

phase that follows washing and rinsing, but part of it will remain in the stopper. The percentage of moisture that is left in the stoppers will depend on parameters such as stopper compound, duration of the exposure to water before washing, duration of the drying cycle after washing, temperature at drying, storage conditions after drying, etc. Typical numbers for moisture content of elastomeric stoppers as delivered by closure manufacturers and as measured by loss on drying are in the order of magnitude of 0.1–0.4% [7–8]. Before aseptic filling, elastomeric closures are however subjected to sterilization. In most of the cases, this is done by steam sterilization of the closures, followed by drying. During the first part of this process, closures are brought in a saturated steam environment, typically for 30 min at 121 °C. The objective of this process obviously is to bring stoppers in a sterile state, ready to be used for filling. However, the side effect of it is that stoppers again will absorb water (steam!) and that the moisture level of the stoppers increases to levels that are four to five times the initial level before sterilization. At longer sterilization times, the effect is even more pronounced [9–10]. In order to reduce this level again, stoppers are dried. The moisture level after drying can be influenced by varying temperature and pressure during drying and by the length of the drying cycle [9–13].

In recent years, a number of “low residual moisture” rubber formulations have been brought to the market. They are characterized by a considerably lower moisture pick up during steam sterilization in comparison with other traditional rubber formulations that are used for lyophilization stoppers. This feature of those formulations can be attributed to their composition in that they do not or only contain little rubber ingredients that easily absorb moisture. Furthermore, they are also characterized by drying rates that are comparable to those of other more moisture absorbing formulations. The moisture absorption and drying behavior of such rubber formulations is illustrated in Fig. 6.

The advantage of this type of rubber formulation is that the stoppers at the beginning of the drug life cycle contain less moisture. Since the moisture in the stopper is in the immediate vicinity of the lyophilized drug and is therefore, by desorption from the stopper, easily accessible, the use of low residual moisture stoppers is

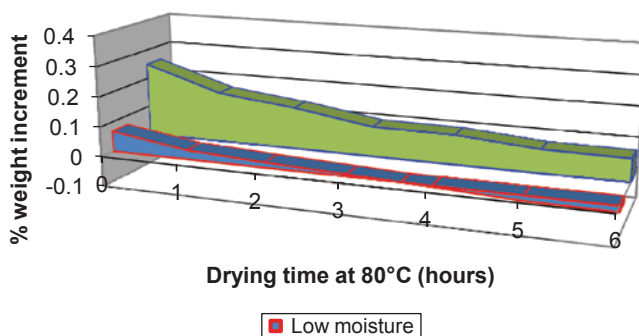


Fig. 6 Moisture absorption/desorption of a low moisture absorption rubber compound in comparison with a typical compound (both bromobutyl)