obscure the bubble point. Therefore, the diffusion test has been developed as an integrity test for filters with large surface areas. A *pressure hold test* also can be applied to large surface area filters. The filter manufacturer will recommend the best integrity test for the filter system in question.

These are tests to detect the largest pore or other opening through the membrane. The basic test is performed by gradually raising air pressure on the upstream side of a water-wet filter. It is imperative that the filter be completely wetted or else the integrity test will fail because applied pressure gas will easily pass through pores not filled with liquid. Either water for injection or actual product is used to wet the filter prior to performing the prefiltration filter integrity test. The bubble point test keeps raising pressure until a pressure is obtained where air bubbles first appear downstream from the filter.

The principle of the bubble point test follows the fact that a fully wetted membrane filter of very small pore size will hold liquid in the pores by surface tension and capillary force. The pressure of a gas required to force the entrapped liquid through and out of the fully wetted pore capillary is called the bubble point because after the liquid is forced out, air bubbles will appear (Fig. 18-5). The bubble point is a function of the type and pore size of the filter membrane, the surface tension of the liquid and temperature. The equation for bubble point pressure is

$$P = 4\,k\,\gamma\,\cos\Theta/d \qquad \text{(Equation 1)}$$

where P is the bubble point pressure that is directly proportional to the shape correction factor of the filter, k, the liquid surface tension, γ, and the liquid contact angle, Θ, and inversely proportional to the pore diameter, d. The bubble point pressure correlates to the microbial log reduction value as shown in Figure 18-6. Table 18-3 provides the standard bubble point ratings for various types of membrane filters (although these ratings are subject to change).

The diffusion or forward flow test raises pressure to some point below the known bubble point pressure, then diffusion flow (usually in mL/min) is measured. The principle of the

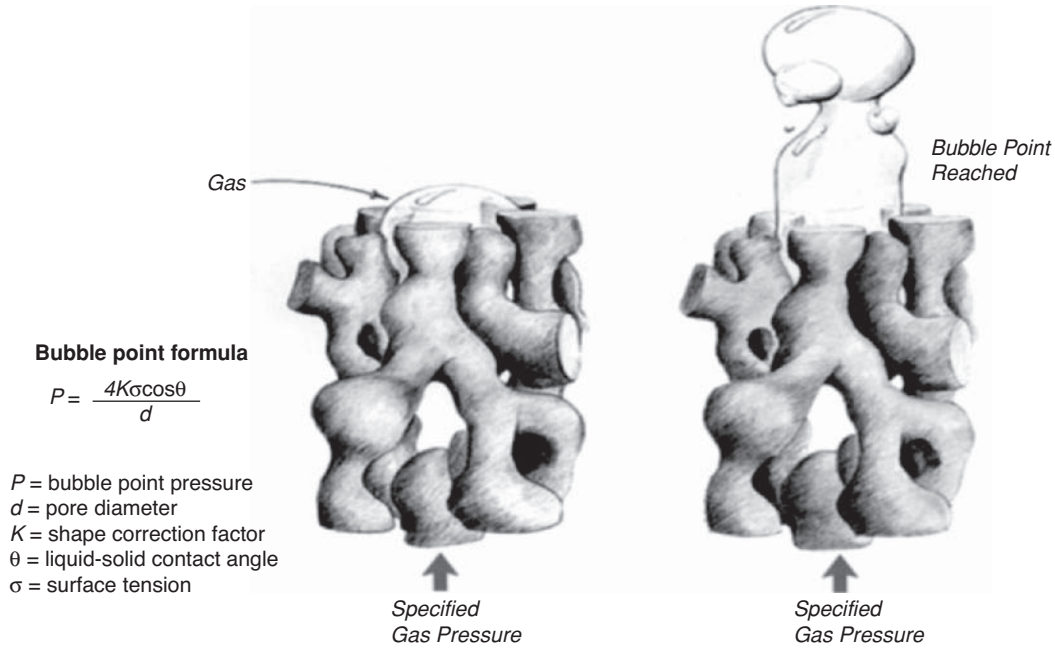

Figure 18-5 Bubble point filter integrity test. The bubble point test is based on the fact that liquid is held in a capillary tube by surface tension. The minimum gas pressure required to force liquid out of the tube is a direct function of tube diameter. The pressure required to force liquid out of a liquid-filled capillary must be sufficient to overcome surface tension and is a direct measure of effective. *Source*: Courtesy of Millipore Corporation.