where the bubble point pressure, P, is directly proportional to the surface tension, γ. The surface tension of water is 72 dyn/cm (contrasted with 21.3 dyn/cm for isopropanol) meaning that water has very high cohesive (attraction) forces for the capillary walls of a membrane filter. That is why it requires a very high amount of pressure to overcome this cohesive force and drive water out of the pores of a membrane filter.

Surface-active agents are amphiphilic wetting agents that lower the surface tension of water and are positively adsorbed at the liquid/air interface, thus preventing proteins from adsorbing at this interface and minimizing protein denaturation (aggregation) due to hydrophobic (air) interactions. Thus, the presence of surface-active agents in aqueous solutions will depress the bubble point compared with water alone.

Sometimes, the depressed bubble point can be restored by copious amounts of rinsing the filter with water. However, this is not always successful. If not with the product in question, then filter validation studies need to be conducted using the final product formulation containing the required 10^7 organisms (*B. diminuta*) per cm^2 filter surface area.

A simple relationship can be applied between the minimum acceptable product bubble point pressure and the manufacturer's stated minimum allowable bubble point:

$$P_p = \frac{P_o}{P_w} P_m \qquad \text{(Equation 4)}$$

P_p = minimum acceptable product bubble point
P_o = observed bubble point using product
P_w = water bubble point
P_m = filter manufacturer's stated minimum allowable bubble point

AUDITING FILTRATION PROCESSING AND FILTER VALIDATION

When the FDA or other current good manufacturing practice (cGMP) compliance auditor inspects a filtration process, they will expect to see validated data on the effect of product and process properties such as flow rate, pressure drop, viscosity, pH, temperature, organic content, and ionic strength on the bacterial retention properties of the filter. They also will ask for data supporting the compatibility of the product and the filter and how the bacterial challenge test was done and validated. Other information reviewed will be assembly and sterilization of the filter, validated filtration time limits, and integrity test methods and specifications.

ONGOING CONTROVERSIES

Sometimes, evidence is reported that 0.2 μm filters do not remove all possible microbial contamination (9,10), potentially necessitating the need to use certain types of 0.1 μm membrane filters (11). However, most of the parenteral pharmaceutical industry continues to use 0.2 μm filters although now employing redundant (two 0.2 μm filters side-by-side) filtration systems. Double filtration indeed increases the probability of adsorptive organism capture of organisms, such as "L-forms" smaller than 0.2 μm filter pore size (12). Pre and postfiltration integrity tests must be done on both filters and, although some exceptions exist, all four integrity tests must pass.

Ongoing technical issues or controversies in sterile filtration technology include the following:

1. Defining "worst-case" conditions for filter validation studies
2. The need for validating the removal of the smallest types of organisms, for example, mycoplasma and viruses
3. Effects of the filter and the process of bacterial deformation
4. The potential for air entrapment during filter sterilization by steam
5. Is there really a significant trend toward replacing 0.2 μm filters with 0.1 μm filters as final sterilization filters?