



Parallel Integrity Testing of Small Venting Filters



Application
Note

Integrity
Testing

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Introduction

Sterilizing grade venting filters are used to avoid the potential risk of air-borne germs contaminating containers like fermentors or cell-culture vessels. Sterilizing grade filtration can only be guaranteed when the filters used are tested for integrity. Therefore, such filters are routinely tested by the bubble point or similar tests. Depending on the program settings and the actual bubble point (BP), it can easily take 10–20 min to perform one such test. When a large number of filters are used and tested every day, it makes sense to think about how to make the test procedure more efficient without increasing the risk of overlooking defective filters.

This article describes a method by which Midisart venting filters can be tested efficiently by means of parallel testing. This parallel testing method drastically reduces the time required for testing, in turn yielding a clear economic benefit for users without compromising safety.

Method

How to Perform Bubble Point Tests Using the Parallel Method

Small venting filters of the type Midisart 2000 with a pore size of 0.2 μm and an effective filtration area of 20 cm^2 were used for this investigation. To prove their ability for detecting a single defective filter within an array of 10 filters in a parallel arrangement, one filter of pore size 0.2 μm was replaced with a filter with pore size 0.45 μm . The theory behind this set up was that, although the 0.45 μm filter was perfectly intact and within specification for 0.45 μm filters, it should not pass the integrity test run on bubble point limit values for 0.2 μm filters. If this theory applied, the question would then be to determine if it is possible for an automatic integrity tester to reliably detect the out-of-specification Midisart between the 0.2 μm standard filters.

An essential prerequisite for performing bubble point tests is that the membrane is wetted completely with a suitable wetting liquid. Because the PTFE membrane of the Midisart filters is extremely hydrophobic and not spontaneously wettable by water, a 60% mixture of isopropyl alcohol (IPA)-water-mixture was used for wetting the membranes. To flush each filter with 20 ml of 60% IPA, a disposable syringe was used to apply the wetting solution in the direction of filtration. Because the testing procedure forced wetting liquid out of the pores, any filters used for repeated testing were re-wetted in the same manner as described above to avoid any effect on the test results.

In the first step, the filters were wetted and then tested individually using the Sartochek 4 automatic integrity tester. The test results were documented electronically and additionally printed out on paper.

In the second step, the same filters were mounted on the Midisart manifold (figure 1) containing an array of 10 Midisarts and the manifold was subjected to a parallel bubble point test using the same test unit. The results were documented.



Figure 1: Test arrangement for parallel integrity testing of 10 Midisart venting filters.

To show that it is possible to detect a single defective filter amongst 9 others, one Midisart 2000 filter with pore size 0.2 μm (min BP = 1.4 bar) was replaced with a Midisart 2000 filter with pore size of 0.45 μm (min BP = 0.9 bar) as described above. Then, the complete manifold with 9 intact plus one assumedly "defective" filter was tested. Although the 0.45 μm filter was intact, it should theoretically be identified as defective within the specification for the 0.2 μm filters ($\text{BP} < \text{BP}_{\text{min}}$).

The stabilization time was set to 5 min and a minimum BP of 1.4 bar was programmed.

Before testing all filters separately as described above, the test series was started with a leakage test to prove the validity of the complete test setup. For this purpose, all valves of the test manifold were closed and a pressure hold test ($P = 2$ bar, $t = 5$ min.) was run with the integrity tester Sartocheck 4. The pressure was kept pretty stable during the test without any signs of leakage.

Results

An average bubble point of 1.69 ± 0.025 bar was found for the 0.2 μm Midisart filter, while the 0.45 μm version had a significantly lower BP of 1.23 bar (figure 2). This meant that the 0.45 μm filter failed the test as soon as the BP limit (BP min) for the 0.2 μm filter was used as test criterion.

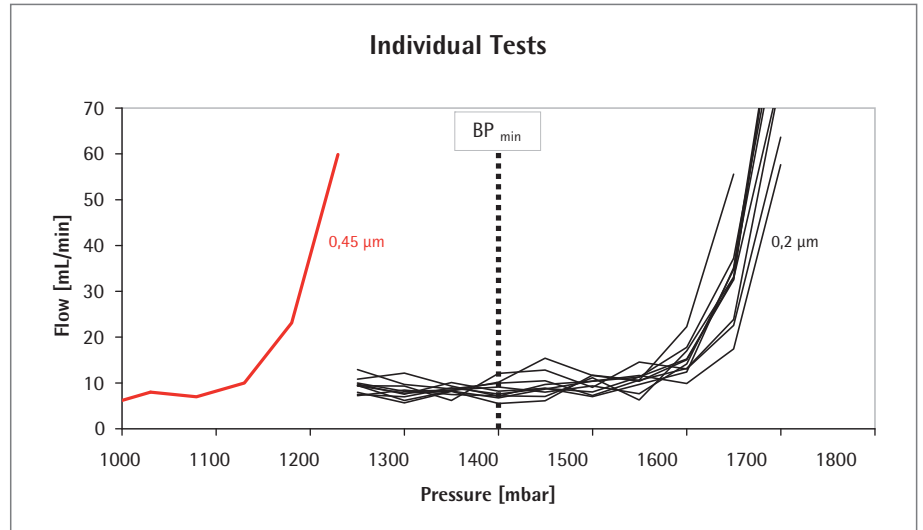


Figure 2: Test results of the bubble point tests for individual Midisart filters. Each curve represents the measurement of a single filter. 10 Midisart 2000 filters with a pore size of 0.2 μm (black curves) and one Midisart with a pore size of 0.45 μm (red curve) were tested.

The parallel test of the 10 "intact" Midisarts resulted in a BP_{all} of 1.57 bar (figure 3). This value correlate nicely with the BP values measured for the individual filters. The measured BP of the parallel test was slightly lower compared to the BP of individual tests due to the fact that the flow through the 10 filters is higher which then consequently leads to an earlier detection of the BP criterion. The test was classified as "test passed" and therefore all 10 filters showed integrity.

In the next step where one "intact" Midisart was replaced with the "defective" filter (0.45 μm) and the array of the 10 filters (9 "intact" plus 1 "defective" with a low BP) was subjected to a BP test at the identical

test parameter settings, the test resulted in a BP of 1.23 bar and the test was classified as "test failed" (figure 3). The BP value of all 10 filters was clearly defined by the filter with the lowest BP (1.23 bar) which was the so-called "defective" one. This meant that the "defective" filter was successfully detected when 10 filters were measured in parallel.

To confirm this result, the defective filter was pneumatically decoupled by closing the connected valve and the remaining 9 intact Midisarts were retested after re-wetting. This test resulted in a BP of 1.57 bar, i.e. it was identical to the test result obtained when all 10 "intact" filters were tested.

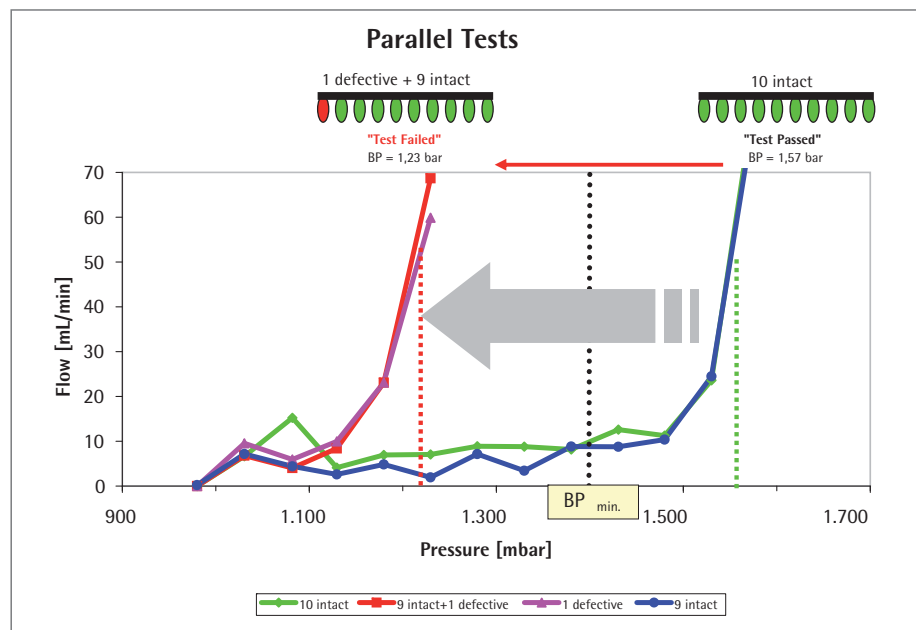


Figure 3: Test results of parallel bubble point tests of 10 filters arranged on the Midisart test manifold. Substituting one intact filter for a "defective" one (0.45 μm pore size) led to a clear shift in the bubble-point curve and finally resulted in a failed test. The filter with the lowest BP also defined the BP when multiple filters were tested in parallel. Therefore, a single defective filter can be reliably detected within a multiple testing manifold.

Discussion

The Bubble Point Test

The bubble point is defined as the pressure at which the wetting liquid is forced out of the pores, thereby creating bubbles. By increasing the pressure on the upstream side, the differential pressure increases and finally overcomes the capillary forces to consequently press water out of the pores of the filter.

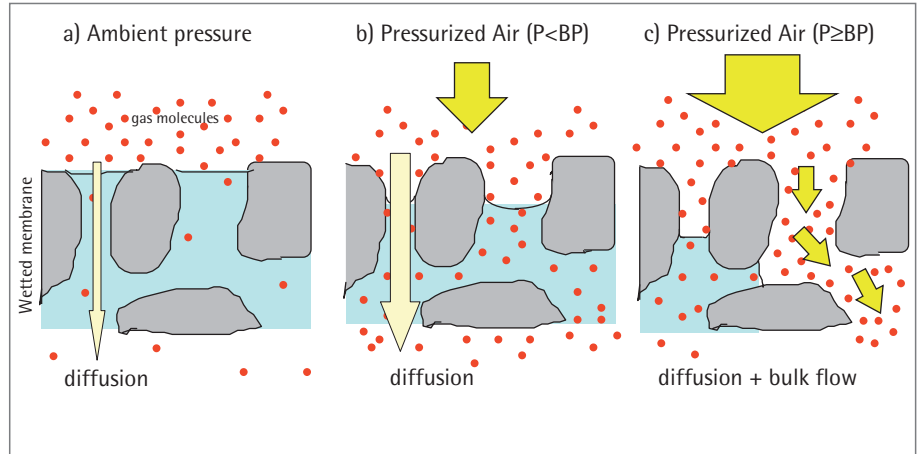


Figure 4: When a differential pressure is applied across a completely wetted membrane, the pores are blocked and only low quantities of gas molecules have the chance to pass the membrane by diffusion. When the differential pressure exceeds the bubble point, the wetting liquid is forced out of the biggest pores, leading to an over-proportional increase of air flow. This behaviour is used for identifying the BP of a membrane.

Below the bubble point pressure, only diffusive flow through the wetted pores takes place. In that situation the amount of diffusive flow is relatively low, and a linear relationship exists between test pressure and air flow rate. When the test pressure is increased incrementally to the bubble point, the air flow starts to increase over-proportionally because diffusive flow occurs at this point in parallel with bulk flow through opened pores. This bulk flow is much bigger than the diffusive flow and can be used to detect the bubble point. In principle, the automatic integrity tester checks the air flow by measuring the

pressure decay in the filter housing on the upstream side of the filter. The test pressure is increased in increments of 50 mbar and the air flow rate is measured for each step. The resolution of the bubble point measurement is limited by the size of the increment (± 50 mbar) but can also be adjusted when higher accuracy is required or test time should be shortened. The test device determines the point of over-proportional increase of the air flow using internal algorithms. This correlates with the point where the first pores open and enhanced flow starts. The integrity tester uses this pressure as the bubble point.

The bubble point therefore reflects the pore size of the largest pores within the membrane, namely because the pores with the largest pore diameter offer the lowest capillary forces and the liquid is removed more easily than through smaller-diameter pores.

This fact makes sense because exactly those large pores offer a risk for micro-organisms to pass the membrane, which consequently would lead to product contamination.

It should be mentioned here that the bubble point per se does not tell anything about the retention capabilities of the membrane, but is only a robust physical test. To determine the retention capability of a filter, sophisticated microbiological tests must be performed and correlated with the results of the integrity tests. Such tests are performed by the filter manufacturers during filter validation and for the purpose of quality checks. Filters have to

pass the bacterial challenge test (BCT) which means they must be able to produce a sterile filtrate after filtering a test solution containing 10^7 bacteria (*Brevundimonas diminuta*) per cm^2 filter area (HIMA document No. 3, VoP. 4, 1982). The limit value (BP min) is defined when correlating the test result of the BCT (test passed or failed) with the BP of the same filter and adding a specific safety margin.

As soon as the BP of a filter drops below the limit value (BP min), sterile filtrate or sterile air filtration cannot be guaranteed. Consequently, such filters may not be used in pharmaceutical production process. The facts discussed above underline the critical importance of filter integrity testing within biopharmaceutical production processes. Therefore, it is necessary to reliably detect defective filters within a multiple-filter arrangement and parallel integrity testing.

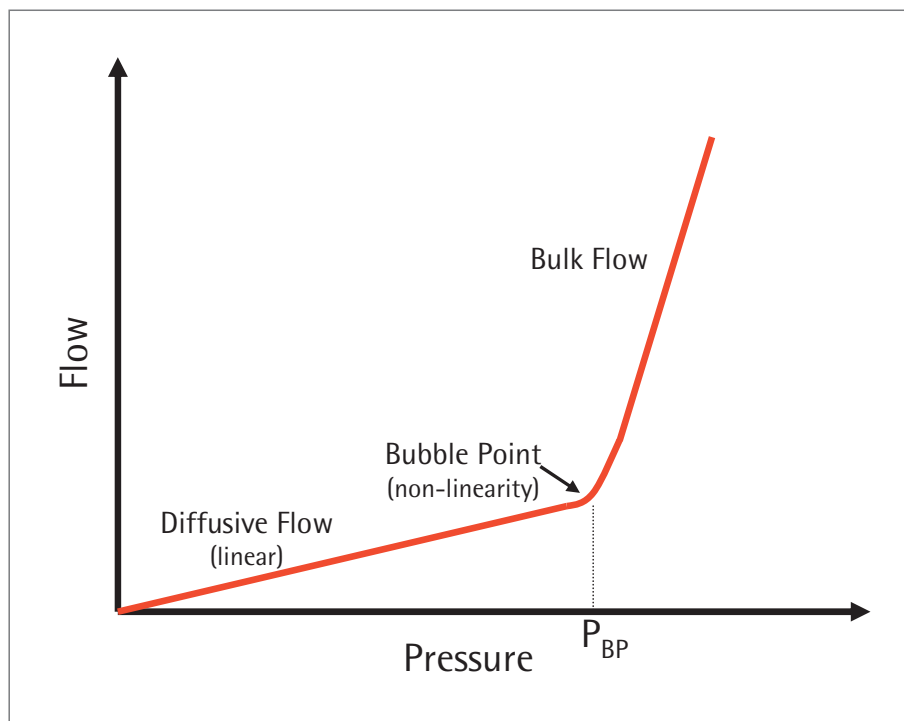


Figure 5: Air flow curve plotted for a wetted membrane during a standard bubble point test. At the bubble point, the curve starts to be non-linear due to the enhanced air flow through opened pores.

Identification of Defective Filters

Obviously, a failed filter integrity test does not identify which of the parallel tested filters is the defective one. Consequently, all 10 filters have to be tested individually to achieve safety.

The Midisart test manifold was designed to allow a different approach. Short tubes can be connected to the hose barbs of the filters and the other end can be hung in a water bath. The bubble point test is started and the test pressure is reached; the diffusion-driven air flowing through the wetted membrane causes the air bubbles to come out of the tube slowly. As illustrated above, the bubble point is characterized by a disproportionate increase in air flow. This sudden increase in flow can be visualized by a sudden increase in air bubbling out of the tube. A defective filter reaches the BP earlier and can be identified simply by observing the air bubbles that leave the different tubes. As soon as the defective filter is identified, it can be pneumatically decoupled from the manifold by closing the valve and the remaining 9 filters can be tested afterwards. The parallel procedure avoids all 10 filters having to be tested individually.

In this context, it is important to note that a failed test does not automatically mean that a filter is really defective. When filters repeatedly fail integrity testing, the correct wetting of the membrane should be checked. A membrane that is not perfectly wetted will definitely fail the test although the membrane itself is functioning properly within its sterilizing grade. In such a case, the wetting procedure should be improved and the test repeated.

Conclusion

In conclusion, the data presented above clearly show that a single defective filter reliably leads to a failed integrity test when tested in a multiple arrangement together with 9 intact filters. The relatively small filtration area of 20 cm² produces a low diffusion rate for the single elements. In this situation, the masking effects common with larger (pleated) filter elements play a negligible role. When more than one filter is tested for integrity, the filter with the lowest bubble point determines the BP of the multiple filter arrangement. This observation underlines the safety of parallel testing such small filters and proves that a defective filter will lead to a failed test. The time required for the testing procedure can thereby be reduced by 90%. This allows more filters to be tested in a given time frame which generates an economic benefit for users.

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