ASSESSMENT OF DIFFERENTIAL PRESSURES ACROSS STERILIZING FILTER MEMBRANES WITH VARIOUS TEST SOLUTIONS

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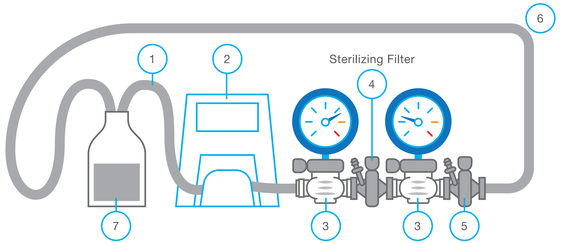
Abstract

FDA recommends monitoring differential pressure across filter membranes during sterile filtration process validation. However, few resources are available to help pharmaceutical manufacturers anticipate expected differential pressures during sterilizing filtration of different solutions. To address this gap, Meissner evaluated differential pressures across different filtration membranes using various test solutions at increasing pump speeds. Specifically, we investigated differential pressures across sterilizing-grade PVDF, PES, and PTFE membrane discs, either in series or with downstream 0.4 µm PES analysis discs commonly used in bacterial retention testing. The test solutions employed for this study include saline, grapeseed oil, FBS, and DMEM cell culture media with 10% FBS. These solutions were chosen based on their differing physicochemical properties and their relevance to the pharmaceutical industry. This work will serve as a reference for pharmaceutical manufacturers and help them anticipate differential pressures across sterilizing filter membranes at different pump speeds based on the physicochemical properties of their drug products.

Material Methods

The test solutions were 0.85% saline, 100% grapeseed oil, fetal bovine serum (FBS), or Dulbecco's Modified Eagle Medium (DMEM) with 10% FBS. Prior to testing, the grapeseed oil was pre-filtered with a 0.2 µm polyethersulfone (PES) capsule and warmed to 30 °C. All other solutions were tested at room temperature. The DMEM + 10% FBS was pre-filtered with a 0.2 µm polyvinylidyne fluoride (PVDF) disc.

Approximately 1 L of test solution was recirculated through two 47 mm discs installed in disc holders using a peristaltic pump at increasing pump speeds. The 47 mm disc membranes were 0.1 or 0.2 µm polyethersulfone (PES), polyvinylidyne fluoride (PVDF), or polytetrafluoroethylene (PTFE), either in series to simulate redundant filtration or with downstream 0.4 µm PES discs to simulate bacterial retention testing. Pressures upstream of each filter disc were measured using calibrated Anderson pressure gauges installed on single-use gauge tees. Differential pressure was determined by calculating the difference between the upstream and downstream pressure gauges. All values below 2 psi were recorded as 0 psi.

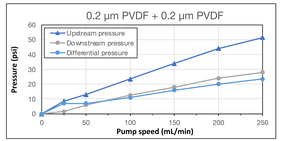


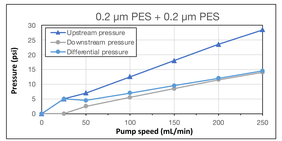
1. Upstream TPE pump tubing
2. Peristaltic pump
3. Pressure gauge, Single-use Gauge Tee (SGT), large clamp, 2x small gaskets, and clamps
4. Sterilizing filter in holder
5. Redundant sterilizing filter or 0.4 µm PES analysis filter in holder
6. Downstream silicone tubing with fitting, small gasket, and clamp
7. 1 L media bottle containing test solutions

Results

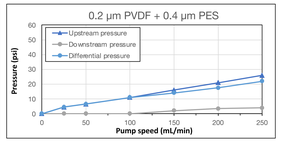
0.85% Saline

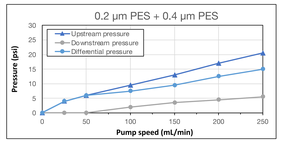
Redundant Filtration





Bacterial Challenge Test

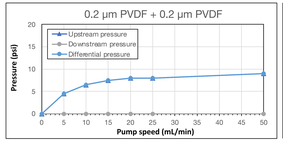




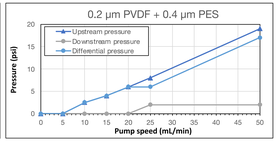
With saline during redundant filtration, the influent gauge pressure was approximately twice the differential pressure across the first filter at higher pump speeds. During filter validation, the 0.4 µm analysis filter contributed very low differential pressures, particularly at low pump speeds.

FBS

Redundant Filtration



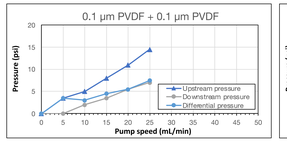
Bacterial Challenge Test

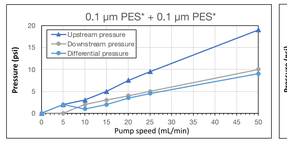


With FBS, the differential pressure was not evenly distributed across the redundant filters. During filter validation, the 0.4 µm analysis filter contributed minimally to the differential pressure on the 1st filter. The increased pressure on the 0.2 µm filter is likely due to the filter plugging, and the low pressure on the analysis filter is due to low flow. Pressure increases as flow decreases when using a constant pump speed.

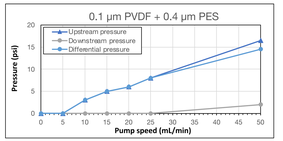
DMEM + 10% FBS

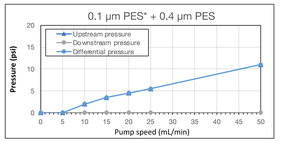
Redundant Filtration





Bacterial Challenge Test



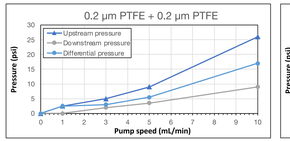


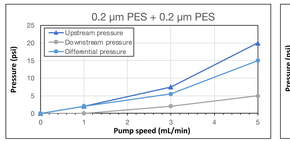
In DMEM + 10% FBS, the redundant 0.1 µm filters distributed the pressure across each filter relatively evenly at higher pump speeds. The 0.4 µm analysis filter contributed very little to the upstream pressure with both PVDF and PES filters. The differential pressures seen on the redundant 0.1 µm filters were similar to the gauge pressures observed on the 0.1 µm filter with downstream 0.4 µm analysis filters.

* dual layer 0.1 µm PES

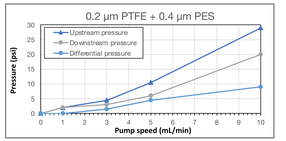
Grapeseed Oil

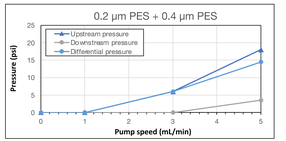
Redundant Filtration





Bacterial Challenge Test





With grapeseed oil, the pressures for the redundant PTFE and PES filters were not evenly distributed; this was more pronounced with the PES filters. The analysis filter contributed significantly to the gauge pressure on the upstream PTFE filter.

Conclusion

In this study, differential pressures across PVDF, PES, and PTFE membrane filters were evaluated during filtration with 0.85% saline, FBS, DMEM + 10% FBS, and grapeseed oil at increasing pump speeds. Our results demonstrate that in non-viscous, aqueous solutions, the feed pressure tends to be distributed evenly across the 2 redundant filters, particularly at high flow rates. Viscous and nonaqueous solutions can behave differently. Bacterial challenge test set ups can accurately simulate the actual differential pressures of the redundant filtration processes for aqueous solutions. Furthermore, downstream PES analysis filters made minimal contributions to upstream gauge pressure during filtration with aqueous, low viscosity solutions. Consideration should be given to the selection of analysis membranes during bacterial retention testing.

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