Application Note

Simplified, efficient sizing of sterilizing-grade normal flow filters for buffer solutions

Introduction

Buffer solutions are required in various process steps of pharmaceutical and biotechnology therapeutics including: cell culture media, chromatography, ultrafiltration, diafiltration, and final formulation. Sterile filtration of buffer solutions using 0.2 µm filters is commonly performed to control process bioburden and remove physical contaminants. Filtering buffer solutions using sterilizing-grade filters provides the benefit of helping to ensure a sterile and endotoxin free final product and can extend the life of downstream chromatography and ultrafiltration steps.

Due to the broad need for buffer solutions throughout a drug manufacturing process, buffer filtration is typically a high volume operation. Thus, efficient sterile filtration of buffer solutions is critical to ensure a successful and timely batch operation.

The Vmax™ filter sizing method is commonly used today in a variety of applications to estimate filter size requirements for normal flow membrane filters. The Vmax™ filter sizing model assumes filter pores plug gradually over time. The Vmax™ technique requires experimental filtration work be carried out at constant pressure using the test solution and a membrane filter.

This technical brief describes the development of $K_{Buf,}$ an efficient and simplified filter sizing tool for buffer filtration which is based on well characterized membrane permeability values. The K_{Buf} sizing method has been shown to closely approximate sterile filter sizing requirements for buffer filtration applications generated through the more laborious Vmax™ sizing method.

Sizing Normal Flow Microporous Membrane Filters

The Vmax™ technique is commonly employed in the biopharmaceutical industry for sizing normal flow filters.[1] The Vmax™ method is based on a gradual pore-plugging model. From the model, the following sizing equation (Equation A) is derived for determining the minimum filtration area requirements for a normal flow filtration process operated under constant pressure.

[1] Merck Millipore Application Note, The Vmax™ Nomograph – A quick reference to estimate filter sizing, Literature Number AN1200EN00, Rev. 3/00

[Equation A]

$$A_{min} = \frac{V_B}{V_{max}} + \frac{V_B}{J_i \, x \, t_B}$$

Where:

- A_{min} (m^2) is the minimum area needed to process the batch
- V_B (L) is the batch volume to be filtered
- t_B (h) is the filtration time
- Vmax™ (L/m^2) represents normalized capacity at time = ∞
- J_i (L/m^2h or LMH) is the normalized initial volumetric flow rate or flux.

Using the Vmax™ method, constant pressure is used to force the fluid through a filter. As the filter plugs, flow through the filter decreases over time. By performing a Vmax™ sizing study using small scale (low area) membrane filters, volume vs. time data can be generated and key sizing parameters of the model, such as Vmax™ and J_i can be calculated.

For sterile filtration of plugging fluids, such as process intermediates in a recombinant protein purification process, the Vmax™ or filter capacity values may range between 50 to 3,000 L/m^2. In this range, the capacity term represented by the V_B/Vmax™ term contributes significantly to the overall filter area requirements.

In contrast for non plugging fluids, such as buffers, the Vmax™ or filter capacity value, can be high (>5,000L/m^2). As a result, the V_b/Vmax™ term in Equation A is relatively small compared to $V_B/J_i \, x \, t_B$ term. In these cases, Equation A may be reduced to Equation B, and sizing filters for low plugging streams, such as buffers, can be approximated based on membrane filter permeability and process time:

[Equation B]

$$A_{min} = \frac{V_B}{J_i \, x \, t_B}$$

Further, Darcy's law[2], which describes the flow of a fluid through a porous media, can be applied to determine the flux of buffer (non-plugging) through a membrane filter:

[2] Lenchi R.W., Williams S., Effect of non-aqueous solvents on the flux behavior of ultrafiltration membranes, 1995, 3-51

[Equation C]

$$J_i = \frac{\Delta P}{\mu \, x \, R}$$

Where:

- J_i ($Lm^{-2}s^{-1}$ or ms^{-1}) is the flux across the filter
- ΔP (Pa) is the differential pressure across the filter
- μ ($kgm^{-1}s^{-2}$) is the viscosity of the fluid and
- R (m^{-1}) is the intrinsic resistance of the membrane

Darcy's law can also be expressed in the following form:

[Equation D]

$$J_i = \frac{Q \, x \, \Delta P}{\mu}$$

In above Equation D, Q = (1 /R), is the membrane permeability. Given that the intrinsic resistance of the membrane, (R) cannot be measured directly, the membrane permeability (Q') for a solution of viscosity, μ, can be simplified to the following form:

$$Q' = \frac{Q}{\mu}$$

[Equation E]

$$Q' = \frac{J_i}{\Delta P}$$

Where:

- Q' ($Lm^{-2}s^{-1}Pa^{-1}$ or more commonly as $Lm^{-2}h^{-1}psi^{-1}$ or LMH/psi) is the permeability of membrane for a given solution of viscosity μ
- J_i ($Lm^{-2}s^{-1}$ or more commonly as $Lm^{-2}h^{-1}$ or LMH) is the flux across the filter
- ΔP (Pa or more commonly as psi) is the differential pressure across the filter

When performing a Vmax™ experiment at a given pressure, using a solution of known viscosity (μ), the flux of fluid (J_i) across the filter can be measured and membrane permeability for solution (Q') can be subsequently calculated.

From Equation D, it can be inferred that the viscosity of the fluid has a direct impact on membrane flux. Fluids of high viscosity should result in lower flux and permeability. For water-like buffers, viscosity can be assumed to be nearly the same as that of water (viscosity of water = 1 cP or 0.001 $kgm^{-1}s^{-2}$ at 20°C), and permeability of the buffer across the filter (Q') can be approximated to be the same as that of water.

Thus, combining Equations [B] and [E] for a "water-like" buffer leads to:

[Equation F]

$$A_{min} = \frac{V_B}{Q' \times t_B \times \Delta P}$$

Using Equation F, the minimum filter area required to process a batch of buffer solution can be calculated with the following information:

1. The permeability of the solution with a particular membrane
2. The batch volume
3. The process time
4. The applied differential pressure.

Although information on process conditions (e.g.; batch time, volume and pressure) is generally known, specific fluid permeability with a particular membrane (Q') is typically derived through Vmax™ experiments.

Alternatively for feed streams such as buffers, the generic permeability value (Q'), representing typical filter permeability for majority of water–like buffers, can be used to quickly and easily estimate filtration area requirements.

Determination of the Generic Permeability Value

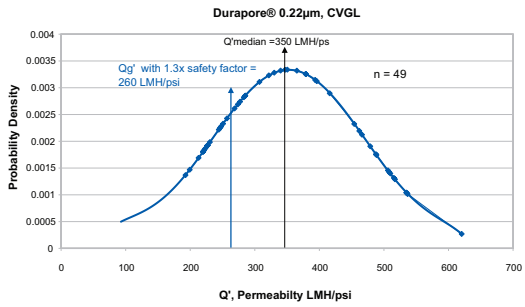
Data was extracted and analyzed from the extensive Vmax™ filtration sizing experiments during process development with non-plugging fluids on sterilizing-grade filters. Three sterilizing-grade filters were studied:

- Durapore® 0.22 µm, Polyvinylidene Fluoride (PVDF), monolayer, sterilizing-grade filter
- Millipore Express® SHF, Polyethersulfone (PES), 0.2 µm, monolayer, sterilizing-grade filter
- Millipore Express® SHC, Polyethersulfone (PES), 0.5/0.2 µm, bilayer, sterilizing-grade filter

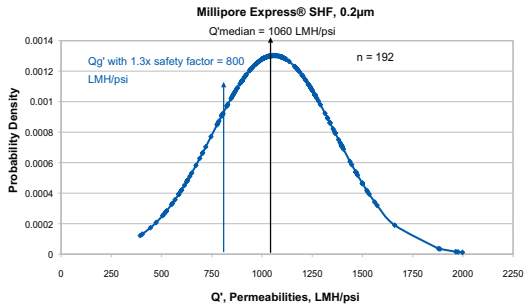
For the development of a permeability based sterilizing-grade filter sizing tool, data points that exhibited Vmax™ values greater than 3000 L/m² (i.e.; non-plugging feed streams) were compiled using OptiScale® 25 disposable capsules[3] to generate a normal curve for each of the assessed sterilizing-grade filters (See Figure 1). All the data points were taken from experimental work with buffers commonly used in the pharmaceutical industry. The variability from the median which was observed for each normal curve (standard deviation) accounts for the total variability experienced and consists of: membrane variability, and solution viscosity variability due to temperature effects, viscosity differences among buffers and test measurement error. A generic permeability value (Q_g') was selected which includes a safety factor of 1.3 from the median of each filter's normal (Gaussian) curve. This (Q_g') permeability value was used to develop the sizing constant for each filter. *Note: A safety factor of 1.3 was previously determined to be optimal for buffer filtration applications and represents a balance between process robustness and filtration cost.[4] This safety factor does not account for viscosity difference among different buffers.*

Figure 1. Normal curves for sterile grade filters. a) Durapore® CVGL membrane b) Millipore Express® SHF membrane c) Millipore Express® SHC membrane

a)



b)



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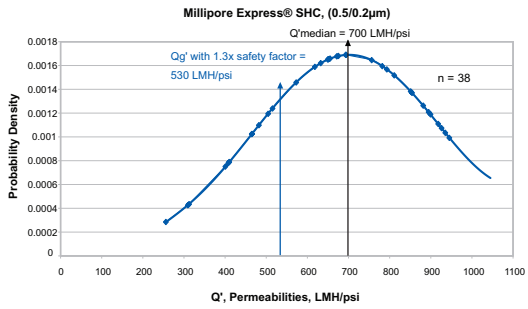


[4] Lutz H., *Rationally defined safety factors for filter sizing*, Journal of Membrane Science, 2009, 341 268-278

[3] Giglia S., Rautio K., Kazan G., Backes K., Blanchard M., Caulmare J., *Improving the accuracy of scaling from discs to cartridges for dead end microfiltration of biological fluids*, Journal of Membrane Science, 2010, 365 347-355

Determination of Sizing Constant (K_{Buf}) For Sizing Tool

The generic permeability (Q'_g) for the filters in Figure 1 can be included in Equation F to provide a convenient estimate on the minimum filtration area required for a batch of buffer solution. The number of 10" cartridges required to filter a buffer batch can be determined using Equation G and the calculated minimum filtration area from Equation F.

[Equation G]

$$\#10" cartridge = \frac{A_{min}}{area\ of\ 1 \times 10" cartridge}$$

By equating Equation F to G, a sizing constant, K_{Buf} was derived to provide a quick and useful estimate on the number of 10" cartridges required to process a given volume of buffer.

[Equation H]

$$\#10" cartridge = \frac{V_B \times K_{Buf}}{t_B \times \Delta P}$$

K_{Buf} is the sizing constant for a given filter which can be applied to water-like (viscosity = 1 cP), non-plugging buffers and is expressed in the following form:

[Equation I]

$$K_{Buf} = \frac{1}{Q'_g \times (Area\ of\ one\ 10" cartridge)}$$

Process Scale Up Size Adjustments

To adjust for device format differences between small-scale process development devices (typically flat disc formats) and process scale devices (typically pleated devices), scaling factors and in-line housing pressure losses of 7% between the inlet and outlet are applied to K_{Buf} to arrive at K_{Buf} final.[3] The K_{Buf} final sizing constant for each filter type can be found in Table 1. The K_{Buf} final sizing constants can be directly applied to Equation H for water-like fluids. A quick reference chart (see Figure 2), developed using K_{Buf} final constants and filtration time of 1 hour, can also be used to estimate filter sizing with reference to the applied pressures (5, 10, 15, or 20 psi) and batch volume. The K_{Buf} final sizing constants and reference charts are applicable for filtering water-like buffers with viscosity of 1cP. *Note: The K_{Buf} sizing method (based on K_{Buf} final constants) should not be used if the purity and viscosity of the fluid is in doubt. If the fluid viscosity or the purity of the fluid is unknown, a definitive Vmax™ sizing assessment is recommended.*[5]

Common buffers with water-like behavior used in the biopharmaceutical industry:

Common Buffers	Limitations
Sodium Hydroxide	Up to 1M and at room temperature
All citrates, acetate, chlorides and tris buffers	
Phosphate buffered saline	
Hydrochloric Acid	
Acetic Acid	

Note: The list of common buffers above provides an overview of buffers with "water-like" behavior. The types of "water like" buffers used in biopharmaceutical industry include, but are not limited to, the above list.

[5] Merck Millipore Application Note, *Filter Sizing Methods*, Literature Number AN1512EN00, Rev. 3/00

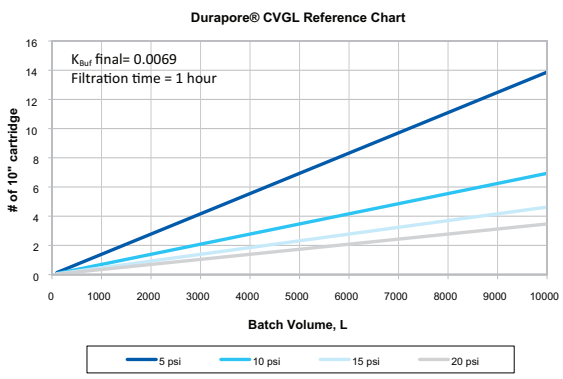
Table 1. Sizing constants and formula for sizing sterilizing-grade filters

Filter Type	K_{Buf}	Scaling factor	K_{Buf} Final (incl. scaling factor and 7% housing pressure loss)	Formula for K_{Buf} Sizing Method (based on K_{Buf} final constants)
Durapore® 0.22 µm, CVGL	0.0056	0.86	0.0069	#10" cartridge = $\frac{V_B \times 0.0069}{t_B \times \Delta P}$
Millipore Express® SHF, 0.2 µm	0.0023	0.89	0.0028	#10" cartridge = $\frac{V_B \times 0.0028}{t_B \times \Delta P}$
Millipore Express® SHC, 0.5/0.2 µm	0.0039	0.87	0.0047	#10" cartridge = $\frac{V_B \times 0.0047}{t_B \times \Delta P}$

Note: V_B is batch volume in liters, t_B is time in hours and ΔP is differential pressure in psi. The scaling factor for each filter type was measured by Merck Millipore.

Figure 2. Reference charts for sizing sterilizing-grade filters for buffer solutions. a) Durapore® CVGL b) Millipore Express® SHF c) Millipore Express® SHC

a)



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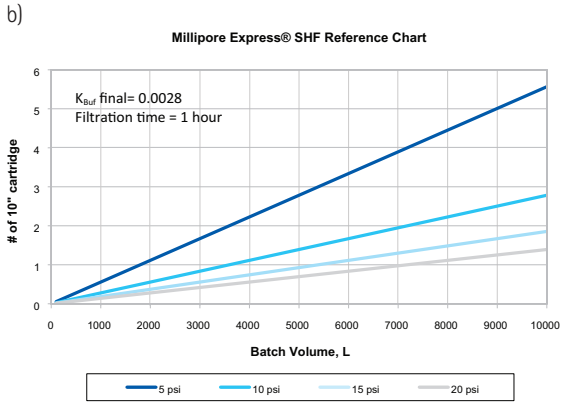

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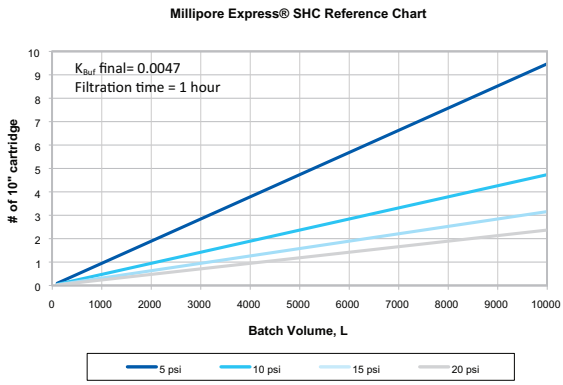

Validating The Sizing Tool Results

To verify the accuracy of filter sizing using the K_{Buf} sizing method, filter area recommendations provided by the K_{Buf} sizing method were compared to the filter area requirements determined using volume vs time data collected from Vmax™ experiments with common buffers in biopharmaceutical purification. Since the K_{Buf} method was developed for sizing water-like buffers, this verification was done for each of the three types of sterilizing-grade filters: Durapore® 0.22µm, Millipore Express® SHF and Millipore Express® SHC using only buffers with water-like behavior (Q'=Q'median). As seen in Table 2, filtration area estimates obtained from Vmax™ and K_{Buf} methods for the three filter types were compared.

Filtration Sizing With Vmax™ Method

Vmax™ and J_i sizing parameters of the gradual pore-plugging model were obtained experimentally. Time (t) and filtrate volumes (V) captured during small scale filtration trials were used to plot the line: t/V= f(V); where Vmax™ is the inverse of the slope and J_i is the inverse of the Y-intercept. The minimum area, A_{min}, needed to process the batch was then calculated using equation [A], experimental Vmax™ and J_i, process volume and 1 hour process time.

Using the Amin result, an initial safety factor (SF) of 1.3, appropriate scaling factor (ScF) for the chosen membrane and in-line housing pressure loss of 7% was applied to account for the scale up differences between disk and pleated devices.[3,4,6] The final process configuration was recommended and the overall safety factor was calculated (ratio between the process filter area and the minimum area needed for the process as determined from Vmax™ calculations).

Filtration Sizing with K_{Buf} Sizing Method

Using the reference chart for the appropriate membrane, a given batch volume and assumed pressure to be applied at production floor, the number of 10" cartridges can be estimated for each membrane at a filtration time of 1 hour. For filtration times different than 1 hour, the number of cartridges should be adjusted accordingly. For example, if the filtration time is 2 hours, the number of cartridges would be halved of the amount sized by the reference chart. Conversely, if the filtration time is only 30 minutes, the number of cartridges required will double. Alternatively, the number of cartridges needed to process a buffer batch could be estimated using the formula for K_{Buf} sizing method found in Table 1 for each filter type and by applying the batch volume, process time and applied pressure to the formula.

CASE STUDY: To filter 5,000 L of NaHS buffer using Durapore® 0.22 µm, Polyvinylidene Fluoride (PVDF), monolayer, sterilizing-grade filter in 1 hour at 10 psi applied pressure, two different methods can be used to size the number of cartridges required for processing the volume of buffer. By using Vmax™ method (performing a lab bench trial) the minimum filtration area (Amin) required is 1.93 m^2. Considering safety factor of 1.3, scaling factor (scaling factor for the Durapore® membrane is 0.86) and inline housing pressure loss (7%), the final (adjusted) filtration area required would be 3.12 m^2. Hence the actual calculated 10" cartridge required would be 5 units of Durapore® 0.22 µm, Polyvinylidene Fluoride (PVDF), monolayer, sterilizing-grade filters. Given that a 10" Durapore® cartridge has an area of 0.69 m^2, 5 units of 10" cartridges will provide 3.45m^2, resulting in overall safety factor of 1.8.

An alternate method to estimate the filtration area required to filter the buffer batch will apply the K_{Buf} method. From the quick reference chart (Figure 2a), we can derive that approximately 4 units of Durapore® 0.22 µm, Polyvinylidene Fluoride (PVDF), monolayer, 10" cartridges would be sufficient to perform filtration of 5000L of this buffer. This configuration results in safety factor of 1.4 relative to the calculated Amin value from the Vmax™ trial. Comparison of filtration area values obtained by the Vmax™ and K_{Buf} methods indicate that K_{Buf} sizing method results in 20% less filtration area recommended to process a given volume of buffer than Vmax™ sizing.

[6] Giglia, S, Yavorsky D, *Scaling from disc to pleated devices*, PDA Journal of Pharmaceutical Science and Technology, 2007, 61 314-323

Table 2. Comparison of Vmax™ and K_{Buf} method filter sizing recommendations

Case Study	Filter Type	Area of 1x10" (m2)	Buffer	Process conditions			Vmax™ sizing						K_{Buf} constant sizing				K_{Buf} Area/ Vmax™ Area
				V_B (L)	ΔP (psi)	t_b (h)	Permeability (LMH/psi)	A_{min} (m^2)	Area with SF, ScF and 7% housing loss (m^2)	Conf.	Final Filtration area (m2)	Overall SF	# 10" required	Conf.	Filtration Area (m^2)	Overall SF	
1	CVGL	0.69	NaHS	5000	10	1	350	1.93	3.12	5 x 10"	3.45	1.8	3.5	4 x 10"	2.76	1.4	0.8
2	SHF	0.54	1M Sodium Acetate	5000	5	1	1060	0.93	1.45	3 x 10"	1.64	1.8	2.8	3 x 10"	1.62	1.7	1.0
3	SHC	0.49	100mM Glycin	10000	21.8	1	671	0.72	1.15	3 x 10"	1.47	2.0	2.2	3 x 10"	1.47	2.0	1.0

Summary

From the comparison of filtration area sized using Vmax™ or K_{Buf} sizing method, (Table 2), K_{Buf} sizing results were similar to Vmax™ sizing results for the three sterilizing grade filters. K_{Buf} sizing method results were within 20% of Vmax™ results and had an overall safety factor of 1.4 to 2 which is considered acceptable. The above discussion and comparative data analysis indicates that the K_{Buf} sizing method provides a reasonable approximation of sterile filter sizing for buffer filtration applications. The comparison was for solutions with permeability similar to water and Vmax™ value greater than 10,000 L/m^2. Vmax™ sizing method accounts for viscosity variability whereas K_{Buf} method does not. Changes in viscosity, membrane, process may result in larger differences in filtration area sizing between the Vmax™ and K_{Buf} method.

Considerations For Applying K_{Buf} Sizing Method

The simplified K_{Buf} sizing method is only applicable to Durapore® 0.22 µm, Millipore Express® SHF and Millipore Express® SHC sterilizing-grade filters and applies to non-plugging solutions with viscosity +/-20% of 1 cP. Other sterilizing-grade filters or small scale devices may not provide reliable sizing results due to differences in membrane permeability and device scaling factors.[3] The K_{Buf} sizing method accounts for inline housing pressure losses of 7% but does not include other process considerations such as piping and system effects. Housing pressure loss increases exponentially with increasing flow rate and may be different for membrane of different permeability.

Plant piping; elbows and valves, head pressure due to elevation of filters or tanks and housing design restrictions (inline versus T-line), are among the many factors that can impact the effective pressure applied to the filter resulting in longer process times.

Additional safety factor or increasing applied pressure to the filter assembly to increase the effective pressure across the filter may be considered to overcome the impact of system and piping losses.[7]

[7] Royce J., Wilkins R., Merck Millipore Application Note, *Considerations for sizing and selecting sterile buffer filters*, Literature Number AN1047EN00, 2006

Conclusion

A simplified sizing method (K_{Buf}) has been developed for sterile buffer filtration applications and is shown to closely approximate filter sizing requirements generated through the more laborious Vmax™ sizing method. The filter area configuration suggested by the K_{Buf} sizing method maintained adequate filtration area safety factors (filter area safety factors ranged 1.4 to 2.0) and aligned within 20% of the filtration area configuration obtained from the Vmax™ sizing model for solution with Vmax™ value greater than 10,000 L/m^2 and viscosity similar to water. Vmax™ sizing experiment should be carried out if the viscosity, cleanliness of the solution is in doubt.

For water-like feed streams, such as buffers, which typically have low particle loads and are low fouling, the K_{Buf} sizing method provides convenient, efficient and accurate sizing information. The K_{Buf} sizing method is limited to non-plugging buffers with viscosity similar to water and is applicable to estimate buffer filter sizing requirements for Durapore® 0.22 µm, Millipore Express® SHF and Millipore Express® SHC sterilizing-grade filters.

Note: In determining the final filter sizing recommendations, the user should consider any additional process impacts from fluid's characteristics (purity, viscosity, temperature, etc.) and system design.

References

Brown A.I., Levison P., Titchener-Hooker N.J., Lye G.J., *Membrane pleating effects in 0.2 µm rated microfiltration cartridges*, Journal of Membrane Science, 2008

Merck Millipore Application Note, *Buffer filtration – Sizing constant method for Durapore® 0.22 µm Cartridge Filters*, Susan Moore, 1999

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Lit No. TB4462EN00 DP SBU-12-06677 12/2012 Printed in the USA.