beneficial for drug stability. For this reasoning to be valid, there are however a number of conditions to be met. The first of those conditions is that the stoppers that are sterilized and dried do not pick up moisture again between the time of drying and the time of being placed on vials. Under normal practical conditions, this is not an issue, since the duration of the storage and the storage conditions of the stoppers after drying are not excessive, and since stoppers that pick up less moisture during steam sterilization display the same behavior upon exposure to atmospheric moisture. A second condition however is that the moisture desorption mechanism from the stopper is not outscored by a second mechanism of moisture transfer to the drug product, namely permeation through the stopper. Desorption of moisture from the stopper and permeation of moisture through the stopper are two phenomena that run in parallel. However, whereas moisture absorption/desorption ("D" in Fig. 5) is determined by stopper composition and the presence of materials with a 'hydrophilic' character, stopper permeation ("P" in the figure) is related to stopper permeability, which is a different physical principle. The moisture that is most readily transferred to a lyophilization cake is the moisture that is left in the stopper after steam sterilization and drying. This water has the shortest way to the cake as it does not need to permeate through the stopper. Desorption of water from the stopper is a phenomenon that starts right away after complete stoppering of the vials. Permeation of water through the stopper is an effect that plays a role on the longer term, since the water that reaches the cake in this way first has to permeate through the entire thickness of the rubber stopper in its penetration zone. The ideal lyophilization stopper shall therefore have both a low residual moisture level at stoppering and a low moisture permeability, or more in general a low gas permeability. Stopper permeability equally depends from stopper composition, but not in the same way as absorption/desorption does. Stopper permeability is primarily dictated by the permeability of the elastomer that is used as base polymer in the rubber, and in second place by the type of fillers that are used in the rubber. Low gas permeability is always achieved by the use of halobutyl elastomer (bromobutyl or chlorobutyl) as elastomer base in lyophilization closures. Fillers that are used are always silicates, but depending on the type a lower or higher permeability will be reached. Blending of bromobutyl or chlorobutyl with elastomers that have a higher permeability such as polyisoprene or styrene butadiene in rubber formulations for lyophilization closures from a perspective of stopper permeability is not indicated. Such blending sometimes is undertaken in rubber formulations for vial stoppers for liquid-fill applications or for plungers for prefilled syringes, in order to improve the mechanical performance of the material, e.g., by increase of its elasticity. A discussion of the role of water absorption and of water permeability can be found in [13–14].

Fluoropolymer Coatings

Whereas the base polymer used for rubber compounds for lyophilization closures is always halobutyl, more and more lyophilization closures, especially for biologicals, are closures that at their surface are covered with a fluoropolymer coating. If