The Integrity Tests
Choosing Diffusive Airflows or Bubble Points

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This article critiques the diffusive-airflow and bubble-point tests for their comparative suitability for integrity testing in pharmaceutical processes.

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Filter-integrity testing is just one of a series of interdependent activities that, properly combined, result in the preparation of sterile drugs. Integrity testing, bioburden studies, and process validation are the building blocks of this practice. Each of these components has its own complexities, and each has its area of mystery, in which some of the influencing factors still are not fully understood.

Integrity testing of filters is central to the practice of sterile filtration, standing between certain success and potential failure. Integrity tests frequently are used and are generally well known (1, 2). Matching the proper test to a given application is less understood. Our purpose here is to help clarify the situation with regard to diffusive airflow and bubble point testing.

The pressure hold/decay test and the water intrusion test are more restricted for specific applications, and will be dealt with in another article.

Integrity Test Purposes

Integrity testing is useful for several

purposes. Chief among these may be the identification of a *sterilizing filter*, one suitable for sterilizing filtration. The correlation of integrity test values with the degrees of organism retention, soon to be discussed, identifies the sterilizing filter, defined by the Food and Drug Administration as a filter that resists challenges of 1×10^7cfu of *Brevundimonas diminuta* per cm^2 of effective filter area (EFA), at pressures up to 30 psi (2 bar) (3). It should be understood, however, that a filter thus qualified does not automatically ensure a sterile effluent. That achievement is the result of several factors, documented experimental success of which constitutes validation (4).

Integrity testing is also used to affirm the correctness of a filter's label. Manufacturers characterize each filter pore-size rating by a distinct integrity-test value. The pore size of a filter qualified for trial in a sterilization thus is designated by its performance characteristics.

By meeting the present FDA definition, the sterilizing filter is conventionally classified as 0.2/0.22 μm-rated. A filter has no reliable rating at the moment it is removed from its shipping container preparatory to use. Only a properly performed integrity test attests to its identity. Even its identifying label is no guarantee; mistakes do occur. Only integrity testing provides confirmation.

Integrity tests also can disclose whether a filter has undergone even subtle structural changes as a result of exposure to the drug preparation or process conditions. Before-and-after testing can reveal pore-size alterations that impair filter retentivity.

Conversely, constant before-and-after test values can reassure the process operator that the filter—and thus the sterilizing filtration—has experienced no alteration during the process.

Correlation with organism retention

In performing sterilization exercises, one must make sure that one is using a filter that will retain the required biological challenge. This can be done in two ways. Most directly, one can challenge filter with the bacterial load used to define a sterilizing-grade filter. Sterile effluent positively proves that the filter performed to specification. This test, however, would contaminate the filter and destroy its usefulness as a process filter. What is required is a nondestructive integrity test that correlates reliably with the filter's organism-retention capabilities.

Such a correlation exists, of course: the bubble-point method depends on the relationship between a membrane's pore-size rating and its organism-retention qualities. This correlation allows nondestructive integrity-test analyses to substitute for direct organism challenges. Figure 1 illustrates such typical relationships between bubble-point measurements and microbial log-reduction ratios, comparing data reported by Reti (5), Elford (6), Pall and Kirnbauer (7), and Leahy and Sullivan (8), as plotted by Johnston and Meltzer (9).

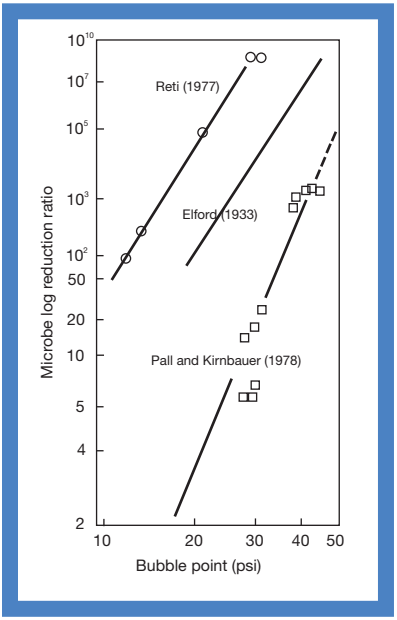

Figure 1: Correlation of bubble point to microbial retention.

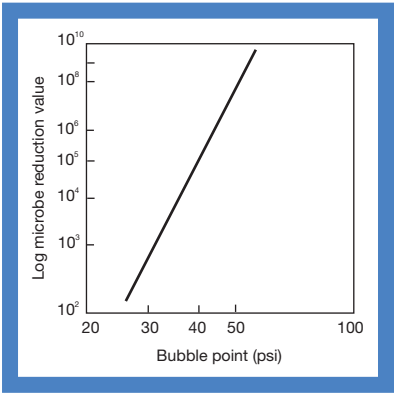

Figure 2: Effects of bubble point changes on microbial retention.

Figure 2 shows that an ~10% change in bubble point (and subsequent changes in permeability and pore size) yields a tenfold change in the microbe-reduction ratio. The data suggest that, when one attempts both to measure such large reduction ratios and to reproduce the results within ±10%, one should expect to see tenfold variations in the microbe-reduction ratio. In other words, if 10^7 is a true value, one may find numbers anywhere between 10^6 and 10^8. An uncertainty of 10% inheres to the bubble point measurement as it is ordinarily conducted.

Capillary rise equation

With the exception of the water-intrusion test, filter-integrity tests measure airflows that result when wetted membranes are exposed to air pressures. These, in turn, depend on the physics of the capillary-rise equation.

Water will rise in the capillary tubes of a given material to an extent governed by the diameter of the tube. The narrower the capillary, the greater the rise. The material of the tube and the properties of the liquid also influence the extent of rise. The liquid must wet the solid: water rises in a glass tube because the attractive hydrogen-bonding force between the water molecules and the silicate anions of the glass causes the water to spread over the glass, even against the force of gravity. Water will not rise in a polyethylene tube or capillary, nor will mercury rise in a glass capillary.

A concave meniscus within the capillary signals such mutual molecular attraction (see Figure 3). In the absence of an attraction to the solid surface, the liquid molecules bond only to one another, producing a convex meniscus.

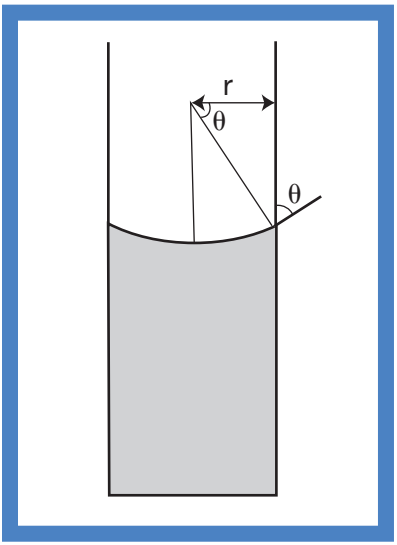

Figure 3: Capillary rise and liquid angle θ.

The liquid rises only until it is balanced by the opposing force of gravity. The rise is governed by the propensity of the liquid to wet the solid capillary surface, expressed by cos(θ), where θ is the angle of wetting or contact angle, a measurement that reflects the avidity of liquid-solid attraction. This can be considered an adhesive force that bonds the water layer to the glass surface. When the wetting is perfect, the angle of wetting is zero. When the attraction is less than perfect (mirroring differences in the cohesive energy densities between the liquid and solid molecules [*i.e.,* when adhesion is less than cohesion]), the liquid is repelled and tends to form droplets, not a film. Within a tube, a nonwetting liquid exhibits a convex meniscus, the upper curve of the free-falling drop. Where perfect wetting exists and the wetting angle or contact angle θ is zero, cos(θ) has a value of 1.

The water molecules that spread upward along the capillary walls are hydrogen bonded to other water molecules and eventually, through a chain of hydrogen bonds, to water molecules removed from the attracting influences of the silicate walls. The mass of water is therefore lifted by the cohesive forces operating within the water bulk. This is the surface tension, θ, in the capillary-rise equation. The lifting ceases when the mass of water is balanced by the opposing gravitational pull.

For the bubble-point measurement, we assume that the filter's pores act as capillaries when wetted with water. Expelling water from the pores requires an added force to destabilize the capillary-rise equilibrium. Air pressure applied to the surface of a wetted membrane contained in a suitable holder would be such a force. Enough pressure would have to be exerted to overcome the bonding forces anchoring the water molecules to the pore surfaces. The bubble point equation is therefore written as

$$P = 4\theta \cos(\theta) / d$$

where P is the pressure required to expel the liquid (test liquids other than water may be used) from the filter pore, d is the pore diameter, u is surface tension, and u is the angle of wetting.

Consider pores of different diameters. In a wider capillary, a smaller proportion of the contained water

contacts the pore walls. There is less of the water-bonding-to-wall effect. Because there are fewer bonds per unit of liquid surface area, the water rises to a lesser height and less pressure is required to expel the water from the pore. Visualizing the membrane as an array of capillaries of differing diameters (because of the pore-size distribution), then the impress of air would cause the liquid to be expelled first from the largest-diameter capillaries. This is expressed mathematically in the bubble point equation by the inverse relationship of P and d.

Assuming the capillary-rise phenomenon applies to the pores of a membrane filter, the applied air pressure expels the water first from the largest pores. The stream of bubbles follows, marking the bubble point.

Gas permeation of wetted filter

When air or nitrogen pressure is applied to a water-wetted filter, the gas molecules dissolve on the higher-pressure upstream side and diffuse to the downstream side, where, under lower pressure, they come out of solution as microbubbles or water displacements. The rate of this diffusive airflow is a function of the applied pressure differential. Over a span of test points of progressively increasing pressures, the diffusive airflow rate traces a straight line of moderate slope until it begins to curve upward. Above the region of curvature, the airflow again forms a straight but more steeply sloping line. This steeper airflow line is understood to represent the viscous flow or free passage of bulk air through pores blown free of water in conformity with the capillary-rise phenomenon. The larger the diameter of a pore, the more easily it is emptied of liquid.

Knee area of the airflow curve

Some investigators consider the first break in the straight diffusive airflow line to be the bubble point, the beginning of bulk airflow. Others believe that the initial upturn of the curve is still part of the diffusive airflow caused by anisotropic pore structures (*i.e.,* funnel-shaped pores) that point downstream and more readily empty their contents under mounting pressures. The progressively thinning films of water they contain offer less impediment to diffusive airflows (see Figure 4). Thus, the exact location of the bubble point on the curve is a matter of dispute. Beyond the bubble point, the continuing upsweep in airflow is a result of the successive opening of smaller and smaller pores, as mounting gas pressure clears them. Microporous membranes with narrower pore-size distributions show sharper intersections of the two flow lines (7).

The bubble point

Somewhere on this curve, the set of the largest pores is emptied of water, and the first bulk airflow begins (see Figure 5). This locus is the bubble point, an intrinsic characteristic of each particular filter–fluid combination. As a measure of the largest

pores in the filter, the intrinsic bubble point has direct implications for the passage of particles through the filter unrestrained by size. It may differ, however, from the perceived bubble point, the point at which the flow of bulk air becomes apparent to the eye or test instrument. It is also possible that even larger pores may be present, large enough for organisms to penetrate, but they may be too few to yield airflows large enough to detect. The perceived bubble point is almost certain, therefore, to be higher than the intrinsic bubble point (10).

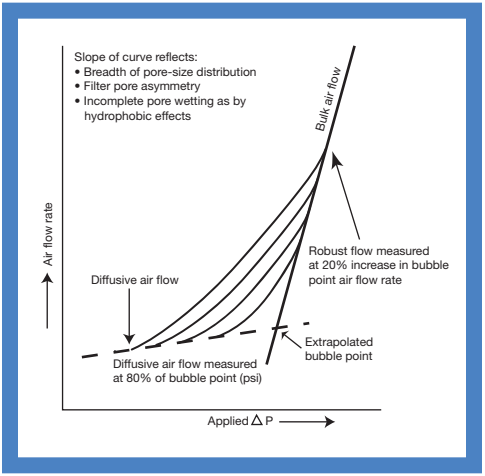

Figure 4: Bubble point curve slope at different membrane configurations.

The bubble point is so called because the frank passage of air through the vacated pores is visible as bubbles rising through a water overlay. This is the end point in the manual bubble-point procedure, the pressure level at which "a steady stream of bubbles" is detected. Alternatively, one may measure with greater accuracy and convenience the volume of water displaced by the escaping air.

Because the bubble-point pressure is a function of the largest-diameter pores present, with the noted implications for the size of particles the filter can retain by sieving, the minimum acceptable bubble-point value of a filter (described in pounds per square inch) is that which correlates with complete retention of the filter manufacturer's *B. diminuta* challenge.

Bubble point numbers are generally used to identify the membrane's presumed pore-size rating. Conceptually, the bubble point is a work function, representing the force necessary to break the bonds of the intermolecular attractions that characterize the wetting of the filter's solid surfaces by the liquid (11). The bubble point changes, therefore, for each liquid–solid pair (12). Thus, the bubble point is not an absolute measure of specific pore sizes. As the *Aerospace Recommended Practice* explains, "No bubble point test measures actual pore size, but only allows correlation of the measured capillary pressure with some dimensional characteristics of the pore structures" (13). At best, the numerical pore size values assigned by a membrane manufacturer to its filter products must be regarded as the individual manufacturer's ratings, ungraced by any industry-wide procedural standard.

Uncertainty of bubble point location

Beginning at the origin, the plot of diffusive airflows against progressively rising pressures, assayed incrementally to approximately the 80% level, describes a straight line. The upward curve begins somewhere above this point. The measurement loses some of its reliability along with its linearity, and the implications for organism retentions become vague. The bubble point, for its part, has its own uncertainty. However, extending the measurement of diffusive airflow testing to conjoin the bubble point analysis restricts the area of uncertainty, thereby limiting and reducing its liability, and making more confident the bubble point relationship to organism retentions.

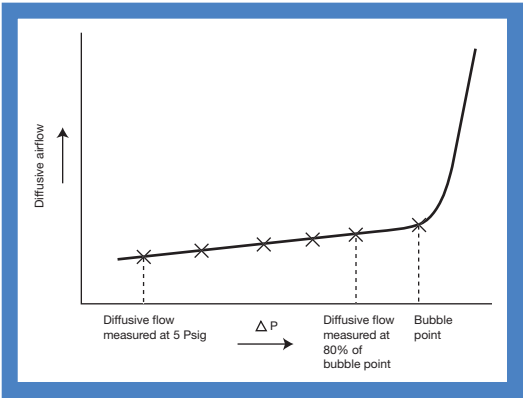

Figure 5: Diffusion and bubble point stages at different pressures

The diffusive airflow (forward flow) is a function of the total porosity (the aggregate surface area of the pores), rather than the diameter of the set of largest pores. Because the filter pores accumulate particulate matter retained during its service life, the pores become progressively constricted or obstructed. The ineluctable result is a diminution in the filter's total porosity. This, in turn, lowers the diffusive airflow rate. The conventional teaching is that only an airflow rate in excess of a given amount signals a flaw. Diminished flow is automatically seen as acceptable. Yet, obstruction-diminished flow may mask an elevation in a diffusive airflow caused by a flaw (14).

Manufacturers usually build safeguards into their diffusive airflow specifications to avoid such maskings. They do not, however, always specify the margin of safety.

The diffusional airflow rate is a function of the filter's total porosity, which may certainly change as particle accretion clogs pores. In effect, therefore, one is dealing with different total porosities in the pre- and post-filtration contexts. The rate of diffusive airflow as a function of applied pressure requires experimental definition for each filter in each of these contexts. A single measurement point cannot provide a complete definition. Multipoint measurements before and after filtration are necessary, particularly for filters with long service lives, as in sterile venting or water system applications.

When a drug product is used to wet the filter, the bubble point will change, usually decreasing, because of the difference in surface tension

between water and the process liquid. It should not be difficult, however, to determine the 80% bubble point pressure appropriate to the new fluid, according to the bubble point.

Diffusive airflow, however, presents a different problem, and the operator cannot assume that a simple numerical adjustment will suffice. The diffusive airflow displacement reflects not only the shift in bubble point occasioned by the liquid's surface tension, but it may increase or decrease according to the solubility of the ambient gas (air or nitrogen) in the product as compared to that in water.

Limitations of bubble point

Whether a filter's diffusive airflow interferes with accurate determination of its bubble point depends on the filter's effective filtration area and the length of time needed to arrive at the bubble point. During the progressive pressure increases on the way to the bubble point, diffusive airflow will occur. If, in the interval over which the bubble point is reached, diffusing air volume increases enough to substantially match free airflow at the bubble point, determining the bubble point becomes uncertain. This effect becomes more noticeable when liquids of lower surface tension are involved, such as solvent–water mixtures. Generally, the diffusive airflows from 10-in. cartridges begin to interfere significantly with the bubble point as the test is commonly run. Even multiple 10-in. cartridges can be successfully bubble-pointed, provided that the pressure is brought up rapidly to just below the presumed bubble point, and then carefully (but not leisurely) raised to the actual bubble point. There are limits even to this helpful technique. At some point, the area of the filter is large enough to allow diffusive airflows that will interfere with the bubble point regardless of how expeditiously performed. The dimension at which this occurs will differ from filter to filter and so cannot be precisely predefined.

Consider a 10-in. cartridge with a diffusive airflow of 15 mL/min. At its bubble point, it will have a free airflow far in excess of 15 mL/min, perhaps ~540 mL/min. Three such cartridges joined end-to-end into one 30-in. assembly would have a diffusive airflow of 45 mL/min but the same free airflow at the bubble point (namely, ~540 mL/min). A 90-in. assembly of three 30-in. assemblies would have a diffusive airflow of ~136 mL/min and the same 540-mL/min free airflow at the bubble point (unless, of course, the bubble point is reached simultaneously in more than one cartridge, at which point the air flow jumps to a multiple of 540 mL/min). At this level, the difference between 135 and 540 mL/min is still large enough to distinguish between the two different airflows, provided one minimizes the time taken to reach the bubble point. If, however, the pressure ramp-up takes 4 or 5 minutes, the diffusive airflow will be indistinguishable from the bubble

point: the total diffusive airflow volume and the free airflow (at the bubble point) will be equal. If a 360-in. assembly of twelve 30-in. cartridges is involved, its diffusive airflow will be 540 mL/min, no matter how fast the bubble point is determined. Diffusive airflow will interfere with the free airflow measurement.

Diffusive airflow

When air or nitrogen pressure is applied to one side of a wetted filter, gas molecules on the higher-pressured upstream side dissolve in the fixed water layer within the pores in conformity with Henry's Law: gas dissolves in a liquid in proportion to its partial pressure over the liquid. Gas comes out of solution on the downstream side as microbubbles or volume displacements, again according to Henry's Law, which will govern the rate of microbubble formation or liquid displacement, according to the experimental arrangement. Thus, the diffusive-airflow rate is a function of the transmembrane pressure differential. Experiments have shown that the rate of diffusive airflow at a given pressure differential correlates with particular organism-retention levels.

Diffusive airflow testing is performed in one of two ways. Each has its advocates and champions.

Single-point measurements

The diffusive airflow test, the result of which is a function of the filter's total porosity, is an expression of Fick's Law of Diffusion (5, 15, 16). FDA accepts the single-point diffusive airflow test as an appropriate method of integrity testing. The basis for a correlation between the single-point method and organism retention rates, however, is not self-evident. Single-point integrity testing is usually carried out at 80% of the bubble-point pressure. The measurement is made as far along the straight portion of the diffusive airflow line as possible while avoiding the difficulties of measuring on the curved portion (5).

Single-point testing at 80% depends on the assumption that the diffusive airflow plot for a particular filter, tested at multiple pressures, would extend to the bubble-point level characteristic of integral filters of its type.

Measuring diffusive flows at 80% of the bubble-point pressure cannot demonstrate performance beyond that point (see Figure 5). Nevertheless, single-point integrity testing has a successful history. It is listed by the US Pharmacopeia, accepted by FDA and other regulatory bodies, and relied upon by many filter users, particularly in Europe. This reliance, however, depends on the assumptions that performance at or below the 80% bubble-point pressure correctly indicates performance at higher pressure.

The perceived general high quality of filter manufacture is encouraging to those in the industry, but is irrelevant to the testing of any individual filter (17).

The risks inherent in making these assumptions are unnecessary,

however, since multipoint testing—or a combination of diffusive-flow and bubble-point testing—can reliably assess the filter's condition.

Single-point testing can, in some instances, yield definitive answers. If the single-point reading at the 80% level lies above the straight line characteristic of integral filters of its type, signaling a diffusion rate higher than the maximum allowable, then the bubble point of that filter is too low and the filter has failed its integrity check. Also, an individual integrity test performed using an automated test machine may require about 20 minutes. When numerous tests are involved, the time consumed can be considerable. Single-point diffusion testing, when it can responsibly be applied, can save time and effort, although with some sacrifice of assurance.

Advantages of diffusional airflow testing

Microporous membranes may have pore-sizes smaller than a 0.1-μm rating. The applied pressures needed to reach bubble point may be higher than the filter construction can withstand. If such applied pressures might damage the filter's retentive properties, then diffusive airflow measurements are indicated. Similarly, capsule filters and others contained in polymeric shells or housings may not be designed to endure high pressures. Testing the integrity of these filter devices at the lower pressures required for diffusive airflow determinations provides an acceptable alternative.

As we have said, the bubble point reflects only the largest pores; diffusive airflows mirror the filter's total porosity. The bubble-point forecasts organism retention; total porosity (and therefore diffusive airflow measurement) indicates fluid flow capacity. Estimates of clean-water flow should, however, follow from a comparison of complete diffusive airflow curves, as plotted from multipoint data. Single-point comparisons will not serve.

Detecting incompatibilities

Gross incompatibilities between membrane and fluid may be easy to discern. Subtle effects can be judged by the influence of the medium being filtered on the bubble point of the filter. Any indication that contact between the filter and fluid tends to enlarge the pores is clear evidence of incompatibility. Diffusive airflow measurements may offer an even more sensitive indicator of incompatibility than bubble points. The bubble-point values do not reflect changes in the smaller pores. Diffusive airflow readings, however, reflect the influence of all the pores (total porosity). Diffusive airflow measurements therefore indicate potential fluid–filter incompatibilities with greater sensitivity than do bubble-point determinations alone. Figure 6 illustrates the diffusive airflow analysis revealing flaws induced in a membrane subjected to the stresses of repeated steamings.

Multipoint diffusion measurements

Reliable multipoint testing data can

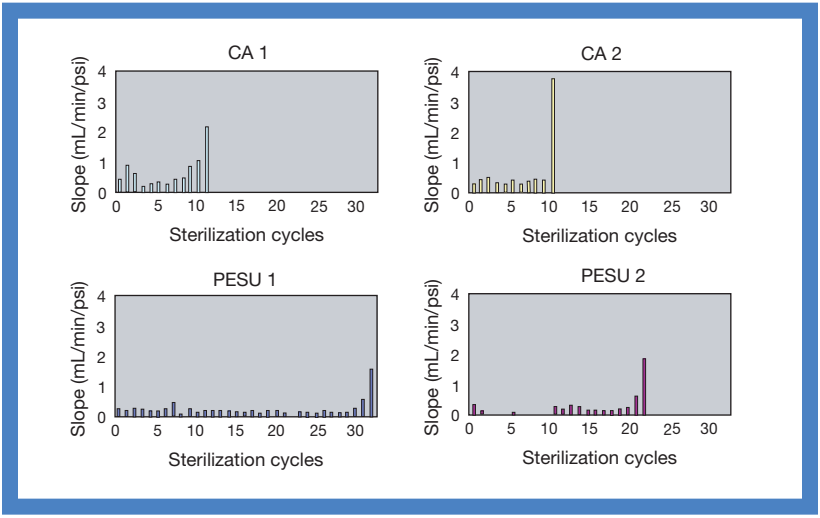

Figure 6: Integrity test data after multiple steam cycles.

be obtained with as few as two test points. Measuring air passage at 80% of the bubble point, or at any selected intermediate point, plus measurement at the bubble point, suffices. Schroeder indicates that use of the (zero) origin point in addition allows the user to draw a straight line through three points (18). A line plotted from the origin through the intermediate test point to the bubble point would affirm the integrity of the filter. Because, diffusive airflow cannot be separated from bulk airflow, however, uncertainty is still introduced into the bubble-point readings. Schroeder suggests that the diffusive airflow linearity curve should be checked "preferably even slightly beyond [the bubble point] for additional safety margin and to make up for potential inaccuracies in the measurement of the test pressure and the wet-flow" (18).

Using multiple points to define the diffusive airflow plot offers certain advantages. Notably, the approach yields a slope that can be compared with curves for other filters or other filter–liquid combinations. This helps turn comparisons of different diffusive airflow lines into a diagnostic and analytical tool for probing differences among various membrane types.

In particular, in the exercise of extrapolating the minimum water-wet integrity test value into the minimum product-wet test value, one must use a valid water:product ratio (19). The water-wet diffusive airflow line should be compared in its entirety with the product-wet curve. The two lines should be completely congruent. A single-point test might not provide sufficient information for a valid comparison.

Neither the bubble-point test nor the single-point diffusive airflow de-

termination by itself serves the purpose of integrity testing as well as do the multipoint analyses. Once the slope of the product airflow line is determined, however, single-point diffusive airflow testing can be accepted in processing contexts. The likelihood in such cases of a dereliction between the 80% test point and the bubble point is judged acceptably reduced by the fuller characterization of the filter type. One can then evaluate the test by noting whether the single-point reading is on, over, or under the diffusive airflow line characteristic of the filter type.

Limitations of single-point diffusive airflow testing

To allow a safety margin, filter manufacturers may provide cartridges that have diffusive airflows of less than the maximum acceptable rate, for example 15 mL/min, at the given test pressure. Consider a 90-in. assembly of nine 10-in. cartridges. Assume eight of these elements have acceptable diffusive airflows of 10 mL/min, but that one, lacking integrity, has a diffusive airflow rate of 55 mL/min. The total diffusive airflow rate for the nine-element assembly would be 135 mL/min, indistinguishable from the 135 mL/min expected for the integral nine 10-in. cartridge arrangement. A single-point test would not reveal the single cartridge's flaw. Because the rate of flow varies with both the pressure and the fourth power of the pore radius, measurements at higher pressures would show markedly higher flows through the flaw. Consequently, plotting diffusive airflows from multipoint pressure data may reveal what a single-point plot cannot.

Diffusive airflow and bubble point

Either the bubble-point or diffusive (forward) flow method can meet the requirement to integrity-test sterilizing filters. The appropriate procedure for any given case depends largely upon the extent of effective filter area involved. The bubble-point technique is appropriate for small filters, typically <500 cm^2; diffusive airflow through them is too restricted to be useful. Filters exceeding 5 m^2 diffuse a large quantity of air, obstructing bubble-point determinations by masking the onset of viscous flow.

In summary, when the filter area is so small as to yield diffusive airflows too minute to permit reliable measurement, the bubble-point test must be relied upon. Conversely, single-point diffusive airflow measurements are indispensable when the large volume of diffusing air distorts the accuracy of bubble-point measurements. In such cases, discerning the bubble point can be extremely subjective. Automated integrity-test machines would eliminate this concern, as well as offering the opportunity to perform tests without violating the integrity of the closed, downstream portion of the system. If either test can be applied, personal preference governs (and seems currently to favor the bubble-point method, especially in Europe).

Both methods serve as integrity tests because their measured values have been experimentally demonstrated to correlate—within the limits presented—with particular organism retention levels, the *sine qua non* of all integrity testing.

In addition to yielding more objective test results, automated devices allow testing without requiring invasion of the equipment downstream of the filter. The avoidance of risk to the asepsis of the system is highly advantageous.

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