Making an Informed Membrane Filter Choice

Criteria to Consider

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Membrane filters can be evaluated using a number of performance factors. Nevertheless, such evaluations are often not made. Three performance criteria in particular are important to every process and product, albeit to different degrees. These three criteria are total throughput, flow rate, and the yield loss associated with the filtration step.

Understanding the process and product (and evaluating the relative importance of these three performance influences) can help guide you in selecting the proper filter. Checking against these criteria in choosing from the array of commercially available compatible filter products will result in lower costs per liter filtered — and may yield other improvements as well.

Product Focus: All products requiring filtration

Process Focus: Downstream processing

Who Should Read: Process development, manufacturing, project managers

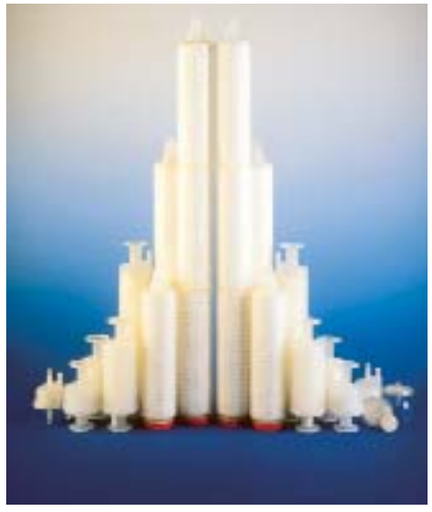
Keywords: Filtration, validation, qualification, scale-up, yield optimization

Level: Biotech basics

The Role of Total Throughput

Simply put, total throughput is a measure of the total amount of filtrate that can pass through a filter before it clogs or becomes unusable. This determines the size and number of filters necessary to process a given batch size. A number of factors affect total throughput: filtration area, geometry, quantity, design, and the pore size rating of the membranes. Large variations in total throughput can be found across the spectrum of commercially available membrane filters (Figure 1). This, of course, can greatly affect the total filtration cost. What may appear to be a less expensive filter may actually significantly increase filtration costs. In general, total throughput becomes more important as the value of the product decreases.

Total throughput can be enhanced by evaluations that lead to appropriate filter combinations. It is advisable to test flat filter combinations during the development phase. These evaluations commonly use 47-mm flat filter composites. Once the optimal combination is defined, scale-up of that combination is performed with small-scale pleated filter devices. The design of such filter devices must be exactly replicated in the final combination that will be validated for the full-scale process. Additionally, test data collected over a period of time will create a database, which can be a foundation for decisions based on experience.



Sartorius (www.sartorius.com)

The Flow Rate Factor

Flow rate comparisons at constant differential pressures can be another important factor in membrane filter selection. The number of filters required to process a batch within a given timeframe is determined by the rate of flow through a selected filter. Again, filtration area, porosity, quantity, design, and retention rating of the membranes all have significant effects on the flow rate of a given filter type. Flow rate comparisons in Figure 2 show significant variations among membrane filters.

Flow rate becomes important in time-sensitive processes, in which manufacturing capacity or product-specific concerns such as product stability necessitate faster processing times. Higher flow rates can alter the capacity and output of a production

process. They may, however, be essential when normal production capacities and exaggerated product demands are not in sync, such as when a manufacturing process requires some flexibility to meet seasonal demands for a given drug product. In some instances, high flow rates are required to avoid drug product degradation. Commonly, degradation is enhanced by prolonged filtration and processing times. The faster the batch is filtered, the less time it has to degrade, and the higher the yield. Prolonged filtration times can cause bioburden levels to build up in front of the final filter. To avoid such microbial contamination, the product may require cooling, prefiltration, or simply the shortest filtration times possible. Experimental evaluation is required to determine the optimal filter for the specific application and process.

Yield Loss

Commonly, each step in a process involves an associated yield loss. This is especially important in bioprocesses with low-volume, high-value drug products. Filtration steps are not immune from this consideration; actually, they can represent some of the more costly losses in terms of yield. Careful filter selection can reduce such yield loss significantly. For high-value products, filter expenses pale in comparison to the cost of using the wrong filter for the job. Yield loss is more complicated than the two factors described above and may depend on a number of mechanisms.

Unspecific Adsorption is one important mechanism for products with protein-based active ingredients or preservatives. It is generally a function of the polymeric molecular properties of a membrane and of the filter device's materials of construction. Unspecific adsorption is generally not affected by flow rate, differential pressures, or pore size — except possibly by prolonged residence times and extensive filtration areas. In some cases, pH may have an affect on the quantity of protein adsorbed. Figure 3 shows large differences in total adsorption among the available membrane types.

Additionally, high unspecific adsorption enhances filter fouling and gel polarization of membranes, which in itself can cause yield loss.

Size Exclusion comes into play when the product of interest is larger than the pores it encounters in the filter. This is especially important at the sterilizing filter (typically 0.2 or 0.22-µm rated) for products larger than 0.05 µm. Material, quantity, and retention rating of the membranes within a selected filter can influence yield loss by this mechanism.

Figure 1: Total throughput comparison of different 10-inch, 0.2-µm sterilizing grade membrane filters using a model solution

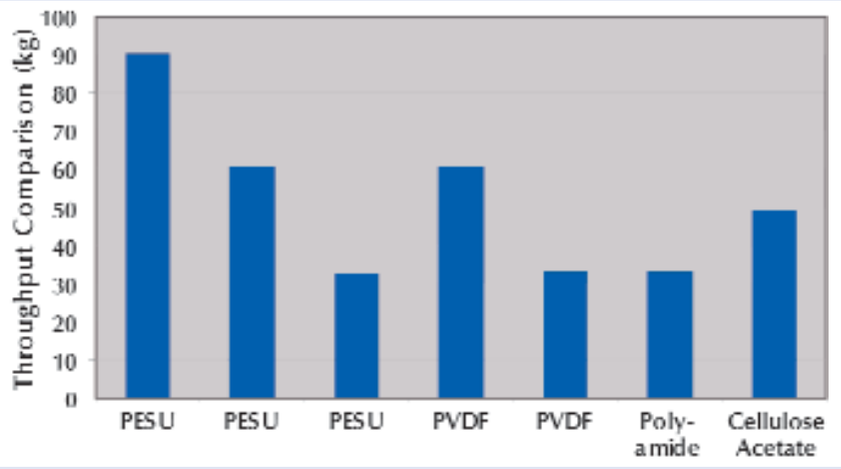


Figure 2: Flow rate comparison of different 10-inch, 0.2 µm sterilizing grade membrane filters using water at 20 °C and 1 bar differential pressure

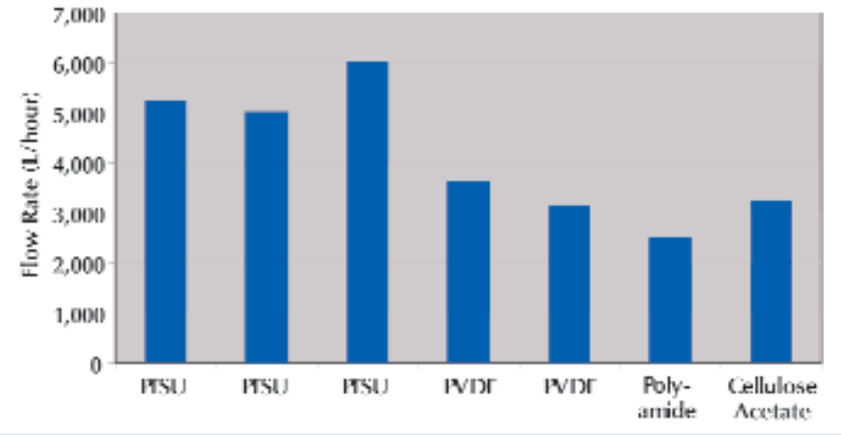
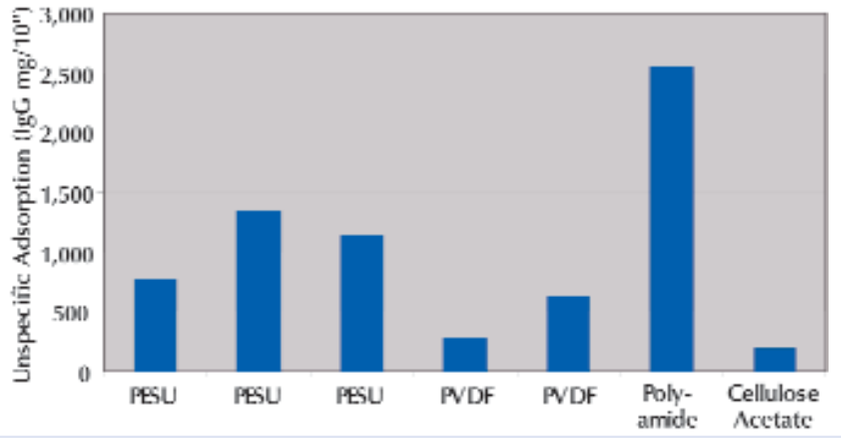


Figure 3: Unspecific adsorption comparison for IgG of different 10-inch, 0.2 µm membrane filter cartridges



Improper filter selection can have a devastating effect on process yield.

The geometry of a filter device can play a role in yield as well. Hold-up volumes, or the amount of filtrate that remains in the filter after processing, can be important in small-volume, high-value operations. Most membrane filter manufacturers make such information available upon request.

Worth the Time and Effort

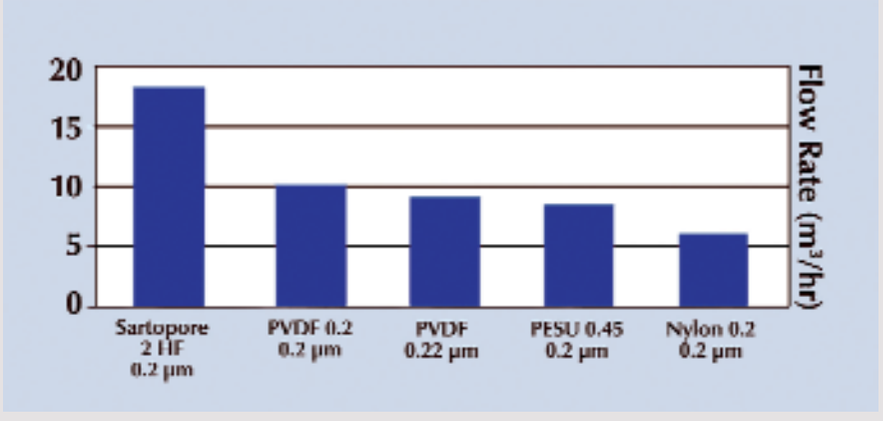
There is no such thing as the perfect membrane filter. Biological processes and products vary greatly — and so does the performance of individual membrane filters. A particular membrane filter could perform exceptionally well in some instances but then fail the performance specifications for another application. Experimental trials must be conducted to evaluate the best filter and filter combination for each application and process. Such tests may be thought of as costly and time consuming, but they will help in the design of an optimal process, which over time will create a higher return by far than would otherwise be realized.

Major filter manufacturers have technical support structures in place for use by their customers. The experience of that support should be tapped to avoid unwelcome surprises later on in a process. Joining the user's application expertise to the manufacturer's separation expertise most often results both in optimized processes and value recovery. This is true both for process developments and amendments to existing processes.

Specific Filters for Specific Applications

Filters for Sterile Filtration of Buffers: The bioburden reduction (or sterilization) of buffers by filtration traditionally makes use of available sterilizing grade filters on the market. With typically large volumes to be processed, the primary consideration is processing time. So this application has a strong emphasis on flow rate, whereas total throughput and yield considerations are minimized. That is primarily because buffers are usually prepurified solutions that require a sterilizing grade filtration step simply to reduce bioburden or ensure sterility. Recognizing that, Sartorius has developed the Sartopore 2 HF line of cartridge filters. Based on the Sartopore 2 Polyethersulphone membrane, the Sartopore 2 HF is a single-layer sterilizing grade filter optimized for high flow rate. With the highest flow rate of any sterilizing grade filter on the market, this filter can process the same volume in one-third to one-half the time of others, as shown in the figure below.

The versatility of polyethersulphone membranes offers compatibility with solutions from pH 1 to 14 and a wide variety of chemicals — as well as excellent wettability.



For Further Reading

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