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White Paper

Sizing Up Successfully

Best Practices for Sizing Sterilizing-Grade Filters for Aseptic Manufacturing of Sterile Drug Products.

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Summary

Sterilizing-grade and bioburden reduction membrane filters are used throughout aseptic manufacturing. Proper filter sizing is an important step in process development: undersized filters can foul prematurely, while oversized filters can lead to economic inefficiencies. Bench-scale filtration tests can be used to model large-scale filtration processes using classical models of filter fouling. These, and more recent advances, improve model accuracy and estimates of filtration area requirements.

This article provides guidance on how to use data from bench-scale tests, typically run under constant pressure, to accurately size filters for production-scale operations. The value of intermediate-scale simulations is also discussed. Well executed bench-scale studies are a quick, easy approach for sizing filters for aseptic drug manufacturing and provide a solid foundation for robust filtration operations on a production scale.

Why is Filter Sizing Important?

Sterilizing-grade and bioburden reduction membrane filters are used throughout biopharmaceutical manufacturing, from media and buffer filtration to filtration of process intermediates and final sterile filtration. Sizing a filter for production volumes is an important, and sometimes tricky, part of process development.[11] An undersized filter will begin to foul before the end of the filtration process, resulting in unexpectedly high pressures or low flow rates while oversized filters can negatively affect process economics by having unnecessary filtration area and increased product hold up in the filter, impacting yield. Bench-scale filtration tests are often used to model large-scale filtration to conserve resources.[6] Filtration models use bench-scale data to estimate the filtration area required to meet process goals such as filtration volume, time, and flow rate, while accounting for membrane plugging, also known as fouling.

Over the years, various filtration models have emerged, each focusing on different mechanisms of fouling.[4]

When performing bench-scale filter sizing studies, it is important to understand the fouling behavior of the process fluid and know the details of the manufacturing process. Process pauses, presence of a prefilter, temperature, and other details of the manufacturing process should be simulated during the bench-scale studies wherever possible. Following initial sizing determinations, intermediate-scale studies are recommended, especially if the manufacturing process will be operated using a different operating mode than the one used at bench scale (constant pressure versus constant flux).

This white paper provides guidance on how to use data from bench-scale tests to accurately size filters for production-scale operations. Beyond process development, filter sizing tests and their impact on scale up to process scale will also be discussed.

Filter Fouling Models can Estimate Filtration Area

The size and chemical profile of particles in a process fluid determine the fouling mechanism and inform the predictive model used to calculate filtration area. There are four classical models of filter fouling based upon the fouling mechanism of different particle sizes, as shown in **Figure 1**.[4] Complete pore blocking assumes that particles foul the membrane by perfectly blocking the pore. Once all the pores are blocked, no additional flow will occur (**Figure 1a**). Standard pore blocking (gradual pore plugging) illustrates how membrane pores narrow over time as foulants gradually adhere to the pore walls (**Figure 1b**). During standard pore blocking, resistance increases until the pores are completely blocked, and flow ceases.

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The intermediate model combines the complete pore blocking model with the possibility that some particles will deposit on top of existing particles (**Figure 1c**). Lastly, surface deposit (cake formation) describes the accumulation of particles much larger than the pore size of the membrane on the filter surface, leading to cake formation (**Figure 1d**).[9] While liquid flow remains possible, resistance increases as the thickness of the cake increases.

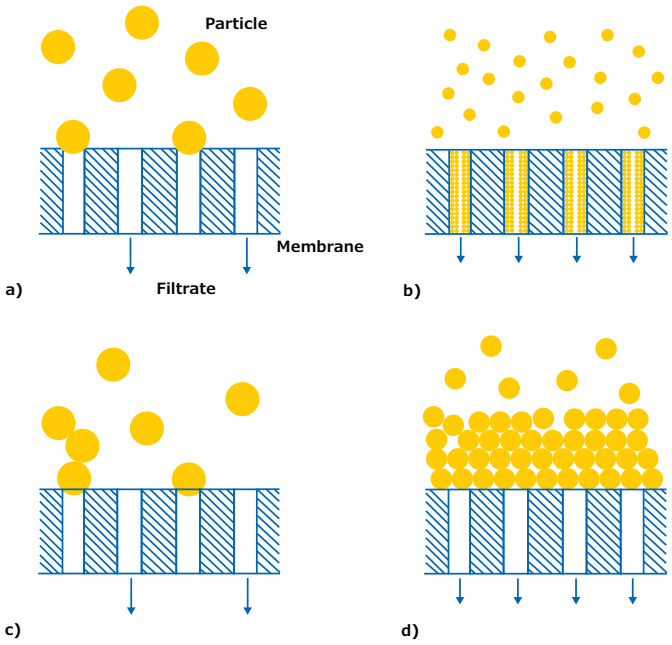

Figure 1: Classical filter fouling mechanisms. (a) complete blocking, (b) standard blocking (c) intermediate blocking, and (d) cake filtration. Reprinted with permission.[6]

The classical models assume that pressure and velocity do not affect the rate of filter fouling. Bolton et al. introduced models that account for particle-surface attraction, or adsorption, which allowed charge-based and hydrophobic-based filter fouling to be modeled.[2] More recent advancements have led to combined models that consider size-based and adsorption-based fouling, that can more accurately predict performance in real-world applications.[3, 6]

However, the filtration model is only half of the filter sizing picture. Representative bench-scale data is required to estimate the appropriate filtration area requirements for production-scale filtration operations.

Constant Pressure Testing Efficiently Estimates Filter Capacity and Membrane Area

Bench-scale membrane filter capacity tests are short-duration tests using representative fluid and small-scale devices run under constant pressure, usually 10-30 psi depending on the application. During these tests, volumetric flow is measured over time and used to calculate filter flux and flux decay.

These tests are efficient with respect to time and resources because they require a small volume of process fluid, simple equipment (**Figure 2**), and the test duration is typically less than 30 minutes. Flux decay can be extrapolated using fouling models to determine the filter capacity for a defined process time, batch size, and flow rate.[1, 8, 12]

Figure 2: Constant pressure filter sizing test set-up. The pressure vessel is filled with product, pressurized, and applied to the test filter. A pressure gauge (p) maintains constant pressure during the test. Valves pre-filter (a), at the filter vent (b), and post-filter (c) allow air venting of the filter before testing. A system vent (v) allows safe release of pressure after the test.

A simple filter sizing tool called Vmax™ can quickly extrapolate the theoretical maximum capacity of the filter from the constant pressure data, if the fouling mechanism is predominantly gradual pore plugging and adsorption.[1,8] The maximum capacity of the filter, or the Vmax™, can be estimated by graphing time/volume by time and taking the inverse of the slope.[12] The Vmax™ term is then used along with the process variables such as batch volume and time to calculate the minimum required membrane area:

$$A_{min} = \frac{V}{V_{max}} + \frac{V}{Q_i * t}$$

A_{min}: minimum filtration area (m^2)

V: batch volume (L)

t: process time (hour)

V_{max}: the theoretical maximum filter capacity (L/m^2)

Q_i: inital flow rate normalized to filtration area (LMH)

The Importance of a Safety Factor

Any estimates of filtration area requirements for larger scale processes should include a safety factor to accommodate device and process variability. The size of the safety factor is dependent on the criticality of the process step (e.g., filtration of cell culture media, process intermediates or final sterile filtration) and stage in product development (clinical versus commercial manufacturing). Safety factors may also accommodate other differences between bench- and production-scale membrane filters including flat versus pleated membrane, piping, batch to batch variation, and variations in operating conditions, as well as the cost and potential impact of process failure. For instance, the proposed safety factor range for sterile filtration of bulk drug substance is 1.4—2.0 while the range for sterile buffer filtration ranges from 1.1—1.3.[7] Differences in the cost ratio and variability of these operations result in different safety factors.

An experienced filter supplier should have modeling tools to help you estimate filtration area requirements with appropriate safety factors for any filtration application.

Filter Capacity Testing: Different Fluids

Fouling fluids

For fouling fluids, the best practice recommendation for a bench-scale, constant-pressure filter capacity test is to capture at least 40% of the flux decay; this will minimize extrapolation error in sizing estimates.[6] Higher flux decays during sizing tests enables more accurate predictions of area requirements from the models.

The fouling characteristics of a process fluid may vary significantly depending on operating flux and pressure. Flux and pressure influence residence time and adsorption interactions with the membrane. If production-scale filtration could occur within a range of fluxes or pressures, or if there is a significant ramp-up period during operation, it is recommended to test the high and low operating setpoints to determine the impact on filter performance.

Low-fouling fluids

Low fouling fluids are defined here as those showing less than 10% flux decay during a filter sizing trial; examples of such fluids might include dilute drug product, some buffers, and serum free cell culture media. Estimating membrane filtration area requirements with these fluids can be challenging as seemingly small differences in filter capacity can lead to large differences in estimates of filtration area requirements.[6] For process scientists who struggle to characterize performance of low fouling fluids at bench scale, this may result in insufficient or oversized filtration areas on scale-up.

For confidence in filter sizing, characterization of low-fouling fluids may need to extend beyond a basic test to better understand the process fluid behavior. Bracketing the desired operating pressure can be useful to determine the worst-case fouling; for instance, a process targeting pressures between 10 psi and 30 psi should evaluate filter capacity under both pressures. Additionally, extending the loading on the sizing filter during the constant pressure test may help define the maximum filter capacity.

Final sterile filtration presents a particular challenge for filter sizing as representative process fluid is typically precious and may appear low- or non-fouling during the Vmax™ study. In such instances, if material is limited and the loading target undefined, it is recommended to cap the estimate of filter capacity; for monoclonal antibodies this may be 3000—5000 L/m^2. This conservative cap can be adjusted if additional data with a particular fluid improves process understanding.

Non-fouling fluids

The required filtration areas for large-scale operations with non-fouling fluids such as common buffers can be sized using filter permeability and process time rather than fouling characteristics.[8] Assuming an unlimited filter capacity, the equation for minimum filter area reduces to:

$$A_{min} = \frac{V}{J_{mean} * t}$$

A_{min}: minimum filtration area (m^2)

V: batch volume (L)

t: process time (hour)

J_{mean}: average flux from the trial data (LMH)

Minimum filter area is directly correlated to the fluid's specific viscosity since flux is inversely dependent on viscosity. If the permeability of a filter with a water-like solution is known, then the minimum filter area can be easily estimated by substituting the flux variable:

$$\text{Average flux [LMH]} = \frac{\text{Permeability} \left[\frac{\text{LMH}}{\text{psi}}\right] * \Delta \text{ Pressure [psi]}}{\text{Specific Viscosity}}$$

The calculated minimum filtration area is not the final recommended filter size. The final recommended filter size will consider the minimum filtration area along with pressure drops due to the filter configuration (i.e., housing type). Consulting the water flow versus pressure drop graphs from the filter vendor aids in determining the appropriate size filter for a given process flow rate, pressure, or required filter configuration.

Filter Capacity Testing: Pumps, Process Pauses, and Prefilters

For the most accurate filter sizing predictions, filter sizing using constant pressure tests should aim to match the manufacturing conditions as closely as possible. Filtration operations using a pump at manufacturing-scale are most accurately sized by using a constant-flow setup at bench scale. Although constant flow sizing is ideal, constant-pressure testing can save time and material.

When constant pressure is used to size a pump-based process, it is important to understand the relationship between pressure and flux early on. If the maximum system pressure is defined, a short series of tests at different pressures will generate information on flux that can be used to characterize the system. Understanding this relationship for any given fluid will facilitate a seamless transition from constant pressure to constant flux operations.

If filter sizing for a constant flow large-scale operation was extrapolated from constant pressure testing using the Vmax™ method, it is strongly recommended to confirm the accuracy of the size estimate at intermediate scale with a pump.

Process conditions and process holds

The process temperature, storage conditions, pH, and concentration should be maintained between bench-scale and production operations as these variables can affect filtration performance.[10] Accurate simulation of process conditions increases the accuracy of filter sizing.

Process holds performed during manufacturing should be simulated during a bench-scale study since the components of a process fluid may aggregate, interact or potentially adsorb to the membrane without pressure or flow. Higher adsorption could accelerate filter fouling.

Presence of a prefilter

The presence of a prefilter can significantly affect filter capacity. Prefilters and sterilizing-grade filters should be tested in series at bench scale, especially if the fluid has a high viscosity.[6] As the prefilter fouls, the pressure drop on the prefilter will increase, resulting in a lower pressure on the final sterilizing-grade filter which is missed if the filters are not run in series.

One goal of filter sizing for serial filtration trains is to determine the optimal prefilter-to-final filter area ratio. Modeling tools can be used to fit data from each filter independently and predict performance at different area ratios. Optimizing filtration area ratios can significantly affect overall throughput and can help identify the most cost-effective filtration train for specific process conditions.

Single or redundant filtration

Many processes implement redundant filtration for critical final filtration operations. Redundant filtration uses two identical sterilizing-grade filters arranged in series and lowers the risk of having to reject a batch of drug product if the primary sterilizing filter fails a post-use integrity test.

Compared to processes using a single sterilizing-grade filter, redundant filtration reduces filter permeability by half, resulting in a doubling of the system pressure. For non-fouling fluids, if a single filter is used to determine optimum filter size for a redundant filtration process, then a system pressure corresponding to half of the maximum pressure should be targeted. Using this approach, when the redundant filter is added at process scale, the correct system pressure will be reached. Alternatively, for plugging fluids, bench-scale studies should be performed to directly mimic the process by testing at the maximum targeted pressure with two filters assembled in series.

Other Factors that Influence Scale-up

The format of the filter can affect the pressure profiles across a filtration system. Filters with narrower inlet and outlet connections, such as hose barbs, will experience a larger pressure drop than those with larger connections, such as 1½ inch sanitary flanges. Additionally, T-line housings will have different pressure drops compared to in-line housings due to the liquid flow path (**Figure 4**). This applies to both stainless steel housings and plastic single-use capsule filters. Considering these pressure losses is especially important for series filtration, as the inlet pressure on the downstream filter will be reduced due to the pressure drop along the first filter in series.

The impact of pressure losses due to filter format are more pronounced for non-fouling, low viscosity fluids in scale-up. Since the membrane is not fouling, the housing and connections have an outsized impact on the filter's overall resistance and pressure drop. The safety factor may need to be increased as the scaling of non-fouling fluids will not be linear. Additionally, inlet pressures or flow rates may need to be adjusted to meet the parameters used in the bench-scale study.

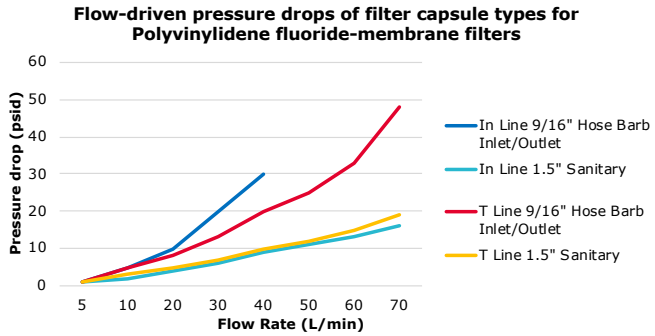

Figure 4: Impact to pressure drop of various filter housing configurations. Restrictions such as hose barbs and T-line housings can increase pressure drop across filters of the same membrane at the same flow rates.

Key Considerations for Any Filter Sizing Study

Filter capacity testing using the constant pressure test is a time-tested procedure for determination of filtration area requirements for sterilizing-grade filters used in aseptic drug processing. Data generated using bench-scale tests are analyzed using filter fouling models to predict behavior for large scale processes.

- Bench-scale testing should model the manufacturing-scale process using appropriate raw materials, flow rates and pressures, the presence of process holds and the use of prefilters or redundant filters. Accurate simulation of process conditions including temperature, pH, storage conditions and concentration, increases the accuracy of filter sizing.
- Low-fouling fluids that yield inconclusive data with a short duration test may benefit from extended filtration test time to observe fouling behavior, running tests at different pressures to bracket fouling behavior, or increasing the safety factor to accommodate variability.
- Filters for non-fouling fluids can be sized based on filter permeability, desired filtration time, and the filter housing configuration.
- Redundant filtration of non-fouling fluids will reduce filter permeability by half, resulting in twice the pressure drop as compared to a single filter.
- Bench-scale filter capacity tests provide a first estimate of filter sizing and should be confirmed at intermediate scale in the mode of manufacturing-scale operation, i.e., constant pressure with a pressurized air supply or constant flux with a pump.

By carefully following these recommendations, you should be able to accurately size sterilizing-grade filters for robust manufacturing operations.

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