Application Note

Performance of Gamma Stable Opticap® XL 50 Capsule Filter with Millipore Express® SPG Membrane vs. Competitor's 50 mm Gamma Stable Hydrophobic PVDF Membrane Filter for a Typical Fed Batch Cell Culture Process

In processes with high cell culture densities and long batch durations, venting single-use bioreactors can be a challenge. Greater sparge flow rates are often required to maintain necessary dissolved oxygen levels and remove carbon dioxide from the culture media in high cell density applications. Increased volumes of gas flowing through a cell culture require a hydrophobic filter capable of efficiently venting the humidified exhaust gas.

Current hydrophobic vent filters do not always offer the flow rates necessary over extended durations to meet process requirements. As a result, filters are often oversized. Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG (Sterile Phobic Gamma) polyethersulfone membrane have been designed to provide high flow rates over extended process durations. The Millipore Express® SPG membrane is a hydrophobic membrane that can be sterilized by gamma irradiation or autoclaving.

This application note examines the performance of Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane for small scale bioreactor applications. This study evaluates the vent filter flow rate and bioreactor pressure under typical cell culture conditions.

Summary

The performance of Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane was compared to Competitor A's 50mm gamma stable hydrophobic PVDF (polyvinylidene fluoride) membrane filter. Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane outperformed Competitor A's filter over the duration of a 12-day fed batch process. The data demonstrates that Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane is robust and better able to handle humidified exhaust streams over extended process durations.

Objective

The objective of this study was to measure and compare venting performance of the Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane with a commercially available hydrophobic vent filter under representative cell culture process conditions. The results presented compare inlet flow rate to the exhaust flow rate to determine the relative flow rate from each vent filter over the duration of a typical cell culture process. In addition to evaluating filter performance by exhaust flow rate, the increase in the internal bioreactor pressure was also used to evaluate filter performance between Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane and Competitor A's PVDF exhaust filter.

Experimental Method

Experiments were conducted to evaluate the performance of the Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane and Competitor A's 50 mm gamma stable filter with PVDF membrane by measuring the flow rate under dry conditions to obtain a baseline airflow rate at different pressures and under representative cell culture conditions.

A Gamma Stable Opticap® XL 50 Capsule Filter with Millipore Express® SPG membrane and Competitor A's filter were attached to separate Mobius® 3L CellReady bioreactors using 24" tubing with 1/4" internal diameter (primary filter). The reactors were filled with commercially available cell culture media and inoculated with a monoclonal antibody producing CHO cell culture. The cell culture process used was a 12-day fed batch process using four feeds. A secondary exhaust path was added to each vessel by connecting a condensate trap vented with a 25 mm hydrophobic PTFE filter to the bioreactor with 1/8" internal diameter tubing (Figure 1). In theory the gas will flow through the primary filter first. As the pores of the filter begin to plug with condensate, the exhaust gas will be diverted to the secondary filter. The exhaust gas was measured from the primary and secondary exhaust on days 3, 5, 7, and 10 using an external flow meter (TSI™ Mass Flowmeter 4140) to ensure all gas vented from the vessel was accounted for. The inlet flow rate was measured using an internal mass flow controller. From the measured inlet and exhaust flow rates, a percent relative exhaust flow rate was determined using the equation:
% Relative Exhaust Flow Rate = (Primary Exhaust Flow Rate / Inlet Flow Rate) x 100.

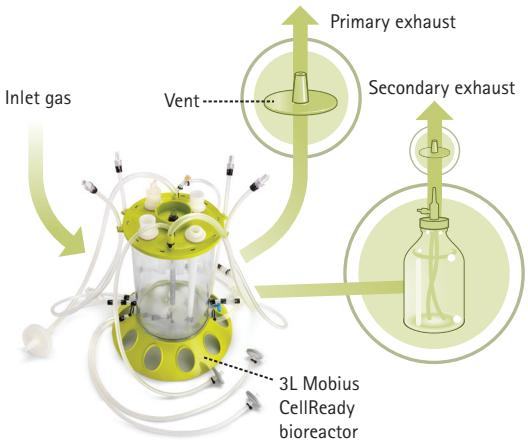

Figure 1.
Bioreactor Assembly with Exhaust Filters

In addition to measuring the exhaust flow rates, the internal bioreactor pressure was measured using a Scilog® pressure gauge (SciPres 080-699PSX) to assess the pressure rise in each reactor with the secondary path closed. As the exhaust filter begins to plug, the amount of pressure it takes to exhaust the gas increases in the bioreactor. Performance of Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane and Competitor A's PVDF filter was evaluated based on relative exhaust flow and vessel pressure at varying inlet flow rates.

Results

Experiment 1: Typical gas flow rates

The first experiment evaluated the performance of flow rate v. differential pressure under dry conditions.

The data (Figure 2) show that the air flow rate through Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane is 80% more than Competitor A's PVDF filters at 5 psi. At 20 psi, the air flow rate through Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane is approximately 50% more than Competitor A's PVDF filter.

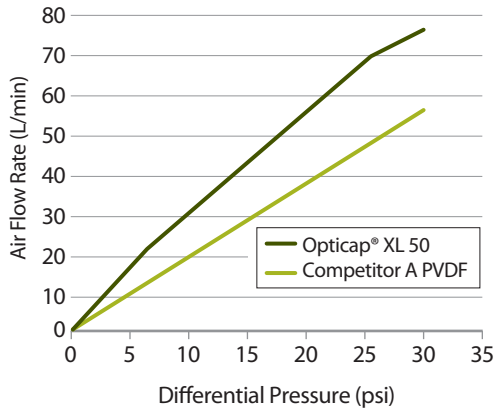

Figure 2.
Comparison of inlet flow rates in Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane v. Competitor A's PVDF Gas Filter

The higher flow rate observed through Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane makes it suitable for a cell culture or microbial fermentation process, where high gas flow is expected throughout the batch duration.

Experiment 2:
Exhaust flow rate compared to inlet flow rates

This experiment evaluated the performance of the Opticap® XL 50 filter compared to Competitor A's PVDF exhaust filter over the duration of a typical cell culture process using multiple inlet gas flows (50, 200 and 500 cc/min). Each condition was performed using replicates of two. In this experiment, the measured exhaust flow from the primary exhaust and secondary exhaust was compared to the inlet gas flow as measured by the mass flow controller.

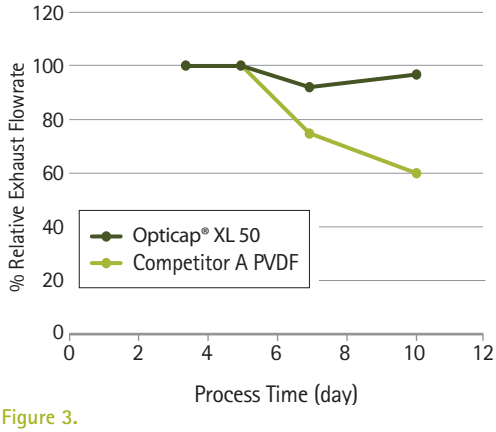

Figure 3.
Comparison of exhaust filter performance using Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane v. Competitor A's PVDF filters: 50 cc/min inlet flow rate

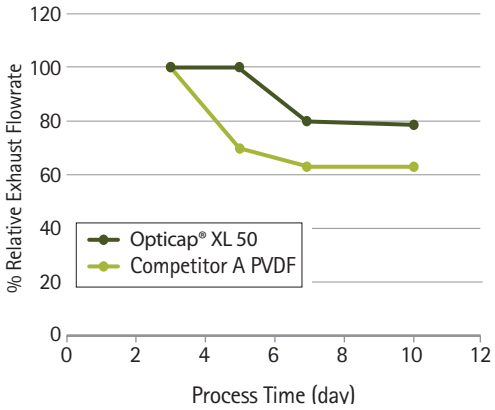

Figure 4.
Comparison of exhaust filter performance using Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane v. Competitor A's PVDF filters: 200 cc/min inlet flow rate

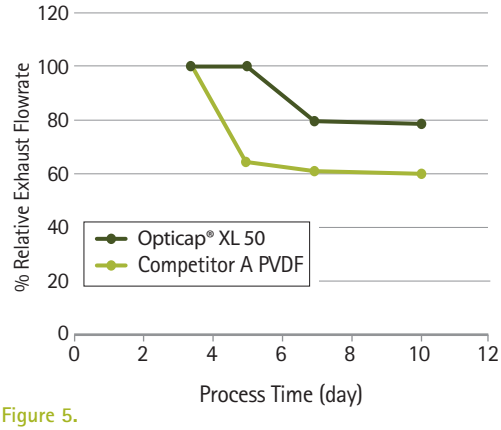

Figure 5.
Comparison of exhaust filter performance using Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane v. Competitor A's PVDF filters: 500 cc/min inlet flow rate

The data shown in Figures 3-5 demonstrates how Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane outperforms Competitor A's PVDF exhaust filter at all inlet flow rates tested. Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane were able to retain 80% of the inlet flow rate after Day 7 at all flow rates tested. Competitor A's PVDF filter began to show signs of blinding after Day 3, when the relative exhaust flow rate decreased to approximately 60% of the respective inlet flow rates.

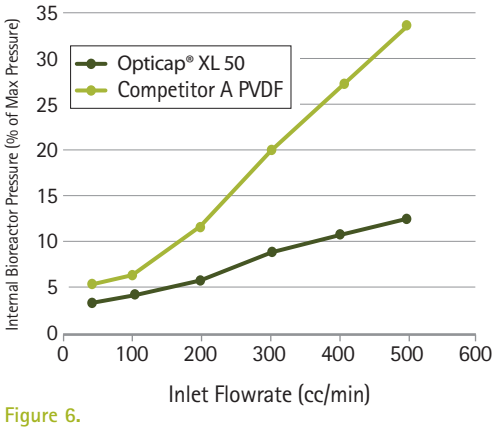

Figure 6.

Bioreactor pressure profile using Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane and Competitor A's PVDF Vent Filters

On day 10 of the experiment the internal pressure of the vessel was measured with the secondary exhaust path closed. The inlet flow rate was increased stepwise. The first increase in the gas flow was from 50 cc/min to 100 cc/min, followed by increments of 100 cc/min until a final flow rate of 500 cc/min was reached. At each step the exhaust flow rate and the pressure in the vessel was measured.

As the exhaust filter becomes saturated with condensate, the filter's ability to flow gas decreases as evidenced by the pressure increase in the bioreactor (Figure 6). If the pressure in the vessel exceeds the maximum operating limit, the batch or experiment may be at risk of failure. This can occur if the vessel cracks due to over-pressurization. Figure 6 compares the pressure in the bioreactors on Day 10 over varying inlet flow rates when using Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane and Competitor A's PVDF filter.

When operating under typical inlet flow rate of <250 cc/min, Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane were able to maintain lower bioreactor pressures at varying inlet flow rates compared to Competitor A's PVDF filter. This experiment demonstrates that Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane's ability to resist blinding* is superior to Competitor A's PVDF filter. When used as a vent filter, Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane provide a wider margin of safety and higher process confidence.

Conclusion

Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane are recommended for small scale bioreactor applications, demonstrating improved performance when compared to Competitor A's PVDF vent filter on the Mobius® 3L CellReady single-use bioreactor. Under typical operating flow rates (<250 cc/min) and inlet pressure (<5 psi), Gamma Stable Opticap® XL 50 Capsule Filters with Millipore Express® SPG membrane exhibited:

- Superior flow rates over extended process duration
- Excellent blinding resistance
- A wide margin of safety for high process confidence

*Blinding: A phenomenon where condensate or foam covers the pores of the filter, preventing active air flow.

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Lit No. TB4213EN00 DP-SBU-11-05673 12/2011 Printed in the USA.