Provantage® Services

Establishing Product Specific Bubble Point Values for Sterilizing-Grade Filters

Integrity testing sterilizing filters is a fundamental requirement of critical process filtration applications in the pharmaceutical industry. Provantage® Services provide integrity testing services that can help you determine the best methods to use to ensure your process meets regulatory requirements.

Background

Pre-use and post-use integrity testing of sterilizing-grade filters is a regulatory requirement, and bubble point (BP) testing is one of the recommended test methods[1,2]. The bubble point pressure is dependent on the pore size and the surface interactions between the filter and the wetting fluid. The minimum bubble point specification of hydrophilic sterilizing-grade filters, established in correlation with bacterial-retention testing, is given for pure water, under standard wetting conditions. Water is therefore the reference wetting fluid recommended for pre-use and post-use integrity testing of hydrophilic filters. The minimum bubble point specification of hydrophobic sterilizing-grade filters may also be established with fluids such as 70/30 IPA. A pre-use bubble point test, assuming that the filter is correctly wetted and good integrity testing procedures are followed, should rarely fail. However, since process fluids may contain components that change the surface interactions between the filter and the wetting fluid, they may alter post-use integrity-test results. It is therefore often useful to determine product-specific bubble point data as this will aid pre-use integrity testing where the wetting fluid is product, and may also aid post-use integrity testing.

Bubble point ratio (BPR) is a proven method for determining minimum bubble point values for non-specified wetting fluids[3,4]. Preliminary testing is conducted on a laboratory scale to determine the interaction of the process fluid with the membrane and

the effects on the bubble point. The expected product bubble point range derived from this study must then be confirmed under normal processing conditions, as part of the performance qualification (PQ), on at least three consecutive filtration runs.

If the PQ results show deviations from the laboratory study then this laboratory validation should be superseded by means of a revalidation using filter devices in the process stream under normal processing conditions. The process scale procedure then involves pre-use bubble point testing of production filters with standard fluid and comparison with post-use bubble point data with the product and is outlined in Appendix 2.

The BPR study is valid only when the test results are confirmed to be reproducible. Acceptable BPR variability is demonstrated by Coefficients of Variation (CV) less than 5%.

EMD Millipore is a division of Merck KGaA, Darmstadt, Germany

When a low batch-to-batch reproducibility statistically invalidates the BPR results, calculation of a meaningful product bubble point specification is not permitted. In such an event it is recommended to flush the filter to remove product residues responsible for bubble point change and re-establish the standard fluid bubble point.

When product bubble point ratios are not applicable and rinsing does not re-establish the standard fluid bubble point, a last resort is to use a lower surface tension reference fluid such as an Isopropyl Alcohol / Purified Water (IPA/Water) mixture. The first effect of IPA is to clean the membrane. The surface tension of IPA is typically far below that of an aqueous product formulation. Thus, the impact of the product on the filter is cancelled out.

Laboratory Study

The bubble point specification for a sterilizing-grade filter is based upon data developed from extensive testing using clean standard wetting fluid under controlled testing conditions. However, it is not always possible or practical to test the filter with standard fluid and under specified wetting conditions in the normal production environment.

Process fluid/drug product components change the surface tension and the contact angle of the standard fluid with the membrane (Figure 1). This action manifests itself as the observed bubble point depression, or in rare cases enhancement. If residual product cannot easily be removed from the membrane filter and the standard fluid bubble point restored by rinsing or flushing, the best alternative is to perform post-use bubble point test using the product as the wetting medium.

Product bubble point specification is determined by a preliminary laboratory scale study. Three to nine filter membranes from one to three different lots are first wetted with standard wetting fluid and bubble point tested. The filters are dried, wet with one to three different lots of the process fluid and integrity tested again. The data obtained from the laboratory experiments are used to calculate the BPR between the process fluid and the standard wetting fluid such as water for hydrophilic filters, at the required temperature. The laboratory scale study provides a minimum product bubble point recommendation and an expected bubble point window derived from the normal membrane manufacturing bubble point range. The protocol for the establishment of laboratory scale product BPRs is outlined in Appendix 1.

The laboratory study is the first part of the validation (Figure 2, Part 1). It is recommended to verify the data under normal processing conditions, as an in-process confirmation (Figure 2, Part 2a) using process scale filters. This is achieved by checking that product wet integrity test results fall within the expected product bubble point window that is calculated from the normal manufacturing bubble point limits and the predetermined BPR.

The product bubble point range obtained from the laboratory study should not be used in place of a standard fluid integrity test of production filters until the validation is completed and the in-process minimum bubble point specification for the product is confirmed. Product bubble point confirmation is part of the PQ of integrity testing, and should be conducted on three consecutive filtration runs, Figure 3. As per the PDA Technical Report No. 26 on Sterilizing Filtration of Liquids[3], "the scale down study is only the first part of the validation; the second part is obtaining additional ongoing product attribute data".

Product surface tension or BPRs should be monitored to ensure consistency of the BPR over time. When a pre-use standard fluid bubble point is performed, that is regarded as a cGMP requirement[1,2], ongoing BP data can be evaluated to account for potential variability among product lots, and verify the reproducibility of the BPR under normal processing conditions.

In-process BPR Validation

If the in-process confirmation study (Figure 2, Part 2a) shows excursions of actual BP results from the expected range, it is recommended to do additional process scale testing. The rationale for this is that there is some in-process parameter that is influencing the bubble point that is not

$$BP = \frac{4.k.\sigma.\cos.\theta}{d}$$

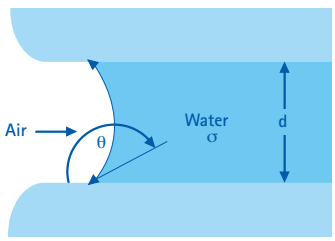

Figure 1.

Bubble point equation. k is the shape correction factor, σ the surface tension of the wetting medium, θ the contact angle and d the pore diameter

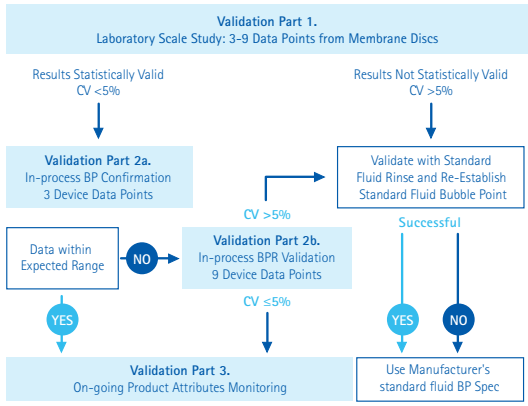

Figure 2.

General approach to the validation of product bubble point specification.

fundamentally included as a part of the laboratory study. Variations in factors such as temperature, filter sterilization, the surface tension of a given pharmaceutical formulation, the contact time, the presence of process components deposited on the membrane, the rinsing and wetting procedures, and the in-process testing procedure may influence the specification given by the filter manufacturer. In this case the recommended course of action is to revalidate the bubble point ratio using the filter device in the process. The aim of this procedure is to establish the in-process minimum bubble point specification by comparing pre-use bubble point and post-use data for the product under process conditions.

Product filters are first tested with standard fluid, using specified wetting and testing conditions. Bubble point values are then recorded. Filters are then submitted to the normal filtration process, using the standard operating procedure (SOP). Following the process, filters are tested again, either directly with the product or after rinsing, if such an operation is carried out in the normal SOP. A ratio of the in-process product bubble point to the standard fluid bubble point can then be established. The expected minimum bubble point specification can be determined by multiplying the specification for the standard fluid bubble point by the bubble point ratio. A minimum of nine measurements, using at least three different filter lots, is required for the calculation of the average BPR (Figure 4). The protocol for the establishment of process scale BPRs is outlined in Appendix 2.

Determination of the BPR Using Historical Bubble Point data

The above laboratory and in-process BPR determinations are the preferred procedures that should be used for new drug applications. However, existing processes may be validated retrospectively by utilizing existing product bubble point data. Two methods may be considered to evaluate the in-process bubble point ratio based on historical bubble point data.

User Historical Data

Where pre-use standard fluid integrity testing and post-use integrity testing with process fluid have been conducted on the same filter device, a simple comparison between pre- use standard fluid bubble points and post-use product bubble point data helps determine the process BPR. Analysis of historical data is valid as long as the coefficient of variation for BPR results obtained from normal manufacturing conditions is less than 5 %. The average BPR is then accounted for and subsequently used to determine the minimum product bubble point specification, Appendix 3, Table 1.

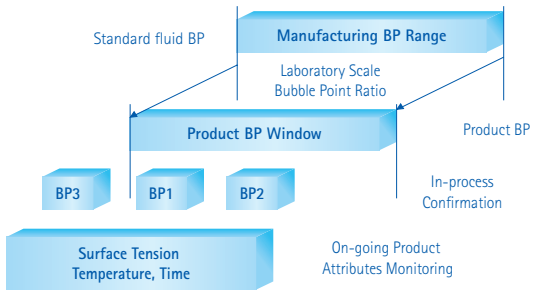

Figure 3.
In-process confirmation of product bubble point determined by the scale down study.

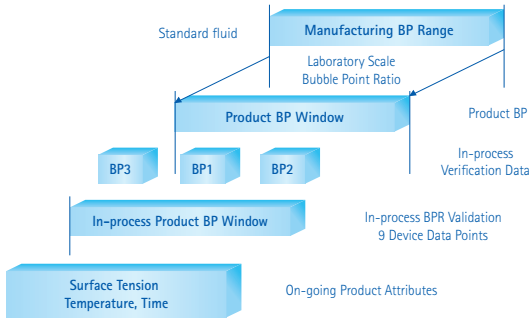

Figure 4.
Revalidation of the BPR under processing conditions.

Provantage® Services & User Historical Data

Ideally, process fluid bubble points are based on actual standard fluid and product bubble point results from the same filter. However, if pre-use standard fluid bubble point data is not available, another option is to consider the filter manufacturers Quality Assurance (QA) lot release bubble point data as the standard fluid bubble point reference. Table 1 shows historical sterilizing-grade (0.22 µm) Durapore® membrane QA release bubble point data.

Membranes & Devices QA Release Data	Number of Data Points	Average Bubble Point Value	Standard Deviation
GVPP membranes	>51,000	55.5 psig 3830 mbarg	1.7 psi

Table 1: Historical QA release BP data for sterilizing-grade 0.22 µm Durapore® membrane.

The comparison of manufacturing data and the end-users post-use process fluid bubble point enables the determination of the process BPR. This analysis based on historical data is valid as long as post-use bubble point results obtained from normal manufacturing conditions are available for at least nine filters, and show a coefficient of variation of less than 10%. The BPR is then calculated by dividing the post-use average bubble point by QA release average bubble point value. The BPR can be applied to calculate the minimum product bubble point specification as shown in the example in Appendix 3, Table 2.

Other Methods to Establish Reliable Post-use Integrity Tests

If none of the above options is applicable, the alternatives are either to validate a rinsing procedure or to use a lower surface tension reference fluid such as an IPA/Water mixture.

Flushing Procedure

Whenever possible, efficient rinsing of the filter with the appropriate cleaning agent could help recover original standard fluid BP values and allow the use of the current bubble point specification as a product release criterion.

The use of WFI at 80°C should help, in certain circumstances, to eliminate the residual formulation components deposited on the membrane. In this case, one must ensure that there are no heat labile process residues on the membrane filter surface and that the system has cooled down to ambient temperature prior to performing a bubble point test. This can be achieved by flushing with standard fluid at room temperature.

Also, the actual cleaning agents used for the cleaning-in-place (CIP) of the filtration system could be used, assuming that the filter compatibility has been demonstrated. The filter must then be thoroughly flushed to completely remove the surface tension-active agents generally contained in detergent solutions.

Whatever procedure is used, the compatibility of the filter with the cleaning agent and the flushing process must be validated.

Testing with alcohol/water mixture

When cleaning is not efficient or practical under the normal operating conditions, a lower surface tension reference fluid such as an IPA/Water mixture can be used. The surface tension of IPA is much lower than water, thus, it is highly unlikely that any residual drug components in the membrane will affect thean IPA/Water mixture bubble point.

References

1. EU, EudraLex - Volume 4 Good manufacturing practice (GMP), Annex 1 Manufacture of Sterile Medicinal Products, November 2008.
2. FDA, Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, September 2004.
3. PDA, Technical Report 26, Sterilizing Filtration of Liquids, Revised 2008.
4. Desaulniers C, Fey T. The product bubble-point ratio and its use in filter integrity testing. Pharm Technol 1990; 14:42–52.

Appendix 1 – Laboratory Scale Study BPR Protocol

Equipment

1. A calibrated and qualified integrity tester.
2. A stainless steel filter holder is used to hold the 47 mm filtration membrane
3. A stainless steel 1.5 inch sanitary tee fitting is used between the integrity tester and the 47 mm holder to provide an expanded upstream volume
4. Stainless steel reservoir
5. Milli-Q® water supplied by EMD Millipore
6. Air or Nitrogen source with pressure regulator
7. Graduated cylinder
8. Calibrated balance
9. Calibrated thermometer
10. Surface tensiometer

Materials

1. **Product samples:** One to three lots of process fluid, 200-250 mL each, supplied by the customer.
2. **Membrane samples:** Three to nine 47 mm discs from one to three different lots of filter membrane used in the customer manufacturing process.

Test Procedure

One to three lots of process fluid are to be tested, with one to three test filter discs per lot. Coefficient of Variation (%CV) between lots should be < 5% to demonstrate the appropriateness of using Product bubble point ratio (% CV = s.d./avg * 100).

Standard Fluid Bubble Point

1. Wet the membrane disc carefully in a clean holder.
2. Flow a minimum of 100 mL of standard fluid through the membrane disc.
3. Add ambient temperature standard fluid through the top of the quick disconnect fitting, using a clean dropper. Avoid air blocks by inserting the dropper nearly to the membrane surface before adding the water. Fill to the top of the fitting, approximately 5 mL.
4. Connect the holder to the integrity tester. Run a bubble point test.
5. Repeat the bubble point test after membrane re-wetting by filling to the top of the fitting, approximately 5 mL. Record both values. Occasionally a membrane disc will exhibit incomplete wetting due to wetting techniques and give a bubble point that is low. If the second bubble point varies more than 1 psi (70 mbar) from the first, repeat the measurement until consecutive bubble points within 1 psi (70 mbar) of each other are obtained with no upward or downward trend. Record all values.
6. Document the final bubble point as the highest bubble point value on protocol attachment.
7. Repeat steps 1 through 6 on remaining membrane discs. As each disc is removed from the holder, lay it on a dry paper towel to dry, recording its number beside it.

For each set of three membrane discs, calculate the average of the bubble point results after stability was achieved and document on protocol attachment. Allow the membrane to completely dry.

Product Bubble Point

Using one of the membrane discs from above, mount the disc in a clean 47 mm stainless steel filter holder and tighten the three bolts. Measure the product bubble point as follows:

1. Apply a minimum of 10 psi (700 mbar) and allow 30 mL of the product to flow through the filter.
2. Perform the bubble point test.
3. Repeat the product wetting using 10 mL of fresh process fluid each time and bubble point measurement step until a stable bubble point is observed. Stability is defined as less than or equal to 1 psi (70 mbar) variation between 3 tests with no upward or downward trend. Document final bubble point in protocol attachment as the highest product bubble point of the stable product bubble points. Some products may contain surface-active ingredients that bind to the membrane material. Therefore, the product wetting procedure must be adequate to determine if there is any effect of flush volume on the bubble point.
4. Following the procedure above, measure the bubble point for each of the remaining discs, 3 test discs per product lot. Document results in protocol attachment.
5. Calculate the average of the product bubble points after stability was achieved for each of the product lots and document in protocol attachment.

Take measurements of room temperature with a calibrated temperature device at least daily during the time that the protocol is being executed. Document readings on protocol attachment.

If the % CV meets the acceptance criteria, multiply the minimum bubble point specification by the overall mean bubble point ratio. Issue a final report with test results and conclusions.

Calculation of the BPR

1. Calculate the three to nine bubble point ratios obtained for each test filter:

$$\text{BPR} = \frac{\text{Product Bubble Point}}{\text{Standard Fluid Bubble Point}}$$

2. Calculate the bubble point ratio mean, standard deviation and % CV for each product lot.

3. Calculate the overall standard fluid, product and bubble point ratio mean, standard deviation and % CV for all product lots. The CV for the BPR is obtained by dividing the standard deviation by the average value. If more than one lot of product is tested then calculate the overall ratio.

4. If the CV meets the acceptance criteria, the minimum product bubble point specification is determined by multiplying the overall mean BPR by the minimum standard fluid bubble point.

Bubble Point Specification =
Average BPR x Standard Fluid Bubble Point Specification

Acceptance Criteria

The bubble point ratio CV for each product lot and for the three product lots should be < 5%. If the results are within specification, produce a report showing the product BPR and the recommended minimum product bubble point.

In the case that the CV is higher than 5%, evaluate the data as per the following steps:

1. If the CV is higher than 5% within the same lot, develop additional data by using three more discs and recalculating the CV. If the CV is still greater than 5%, the data should be analyzed for outlying data points.

2. If the CV between the lots is higher than 5%, evaluate the data for outlying data points and determine if the differences between the lots are related to the surface tension or other causes. If two lots show consistent values and the third lot is different, consult the end-user for availability of a replacement for the third lot. Explain the steps taken and discuss the results in the final report.

3. If there is no special cause found and the CV is still high, document in the final report that the recommended minimum product bubble point could not be determined based on the laboratory scale data and recommend an alternative procedure to determine this value using additional on-going process scale data.

Appendix 2 – Process Scale Establishment of Product BPR Protocol

Materials and Methods

This procedure assumes the following equipment is available for the qualification exercise:

1. A calibrated and qualified integrity tester.
2. Filter set-up (housing, adjacent valves, etc.) must be free of leaks.
3. Pressure gauges are required for controlling the pressure differential when wetting the filter.
4. A stainless steel reservoir containing purified water at room temperature (20 °C to 26 °C) or an outlet on a purified water loop.
5. Pressure regulated compressed air or nitrogen source.
6. A timer and a calibrated thermometer. A temperature measurement system that includes continuous measurement and data logging capacity should be preferred.
7. Nine new filter devices. Each of these nine filters will be pre-tested with water, then used in production and integrity tested again according to the SOP.

Wetting Instructions

The procedure used to establish the initial reference bubble point is critical for the validation study. It is important at this stage to carefully respect the specified wetting conditions and use a calibrated and qualified integrity tester. Thorough wetting is obtained by flowing standard fluid through the filter using either a pressure tank or a pump, as shown in Figures 1 and 2. Table 1 shows recommended wetting conditions for each procedure.

Wetting with a Pressurized Water Tank or Outlet (preferred method)

1. Set up the filtration system as shown in Figure 1 and close all valves.
2. Set the inlet pressure at 40 psig (2.8 barg).
3. Gradually open the upstream valve (V1) and vent the filter housing from the highest point (V2) until all upstream air has been released.
4. Close the vent valve (V2) and continue to maintain the 40 psig (2.8 barg) pressure for at least one minute to dissolve any residual gas within the filter and ensure membrane wetting.
5. Gradually open the downstream valve (V3) and set the differential pressure (P1 - P2) at approximately 3 psig (200 mbarg).
6. Continue to flow standard fluid through the filter at appropriate pressure differential for at least five minutes.

Wetting with a Pump

Using a pump allows recirculation of standard fluid through the filtration system and reduces the volume of water required to ensure proper wetting.

1. Set the pump at the required flow rate.
2. Set up the filtration system as shown in Figure 2 and close all valves.
3. Start the pump.
4. Gradually open the upstream valve (V1) and vent the filter housing from the highest point (V2) until all upstream air has been released.
5. Close the upstream valves (V1 and V2), stop the pump and continue to maintain the pressure for at least one minute to dissolve any residual gas within the filter and ensure membrane wetting.
6. Restart the pump, open the upstream valves (V1 and V2).
7. When all upstream air has been released, close V2 and open the downstream valve (V3).
8. Regulate the pump in order to set the differential pressure at approximately 3 psig (200 mbarg), and continue to flow water through the filter at appropriate flow rate for at least 5 minutes.

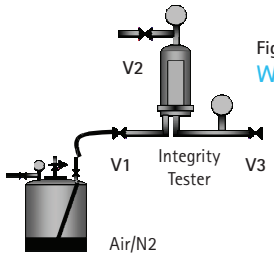

Figure 1.
Wetting with a pressure tank

VS.

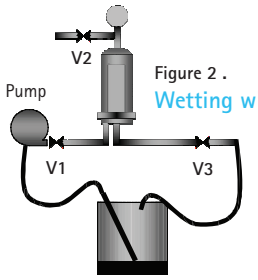

Figure 2 .
Wetting with a pump

Filter Type	Water flow rate (L/min) at 200 mbar	Wetting volume (L) for 5 min pressure	Required volume (L) in recirculation pump
Millidisk® 10	0.5	3	1
Millidisk® 20	1	5	2
Millidisk® 30	1.5	8	2
Millidisk® 40	2	10	3
Millipak® 20	0.2	1	1
Millipak® 40	0.3	2	1
Millipak® 60	0.4	2	1
Millipak® 100	0.5	3	1
Millipak® 200	1	5	2
Optiseal® / Opticap®	2	10	3
Durapore® 5"	3.5	18	5
Durapore® 10"	7	35	8
Durapore® 20"	14	70	12
Durapore® 30"	21	105	15

Table 1: Specified wetting conditions using a pressure tank or source or a pump.

Test Procedure

In-process pre-use standard fluid pre-use bubble point

1. Take a new filter and document the catalogue, lot and serial numbers.
2. If applicable, moisten the filter O-rings with purified water to allow ease of insertion into the filter housing and install the cartridge in the housing used for the validation procedure.
3. Check that the temperature of the standard fluid is stabilized between 20 °C and 26 °C and record the temperature.
4. Make measurements of room temperature during the time the protocol is being executed. Check that the room temperature is in the range of +/- 1 °C of the water temperature, and record the data.
5. Flow standard fluid through the filter at the appropriate pressure differential using one of the two wetting procedures described above. Table 1 shows recommended wetting conditions.
6. Record the inlet and outlet pressures, and the time used for the wetting procedure.
7. Stop the fluid flow, allow the upstream pressure to drop to zero and drain the system by gravity.
8. Connect the integrity tester unit immediately to the system, and start the bubble point program.
9. Record the initial bubble point result.
10. Repeat the bubble point test after membrane re-wetting following procedures 3 - 9 above, until three consecutive stable bubble point values are obtained. Stability is reached when a difference of < 1 psig (70 mbarg) is observed with no upward or downward trend.
11. The average of the three stable bubble point values will be used for the bubble point ratio determination.
12. Remove the filter from the housing, place it in an upright position in an oven, and dry for at least 16 hours at 40 °C
13. Submit the dry filter to the normal filtration process.
14. Repeat steps 1 through 13 on remaining eight filters.

In process post-use product bubble point

1. Take the first filter used in the above study and check the catalogue, lot and serial numbers.
2. If applicable, moisten the filter O-rings with water or the standard fluid to allow ease of insertion into the filter housing and install the dry filter in its housing.
3. Sterilize the filter setup according to the current SOP (autoclaving, steaming-in-place).
4. Run the normal filtration process as per the SOP that is normally used in the process.
5. Document the product lot number, and the temperature of the product and the processing environment.
6. Record the inlet and outlet pressures, the volume of product and the filtration time.
7. Stop the filtration, allow the upstream pressure to drop to zero and drain the system.
8. Measure the bubble point using the integrity tester and the SOP normally used in process.
9. Document the in-process product bubble point result.
10. Repeat steps 1 through 9 on remaining eight filters.

Calculation of the BPR

1. Calculate the nine BPRs obtained for each test filter:

$$\text{BPR} = \frac{\text{Product Bubble Point}}{\text{Standard Fluid Bubble Point}}$$

2. Calculate the average bubble point ratio and the standard deviation.
3. The CV for the bubble point ratio is obtained by dividing the standard deviation by the average value.
4. The minimum product bubble point specification is determined by multiplying the overall mean bubble point ratio by the minimum water bubble point.

Example: Bubble Point Specification = Average BPR x Minimum standard fluid bubble point specification

Acceptance Criteria

If the CV for nine bubble point ratios determined during normal manufacturing conditions is less than 5 %, the average bubble point ratio should be used to determine the minimum product bubble point bubble point specification.

If the CV is higher than 5 %, evaluate the data for outlying data points and determine if the variance is related to the surface tension or other causes. If there is no special cause found, the minimum product bubble point specification can not be used. Post-use testing should be performed with standard fluid, using a validated rinsing procedure, or another reference solvent (e.g. IPA/Water mixture) with a specified minimum bubble point value.

Definitions

Average:

$$\bar{X} = \frac{\sum_{i=1}^{n} Xi}{n}$$

Standard Deviation:

$$s = \sqrt{\frac{\sum_{i=1}^{n} \left(x_i - \bar{x} \right)^2}{n - 1}}$$

Coefficient of variation:

$$CV = s/\bar{X} \times 100$$

Remarks

In order to release the nine validation batches used for the determination of the in-process bubble point ratio, we recommend the following alternatives:

1. Rinse the filter with the appropriate cleaning agent, wet with standard wetting fluid and use the current bubble point specification for that standard fluid as a product release criterion,

or

2. Wet the filter with a reference solvent (e.g. IPA / Water mixture) and use the certified bubble point specification as a product release criterion.

It is strongly recommended that the BPR is periodically monitored after the validation is completed to confirm consistency. Variability in product, operating conditions and environmental conditions may have a significant impact on bubble point values. In addition, any changes of the process parameters, setup or product formulation must be evaluated in terms of their effect on the BPR. Variables to monitor and record are the temperature, surface tension and solution/filter contact time for the specific process/ product formulation.

In Process BPR Logging

Pre-Use Water Bubble Point Data

Catalogue No.									
Filter No.	1	2	3	4	5	6	7	8	9
Lot No.									
Serial No.									
Date									
Water temperature (°C)									
Room temperature (°C)									
Inlet pressure									
Outlet pressure									
Differential pressure									
Time (min)									
Water BP1									
Water BP2									
Water BP3									
Average water BP									

Post-Use Product Bubble Point Data

Product name									
Filter No.	1	2	3	4	5	6	7	8	9
Date									
Product lot No.									
Product temperature (°C)									
Room temperature (°C)									
Differential pressure									
Time (min)									
Volume									
In-process product BP									
IPA 70/30 BP									
Other release test									

Calculation of the In-Process Product BPR

Filter No.	1	2	3	4	5	6	7	8	9
Average water BP									
In-process product BP									
BPR									

BPR Average	Standard deviation	CV (%)	In-process BP specification

Appendix 3 – Example of Process Scale Establishment of Product BPRs Protocol

Production Filter Devices	Bubble Point (mbar)		Bubble Point Ratio In-process
	Pre-use water	Post-use product	
1	3880	2410	0.621
2	3850	2400	0.623
3	3810	2380	0.625
4	3770	2370	0.629
5	3760	2330	0.620
6	3740	2390	0.639
7	4010	2520	0.628
8	3980	2470	0.621
. . .	. . .	. . .	. . .
n	3970	2430	0.612
Average	3863	2411	0.624
Standard deviation	103	56	0.007
CV	2.7 %	2.3 %	1.1 %
Minimum BP specification: 3450 x 0.63 = 2175 mbar			
Maximum BP limit: 4140 x 0.63 = 2610 mbar			

Table 1: Example of BPR calculation based on actual pre-use and post-use BP data.

Production Filter Devices	Bubble Point (mbar)		Bubble Point Ratio In-process
	Pre-use water	Post-use product	
1	N/A	2410	N/A
2	N/A	2400	N/A
3	N/A	2380	N/A
4	N/A	2370	N/A
5	N/A	2330	N/A
6	N/A	2390	N/A
7	N/A	2520	N/A
8	N/A	2470	N/A
. . .	. . .	. . .	. . .
n	N/A	2430	0.612
Average	3830	2411	0.63
Standard deviation	120	56	N/A
CV	3.1%	2.3%	N/A
Minimum BP specification: 3450 x 0.63 = 2175 mbar			

Table 2: Example of BPR calculation based on EMD Millipore's QA release data (see Table 1) and user's post-use BP data.

Bubble Point Table

Membrane Type	Wetting Fluid	Min. Bubble Point Spec (psi/mbar)
Durapore® 0.22 µm Hydrophilic membrane	Water	50/3450
Durapore® 0.22 µm Hydrophobic membrane	60% IPA / 40% Water	18/1240
Millipore Express® membrane	Water	58/4000
Aervent® membrane	70% IPA / 30% Water	16/1100
Solvex® membrane	70% IPA / 30% Water	19/1310

Table 2: Example of BPR calculation based on EMD Millipore's QA release data and user's post-use BP data.

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Provantage® Lab Services network and capabilities allows us to share information and experiences with more than 70 of our qualified experts around the world and provide consistent and best in class services for global customer projects.

The aim of our services is to demonstrate that our products and technologies that are working with your drug product within your specific process conditions are reliable, robust, efficient and provide the highest performance. Achieving this objective is a joint effort where we work hand in hand with you to exchange information and define most efficient validation strategy.

Our range of validation and qualification expertise and capabilities covers our technologies that are used at different steps of your production process. From upstream through downstream purification steps to final fill and finish, we can meet your validation and qualification needs that use any of our products and technologies.

We are also able to adapt our Validation and Compliance Services offering to the needs and constraints of your current drug development step. We can guide and advise you on the validation and qualification scope to meet regulatory requirements while mitigating your production process risks.

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