

however, will reach a maximum amount of moisture as equilibrium develops between the closure and the dry product.

SILICONIZATION OF CLOSURES

Another area where problems may be encountered in processing and use of closures for lyophilization is siliconization. Siliconization is the process of applying silicone oil to the surface of a rubber closure to give the surface adequate lubricity. Lubricity aids in processing or machinability. This is critical in relation to several specific areas, such as the application of the stopper to the vial. Typically a stopper moves down a chute, is applied to the mouth of the vial, which is then placed in the lyophilization chamber. The stoppers are seated in a position that allows sublimation of the water to occur. After sublimation, a vacuum or nitrogen may be used to backfill the vial headspace. The shelves of the lyophilization chamber move to press the stopper into the vial in a closed position, sealing the vacuum or inert gas inside the vial. The seal between the rubber and glass vial must hold for a period of time before the secondary aluminum seal is applied. The application of silicone at an optimized level is important for multiple reasons. In applying the stopper to the vial, the closures are typically placed in high-speed sealing equipment. Any hesitation of the rubber closures can cause a problem with this system. Siliconization is critical to the closures when they are in the lyophilization chamber to prevent the closures from sticking to the shelves after they are pressed into the vials so they cannot be pulled out of the vial when the shelving is raised. Additionally, insertion into the vial needs to be smooth to facilitate the entire process; too much or too little silicone may cause problems with friction during insertion and may cause pop-up of the stopper after it is inserted if there is too much lubricity.

Process for Siliconization

Typically silicone oil is applied to closures during one of the final rinses in the wash process prior to sterilization. A mechanical emulsion of the silicone oil (e.g., Dow Corning 360 Medical Fluid) and water should be made. This is then applied to the rinse water in the washer. The wash cycle should be optimized to assure adequate distribution of the silicone throughout all of the closures.

Some companies may use a pre-made emulsion such as Dow Corning 365 Medical Grade emulsion; however, these types of emulsions contain materials other than silicone oil and water to keep them in the emulsion phase.

Problems with Silicone

Excess silicone may cause various problems with injectable products. These range from droplets in solution to hazing of lyophilized product.

A documented study (12) conducted by Preston et al. showed the potential for the lyophilization cycle with an aqueous solvent vehicle create a residue, found to be sodium bicarbonate from the type I vial and silicone oil from the rubber closure. This caused hazing in the vials.

In addition to the silicone oil itself being found as droplets, there are also documented examples of the silicone oil particles acting as a nucleus to attract other materials, such as proteins. An example of this phenomenon is documented in a study of particle generation of siliconized stoppers and tumor