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Alternative Test Methodology for In-Situ Testing of ePTFE HEPA Filters for Pharmaceutical Applications

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This article presents the study results of using an ultra low poly-alpha-olefin (PAO) challenge and a particle counter to preform leak sizing on an expanded polytetra-fluoroethylene (ePTFE) filter.

Introduction

The benefits of expanded polytetrafluoroethylene (ePTFE) filters, including the significant reduction in energy cost, chemically inert, and increased durability, have long been known in critical semiconductor applications.[1] The use of ePTFE filters in pharmaceutical applications is not widely used due to poly-alpha-olefin (PAO) loading of the filters when using the traditional aerosol photometer method for filter integrity testing.[2] Filter failures pose a significant cost to pharmaceutical manufacturers that produce product in a GxP critical environment. The ability to widely use ePTFE filters in pharmaceutical applications would provide valuable financial benefits in regard to lowering energy consumption, reducing production downtime, and reducing repair time, all leading to an increase in operational efficiency and risk mitigation.

In an attempt to solve silicone gel seal degradation by PAO, a test method, long used by the electronics and aerospace industry in Europe and Asia, was evaluated as an alternative approach to conduct filter leak detection in pharmaceutical applications.[3,4] This alternative test methodology was employed as a means to test ePTFE filters under conditions that would not significantly affect filter loading.[2] An ePTFE High Efficiency Particulate Air (HEPA) filter was subjected to the ultra low PAO test method in an attempt to mitigate the effects of PAO loading and establish a basis for the use of ePTFE HEPA filters in pharmaceutical applications with the same methodology of the microelectronics industry. The test method proved successful in determining leak sizes in the ePTFE filter without any of the negative effects of PAO loading. Under this test method, the use of ePTFE could be validated in critical ISO Class 7 and cleaner manufacturing areas where structural integrity and energy savings are valuable. This article gives a summary of the test methods and shares the results.

Background

From the 1960s to mid 1980s, dioctyl phthalate (DOP) was used in concentrations of 80 mg/m^3 (µg/L) to 100 mg/m^3 (µg/L) as an aerosol challenge for leak testing HEPA filters.[5] In the 1980s, aerosol photometers progressed to using solid state electronics and were utilized as a more sensitive instrument to identify filter leaks. With the implementation of these more sensitive and stable units, the recommendation for DOP aerosol challenge concentrations was reduced to 10 mg DOP/m^3 (10 µg of DOP/L) of air.[6] The early 1990s brought a change to the challenge material, due to DOP being labeled as a potential carcinogen. Emery 3004 polyalphaolefin (PAO) was recognized as a non-hazardous replacement and has now become the industry standard.[7]

An investigative study of current filter test methods was conducted to see if the benefits of ePTFE could be realized in aseptic manufacturing environments. When testing an ePTFE ULPA filter with 15 mg/m^3 (µg/L) of PAO, a pressure drop increase of 96% occurred in approximately 5.25 hours at 650 cfm.[2] The study clearly showed PAO exposure on the order of 15 mg/m^3 (µg/L) was detrimental to ULPA ePTFE filters, due to the drastic increase in the filter resistance (pressure drop) with time. This is due to the loading and occlusion of the pores in the ePTFE.

In addition to filter loading, when considering testing of ePTFE filters with the conventional use of PAO as a challenge aerosol, bleed through also was identified as a potential issue. The is-

sue of bleed through may occur when using thermally generated PAO to test ePTFE filters. This is due to the thermally generated aerosol having a 0.10 to 0.45 mass mean diameter, which is closer to the MPPS of the filter. This creates an issue with a photometer measuring a concentration and looking for leaks at or above 0.01%. The bleed through could erroneously manifest itself as an artificially large leak or in some cases, a continuous leak across the filter measuring a 0.025% or less leak rate. The PAO concentration levels discussed in this article are much lower than the standard levels and require generation by cold PAO generation methods.[8]

Cost Savings

The key with utilizing ePTFE is the overall cost savings to the end consumer. The use of ePTFE has several advantages over standard microglass. The best asset in the pharmaceutical environment is the strength of the material. The strength ranges from 10 to 100 times as strong as microglass depending on the carrier substrate that can be modified to an individual application. This creates a filtration media that does not fail under standard operating procedures, cleaning, installing, testing, and provides a durability to mitigate almost all risks of contamination from airflow. The filter will not shed, tear, puncture, or sustain pleat tip separation. Some standard costs associated with this is a replacement filter, labor for installation, letters to the FDA, follow up qualifications/validations, and worst case a recall. The individual pharmaceutical costs vary, but could easily get into the several thousand dollar range depending on the severity of the failure. The amount would be a multiple of the filter cost.

The energy costs also vary depending on electricity cost. An example would be that comparable filters at 2000 cfm would have a $250/year energy savings at $.10/kwh using ePTFE versus microglass. In a terminal filter application that testing was performed on in this article, the filter would save $32/year energy savings. This is not as significant as the risk mitigation savings, but also offers a payback on the additional filter cost during the life of the filter.

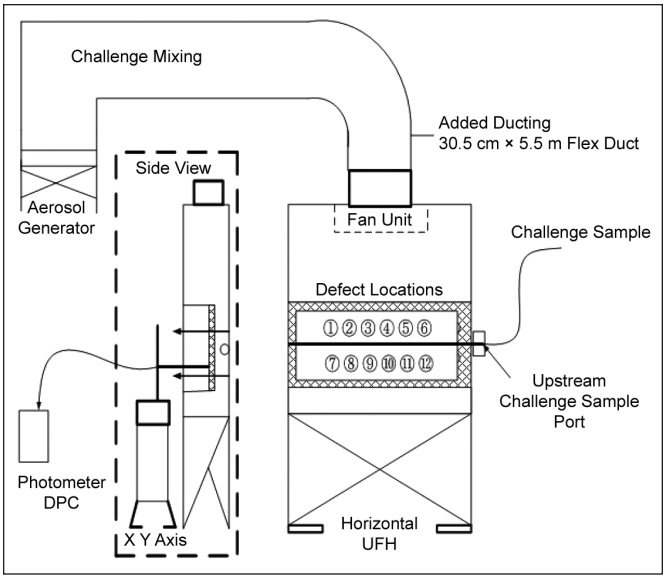

Figure 1. Test setup.

Executive Summary

This engineering study conclusively confirmed utilizing an ultra low concentration PAO challenge as an acceptable form of leak detection on ePTFE filters. This method dramatically reduces the potential of the filter loading issues identified in the prior ePTFE exposure studies.[2] The test method provided a 97+% reduction in PAO exposure to the filter when compared to the currently accepted test methodology outlined.[2] The acceptance and use of ePTFE filters and the ultra low concentration PAO test methods outlined here will greatly enhance the options of utilizing improved technology in pharmaceutical applications. The benefits gained from this will include reduced energy costs and increased operational uptime along with risk mitigation.

Test Overview

The engineering study on the effects of ultra low (< 0.3 mg/m^3 (µg/L)) PAO concentration testing of ePTFE filters was performed at the Baxter BioScience Thousand Oaks location in September 2010 by the authors of this article. The study showed the equivalence and effectiveness of testing ePTFE filters with industry typical concentrations (10 mg/m^3 (µg/L) or greater) and ultra low concentrations of PAO to detect leaks and determine their sizes.

The conventional test method of using a photometer and a ≥ 10 mg/m^3 (µg/L) PAO challenge was employed as a means to size defects created in an ePTFE filter. The results were directly compared to an alternative test method that was composed of using a Discrete Particle Counter (DPC) with a significantly reduced (< 0.3 mg/m^3 (µg/L)) PAO challenge.

Testing was performed by creating 12[1] defects in the HEPA filter of a Laminar Flow Hood (LFH). Comparative test data was then taken using the two methods.

An X-Y axis linear bearing sample probe positioning device was placed in front of the LFH as a means to remove sampling variation due to probe positioning. This unit consisted of a base secured on the floor with movable horizontal and vertical axes for exact probe positioning (±1 mm).

The study was performed using a 610 mm × 1220 mm (2 ft × 4 ft) horizontal LFH as seen in Figure 1. The HEPA filter used for the study was a Type C ePTFE filter, in accordance with IEST-RP-CC001.5, rated for a nominal flow of 630 cfm with an efficiency rating of 99.95% at the Most Penetrating Particle Size (MPPS). The IEST is a recommended practice for all HEPA and ULPA filters between customers and suppliers. The LFH was tested for airflow velocity, leaks, and unidirectional flow prior to beginning the study. Determination of the uniformity of the aerosol challenge was accomplished by fabricating and installing a stainless steel guide upstream of the filter. A sampling tube was then inserted into the guide and positioned so the sample tube opening was located at the end of the guide. A flex duct was attached (30.5 cm (12 in) diameter × 5.5 m (18 ft)) to the inlet of the hood to achieve adequate upstream mixing.

Measurement and test equipment utilized to determine aerosol challenge concentrations upstream of the HEPA filter was a photometer and a laser particle counter in combination

Method	Condition	Instrument	Reported Challenge Measurements
Ultra Low PAO	1	Discrete Particle Counter	~20 × 10^6 ≥ 0.3 μm particles per ft^3 PAO
	2	Discrete Particle Counter	~7 × 10^6 ≥ 0.5 μm particles per ft^3 PAO
Standard PAO Method	3	Aerosol Photometer	~11 mg/m3 (μg/L)
Note: A PAO aerosol produced by a Laskin nozzle of 38 million particles > .3 um is equivalent to approximately .1 mg/m^3 (μg/L)			

Table A. Conditions of test.

with an aerosol diluter. The particle counter and diluter instrument combination was used to determine the actual number of challenge particles for the ultra low level PAO testing (< 0.3 mg/m^3 (µg/L) (conditions 1 and 2)).

Study Conditions

Three evaluated conditions were derived from a combination of the particle sizes (0.3 and 0.5 µm), photometer, and DPC test equipment, and the selected aerosol challenge concentrations (PAO). Table A defines the test instruments, concentrations, and particle sizes tested.

Note: A PAO aerosol produced by a nozzle of 38 million particles > .3 µm is equivalent to approximately .1 mg/m^3 (µg/L).

Test Details

Equipment and Materials

- Discrete Particle Counter
- Portable Self Contained Aerosol Generator
- Poly-alpha-olefin (PAO)
- Photometer
- 2' × 4' Horizontal Laminar Flow Hood
- Aerosol Dilutor
- X – Y Axis Positioning Device
- 12" × 18" Flexible Ducting
- Air Data Multimeter
- Handheld Ultrasonic Aneometer

ePTFE Filter

Defects (12 holes) were made in the ePTFE media by inserting a 30 gauge hypodermic needle into the media twice at each defect site. The average face velocity of 104 fpm (192 m/sec) was determined using the ultrasonic anemometer. The face area of the filter was 6.52 ft^2. The volumetric flow through the filter was calculated to be 675 cfm. Pressure drop across the filter was measured to be 0.16" wc. It was noted this was approximately 25% of the pressure drop of a comparable wet-laid microglass filter (0.58" wc @ 650 cfm) operating at 90% of the airflow volume of ePTFE.

Upstream mixing was verified using a particle counter with ultra low concentrations of PAO as the challenge. Measurements were taken at six locations upstream of the ePTFE filter. The sample locations fell in between the two rows where the defects were created (~4" below and above the first and second rows respectively). The PAO sample reading variance for the six locations was < 1% which is well below the variance limit of ±15% across the challenge area as stated in ISO 14644-3 Section B.6.2.3. as seen in Table B.

The quarter Laskin nozzle generator was used in combination with an aerosol reducer (oil mist eliminator with an 18 gauge capillary bypass) to provide the upstream challenge. Thirty second samples (0.5 ft^3) were taken at each of the six locations and the counts per cubic foot are shown below. The differential pressure of the dilutor was measured at 4.89" wc which corresponded to a dilution factor of 966. The nozzle generator with the aerosol reducer created a filter challenge of approximately 20 million particles at ≥ .3 µm and approximately 7 million particles at ≥ .5 micron per cubic foot of air. The sizing was repeated 10 times to gain statistical significance.

Ultra Low PAO < 0.3 mg/m^3 (µg /L) Challenge using a DPC (Conditions 1 and 2)

The ePTFE Filter was challenged with an ultra low level of PAO in the range of 0.3 mg/m^3 (µg/L), as determined by the photometer. The defect sizes were measured in order starting with defect 1 and continuing sequentially to defect 12. After completing the defect sizing, a new upstream challenge was measured and defect sizing was repeated for a total of 10 runs to give statistically valid numbers.

At the beginning and end of each run, the upstream challenge was recorded. At the end of run 8, it was noted that the upstream challenge was increasing at a significant rate. It was theorized that the increase was related to loading of the oil mist eliminator used to reduce the output of the aerosol generator. Runs 9 and 10 were excluded in the analysis, due to the abruptly rising challenge concentrations.

Standard PAO 10.0 mg/m^3 (µg/L) Challenge using an Aerosol Photometer (Condition 3)

The third condition consisted of utilizing the traditional PAO aerosol/photometer method to size the defects created in the ePTFE filter. The ePTFE filter was challenged with ~10.7 mg/m^3 (µg/L) (average upstream of 10 runs) of PAO using the TEC 1.5 nozzle generator operating at 20 psi. The defect

Sample Location	Counts/ft^3 ≥ 0.3 micron particles	Counts/ft^3 ≥ 0.5 micron particles
1	37890	11224
2	39732	12038
3	39726	12018
4	39484	11868
5	39624	12114
6	38626	11810

Table B. Diluted upstream particle counts at leak detection points.

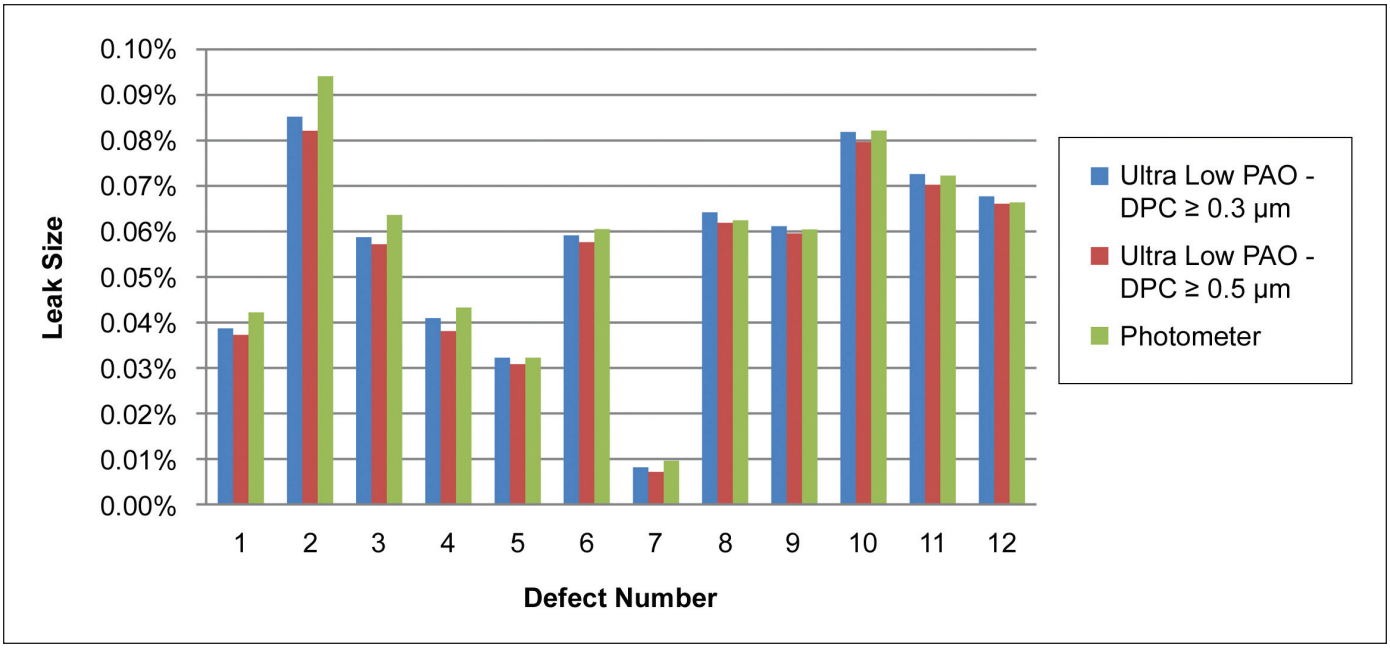

Figure 2. Leak size variation by instrument.

sizes were measured with a photometer in order starting with defect 1 and continuing sequentially to defect 12. After completing sizing for all 12 defects, a new upstream challenge was measured and defect sizing was repeated for a total of 10 runs. The average (over 10 runs) defect size is shown below for each defect 1 to 12.

Summary

The performance of the ePTFE was unaffected during testing. One concern was that the high doses of PAO would affect the outcome of the testing results for which data was gathered over a course of 2 to 3 hrs. The data showed that the ePTFE filter was unaffected by the testing as it maintained efficiency of at least 99.99% and a pressure drop of 0.16" H_2O. This is compared to a capture efficiency of 99.99% and a 0.58" H_2O pressure drop across the glass filter at 90% of the airflow.

The average leak sizes for the three test conditions are shown in Figure 2. A direct comparison of the test method reveals that the particle counter on average sized the leaks slightly smaller than the photometer for both the ≥ 0.3µm and ≥ 0.5 µm particle size distribution conditions.

After reviewing the data presented in Meek's study,[3] it was noted that the particle counter on average sized leaks slightly larger than the photometer. To better understand the repeatability and reproducibility of the measurement and test equipment used in the study, a head to head leak size comparison using 10 photometers was carried out.[9] The same comparison was later carried out using 7 particle counters. The results of the study showed that there was no statistical difference between the leak sizes obtained for the traditional and alternative test methods presented here.

Conclusion

Two test methods were employed to size defects in an ePTFE filter:

- ultra low level (~0.3 µg/l) PAO challenge with a discrete particle counter
- standard level (~10 µg/l) PAO challenge with a photometer

The results indicate that defects in the ePTFE filter can accurately be sized using ultra low level PAO challenges and a particle counter. Under the aforementioned test methods, both DPC test options (≥ 0.3 µm and ≥ 0.5 µm particle count defect sizing) performed adequate in comparison to the photometer.

When comparing both the initial study[3] and this article, the variation of sizing leaks with a DPC falls within the variation of the individual photometer tested in this study. The results provide validity to utilizing low PAO concentrations and DPCs to determine leak size in ePTFE filters. Utilizing this methodology, the loading of the filter will take 150 to 300 times as long based on previous testing. This now provides a method in which the benefits of ePTFE can be utilized in critical pharmaceutical applications.

References

1. Galken, Ned, and Abhishek Saxena, "Air Filtration Applications for Membranes," AFS Web site.
2. Roberts, Ron, "The Effect of PAO Aerosol Challenge on the Differential Pressure of an ePTFE Media ULPA (Experimental) Filter," *Journal of IEST*, 2003, pp. 74-76.
3. Meek, Jim, "Alternative Methods for HEPA Filter Leak Detection," *Pharmaceutical Engineering*, March/April 2011, pp. 1-7.
4. Hale, Dale, "HEPA Gel Seal Failure Study and Conclusions," 2007 ISPE Presentation.
5. Hale, Dean, "HEPA Filter Gel Seal Failure Study and Conclusions," 2006 CETA Presentation.

6. Mil Standard 286, 1956 Department of Defense Test Method Standard.
7. FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing Current Good Manufacturing Practice, September 2004.
8. Farquharson, Gordon, "HEPA Filtration – Specification, Leak Testing, Bleed-Through, and Other Nightmares," 2008 PDA Conference.
9. ISPE White Paper on "A Field Study Comparison of Leak Sizing Capability of Particle Counters and Photometers," currently under development.
10. NSF-National Sanitation Foundation Standard No. 49 for Class II (Laminar Flow) Biohazard Cabinetry Revision May 1983.
11. Moore, Jr., P.E., Don, "Comparative Testing of Challenge Aerosols in HEPA Filters with Controlled Defects," *Pharmaceutical Engineering*, March/April 1994: Volume 14, Number 2.
12. Farquharson, Gordon, "Time for New EU GMP," 2002 PDA Conference.
13. Particle counters are recognized in ASTM and International Standards ISO 21501-4.

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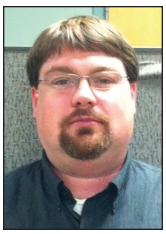

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