluxing of solvent into the component over time. However, the issue of volatile extractables plays a major consideration for lyophilized products. Extractables from a rubber compound are important to consider even with freeze-dried products because they may alter the composition of the reconstituted drug product either directly, by interaction, or indirectly, by changing a formulation parameter such as pH.

There have been several fully documented cases of ingredients from a rubber closure migrating from the closure to the lyophilized drug product, quite often resulting in haze of the reconstituted solution. Pikal and Lang (9) in their study concluded that at the low-pressure characteristics of the environment in the freeze-dryer, vapor phase diffusion is fast enough to allow significant quantities of sulfur and wax, two raw material components of a specific stopper formulation, to transfer from the closure to the product surface where absorption occurs. The lyophilization cycle and the elastomeric closure formulation are two critical variables in this type of occurrence that can lead to unsatisfactory product elegance in the market.

Low molecular weight materials such as oils, waxes, and polymer fragments may become absorbed on the surface of the freeze-dried products, and this may prevent complete dissolution upon reconstitution.