Fig. 1 Half-stoppered vial with drug solution (*right*) and totally stoppered with freeze-drying cake (*left*). In front of the vials: freeze-drying closures with their vent openings facing forward

the shelves in the freeze-dryer that come down and push the stoppers on the shelf below entirely into the vial neck. In most cases, the stoppering takes place with a vacuum still being present in the chamber. After bringing it again to atmospheric pressure, the freeze-drying chamber is then unloaded. What comes out are vials under a certain vacuum containing the drug product in the form of a freeze-dried cake and closed with stoppers that are not secured yet with a crimp cap.

During the primary drying phase, when the water in the vial is converted from the frozen state (ice) into the gaseous state (water vapor), the gases are evacuated from the vial via the vent opening of the lyophilization stopper. Since the pressure is so low, the volumes of gas are appreciable, meaning that for a good functioning the vent opening has to be of a certain size. Studies have shown however that the size of the vent opening is not rate determining for the freeze-drying process [1, 2]. The size of the vent opening is far less important than the resistance formed by the already dried product through which additional gases have to make their way to be evacuated from the vial.

As a result of the freeze-drying process and the transport stages of the vials from the filling station to the freeze-dryer in half-stoppered condition and from the freeze-dryer to the capping station in stoppered but still uncapped condition, the design and the dimensioning of lyophilization stoppers have a number of particularities that are not seen with stoppers that are used for a liquid or a dry powder fill.

Flange thickness

The flange of the lyophilization stopper is that part of the stopper that is above the rim of the vial mouth, when the stopper has been firmly brought into its final seating position. The closure manufacturer has to keep flange thickness well under control