Specifying Microfiltration Systems

This technology can accomplish in one step what other systems can only do in two. Enzyme recovery offers a prime example

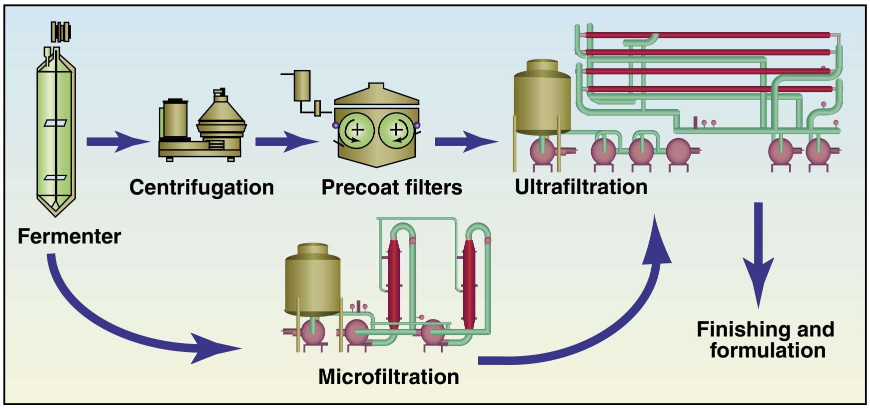

FIGURE 1. In a typical enzyme cell harvest and recovery process, microfiltration replaces the centrifugation and precoat filtration steps

Robert J. Keefe
Niro, Inc. / GEA Filtration

David M. Dubbin
Niro Ltd, UK

In the food, pharmaceutical and chemical industries, microfiltration via ceramic membranes is used for the efficient recovery of a wide range of products from fermentation biomass. In biotech operations, the technology has emerged as an effective method for separating enzymes from fermented mixtures, because it holds back the whole cells and allows the enzyme to pass through and be recovered in the permeate stream.

When compared to traditional separation techniques such as centrifugation and rotary vacuum filtration, microfiltration is much more economically viable. In fact, crossflow membrane filtration can replace a two step process with one, resulting in lower investment and operating costs, higher enzyme yields and simplification of downstream processing methods.

How it differs

The conventional approach for cell-enzyme separation has been either centrifugation or rotary-drum vacuum filtration, followed by pressure leaf filtration to remove the small amount of remaining cell debris. Once separated, the enzymes are concentrated and purified using ultrafiltration, a standard process that has been used for many years (Figure 1).

Although it is fast, centrifugation has a number of drawbacks, such as high maintenance costs, heat production and protein denaturation, most notably, incomplete separation since the method relies on density rather than size differential. Rotary drum vacuum filters and other dead-end filtration techniques also have disadvantages, most notably in terms of overall yield losses.

Several of the more important advantages of crossflow membrane filtration, notably microfiltration, over the conventional technologies are:

1. It is generally more effective in purifying the enzyme, giving higher product yields while maintaining biological activity
2. It eliminates the need for precoat filter aids, such as diatomaceous earth (DE) or perlite that are used as filter media, doing away with the environmental issues associated with disposal of the used media. It also eliminates the cost and difficulties of purchasing and handling the filtration media
3. Crossflow membrane filtration utilizes tangential flow, rather than dead-end filtration like a filter press, so the membranes can be easily cleaned whenever necessary, via clean-in-place and steam-sterilization techniques
4. It allows for better control of the process, and frequently improves the downstream ultrafiltration step
5. Perhaps most relevant economically, both the initial investment and ongoing maintenance costs are lower than those of conventional centrifugation or dead-end filtration

SELECTION CRITERIA

The implementation of microfiltration might differ depending on whether an enzyme producer is putting in a completely new process line or converting and upgrading an existing process. For a new system, it is more economical to use microfiltration to replace both the centrifugation and precoat filtering steps. Where upgrading an existing system, it may be desirable to replace just the precoat filters and leave the centrifuges in place, providing there are no maintenance issues with them.

Process and equipment design and pilot testing are all crucial in order to evaluate and define the specific operating conditions of a microfiltration separation process to ensure success on a commercial scale. The key is to design and run the microfiltration system properly to ensure getting the highest possible capacity to reduce capital costs, and the highest enzyme permeability (or passage of the enzymes through the membrane) to maximize yield and recovery.

One of the biggest challenges in successfully designing an enzyme recovery system, for example, is achieving high permeability of the enzymes through the membrane. The boundary

FIGURE 2. Microfiltration systems that use ceramic membranes are offered for both batch and continuous operations

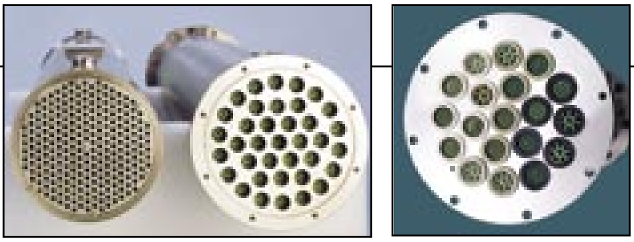

FIGURE 3. Ceramic membrane elements and housings are often used because their open, tubular channels (in contrast to polymeric spirals, which have very narrow channels) are easily able to process a whole-cell broth without plugging by suspended solids

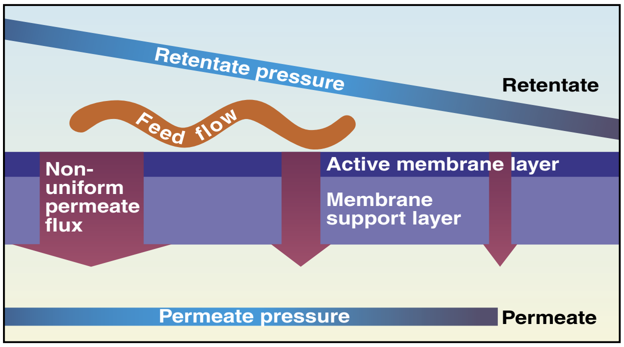

FIGURE 4. In traditional ceramic membrane systems, gel layers form fairly quickly, thereby limiting transmission

layer on the surface of the membrane must be kept to an absolute minimum to ensure good enzyme permeability and make sure the membrane itself does the separation, instead of the boundary layer. From a design standpoint, crossflow velocity, which helps to promote turbulence within the membrane channel and to control the proper transmembrane pressure, is very important in this context.

Batch vs. continuous processes

Perhaps the first design choice is whether to run the system in batch or continuous mode of operation (Figure 2). A batch plant can more easily accommodate changes in the process, such as are common in cell harvesting where the fermentation broth characteristics (viscosity in particular) are variable in nature. Batch processing is also recommended for small-volume separation, where the plant can be arranged in only one or two recirculation loops and the amount of membrane area is not large.

For larger broth volumes that require a configuration comprising five or more recirculation loops, a continuous plant is more efficient. The advantages of continuous operation include minimal residence time to minimize degradation, the ability to optimize each stage to match the anticipated viscosity, and less required membrane area. Diafiltration, which is the addition of water, buffer, alcohol or solvent to improve the recovery of specific compounds, can be automatically adjusted within each loop of a continuous unit, and controls can be optimized accordingly.

There are, however, stringent demands on the control system of a continuous process in terms of maintaining a maximum pressure drop at the design recirculation rate, if overconcentration is to be avoided. Microfiltration plants are typically designed to run with low operating pressure and a pressure drop of approximately 15 psi per element. A higher pressure drop may be infeasible due to the higher energy cost associated with the additional horsepower required and possibly poorer plant performance.

Choice of membrane type

Experience has shown that ceramic membranes (Figure 3) are especially well suited for enzyme recovery. Due to the potentially high viscosity and cell density in processing whole-cell fermentation broths, ceramic membranes are used because of the open, tubular channels (in contrast to the spirals in polymeric membranes, which have very narrow channels). The open-channel configuration, typically with 3-, 4- or 6-mm-dia. channels, is easily able to process a whole cell broth without becoming plugged with suspended solids. In addition, the ceramic membranes are sanitary, able to be cleaned in place or steam sterilized. They are FDA approved as sanitary membranes, they have been around for many years, and they are commercially viable and technically capable.

Another advantage of ceramic membranes is that if fouling does occur, they can be cleaned and put right back online. Ceramic membranes also last for many years, before replacement is required, as opposed to filter cartridges, and other filter media, which are single use.

When testing various ceramic membrane options, the fundamental factor is choosing the right membrane to separate the given substances. Maximizing permeability will allow for high yield and recovery while minimizing the requirement for diafiltration water, which has to be removed in the concentration step. The separation requires a membrane that has a pore size sufficiently large to allow the enzyme to pass through. The pore distribution might be important, as well, depending on the shape of the enzyme molecule. Other factors that impact the separation are surface charge of the membrane, convective forces and electrostatic forces.

Surface properties. The relative surface charge of the membrane itself compared to that of the enzyme is a prime consideration. If both have the same charge, the enzyme may be repelled from the membrane surface, greatly reducing the transmission; whereas opposite charges will attract and potentially improve recovery. Membrane surface properties are also important from the fouling point of view. A hydrophilic membrane is far more resistant to fouling than a hydrophobic membrane.

Convective forces: Membrane filtration is a crossflow technique, but, in fact, there are two forces at play: a shear force parallel to the membrane surface generated by the crossflow velocity, and a perpendicular force on the membrane surface generated by the transmembrane pressure. This perpendicular force is responsible for the formation of concentration polarization, or gel layer formation, a build-up of retained material on the membrane surface. To avoid such buildup, it is important to run a microfiltration process with high surface velocity and low transmembrane pressure, and the forces need to be optimized for proper operation. Gel layer minimization is covered in more detail later.

Electrostatic forces: The size and shape of the enzyme can change with pH and charge, changing the separation characteristics. The effect is particularly noteworthy with diafiltration, where the ionic strength such as salt concentration, can impact the permeability of the enzyme if there is a poor ionic balance. Electrostatic

TWO APPROACHES TO MINIMIZING GEL LAYER FORMATION

For many years companies have attempted to design membrane systems and products that will enhance system hydrodynamics by promoting turbulence in the boundary layer. Some of the early attempts included use of counter-rotating concentric cylinders or discs, introduction of gas bubbles, mechanical devices and pulsed flow systems that reversed flow direction across the membrane. Many systems were tested on a laboratory scale but did not prove to be commercially viable.

Effective microfiltration systems have finally come on the market in the past few years that make it possible to control permeate pressure, and therefore average transmembrane pressure, independently of tangential velocity. In particular, recent developments in ceramic membranes allow transmembrane pressure to be controlled over the entire membrane surface, thereby achieving optimum sustainable product flux. Two of the more prominent developments include variable resistance in the membrane support layer and variable resistance in the active membrane layer.

Such advancements in the surface chemistry of the ceramic membranes allows for the modification of the gradient of the membrane in order to overcome the gel layer — a critical aspect of sensitive separation processes such as enzyme recovery.

Conventional microfiltration

Traditional ceramic membrane technology (Figure 4) only allows control of transmembrane pressure on a macro scale by individual adjustment of the feed and permeate pressures. The transmembrane pressure along the length of any given element varies due to the pressure drop across the element. Since ceramic elements tend to work at higher tangential velocities (up to 6 m/s) than many polymeric systems, there is significant variation in transmembrane pressure, causing very fast formation of gel layer particularly at the inlet, thereby limiting transmission. Meanwhile, the mid point produces an optimum situation; and, at the end of the element there is low flux due to lower-than-optimal transmembrane pressure. As the feed travels along the membrane, less and less of the membrane area is actually utilized, so a gel layer forms very quickly, effectively reducing the length of the membrane that is used efficiently.

Various manufacturers have made modifications to the system design or the membranes themselves to produce "controlled gradient membranes" that reduce the gel layer, allowing for more difficult separations. This is done by controlling the gradient of the membrane, thereby producing a constant flux along the length of the entire element. Such approaches help to maintain a consistent pressure drop over the whole element length thereby minimizing the gel polarization or boundary layer.

Advanced ceramic membranes

Two ceramic membrane solutions have recently surfaced and been proven for producing a controlled gradient membrane that minimizes the gel layer, allowing unique separations to occur. Both approaches modify the membrane gradient helping to eliminate or minimize formation of a gel layer. One has a modified membrane support layer, and the other contains a variable-thickness active membrane layer.

Modified membrane support layer. In the first approach (Figure 5), a porosity gradient over the length of the support layer provides more resistance to flow at the inlet end and lower resistance at the outlet end. This helps achieve uniform permeate flux over the length of the membrane by allowing more flow through the support layer further down the element. This membrane is in use commercially and has proven to work in specific cases.

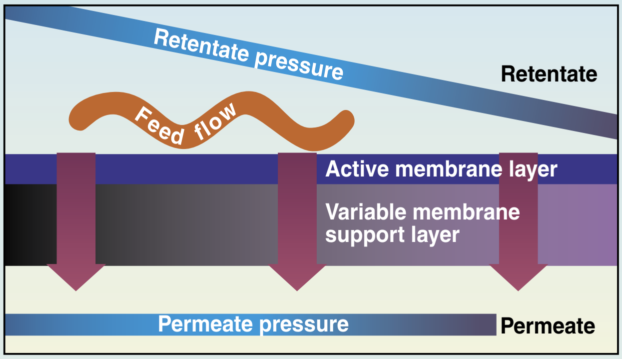

FIGURE 5. One approach to solving the problem in Figure 4 uses a support layer with decreasing porosity down the length of the element in order to provide more resistance to flow at the inlet end and lower resistance at the outlet end

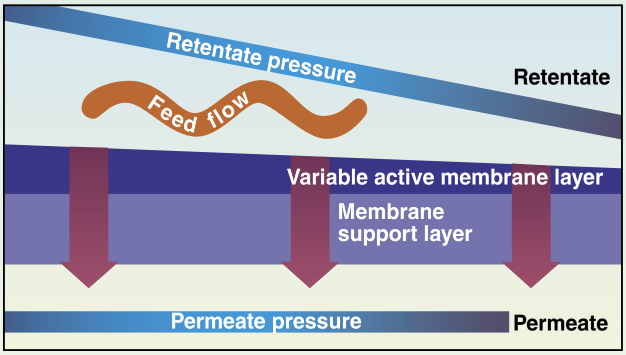

FIGURE 6. A second approach to the gel-layer problem modifies the thickness of the membrane surface itself to accommodate the pressure drop across the membrane

Variable-thickness active membrane layer. The second approach (Figure 6) modifies the thickness of the membrane surface itself to accommodate the pressure drop across the membrane, making it thicker at the inlet end of the element and thinner at the outlet. The decreasing membrane thickness reduces resistance down the length of the element to allow a constant flux across the whole length of the membrane. This membrane has also been proven commercially.

These two approaches in controlling the membrane gradient allow for a constant ratio of the pressure drop to membrane thickness, with the net result being a relatively constant permeate flux rate across the entire length of the element. With this constant flux rate, the boundary layer also remains consistent, allowing for goal product permeability. ❐

charge and pH can also influence an enzyme's interaction with other proteins in the mixture. How the behavior of a protein mixture will differ from that of an individual protein solution can be hard to predict.

The gel layer

Formation of a concentration polarization, or gel layer, is a drawback of improperly designed ceramic microfiltration systems. Under pressure, the solvent and solute are forced against the membrane surface, resulting in an accumulation of rejected solute molecules, in this case the enzyme. This gel layer builds up on the membrane surface, acting as a secondary membrane and interfering with the separation.

There are two ways that formation of a gel layer adversely affects the separation. First, at moderate-to-high solute concentrations, the resistance of the gel layer can be even greater than that of the membrane itself, effectively impeding recovery of the enzyme. Second, the enzyme that is caught in the gel layer is lost, reducing the overall yield.

In many cases the gel layer will tend to be denser when the process unit is separating pre-clarified broth, which can contain small molecules and other proteins. Whole broth will be less affected and the larger cells may also cause a scouring effect which can help to minimize the gel layer. The gel layer is also affected by shear rate at the membrane surface.

The gel layer can be minimized in ceramic membranes by controlling the convective forces, such as tangential velocity and transmembrane pressure discussed above. Typical velocity for this effect is 5 m/s or higher. This is another advantage of crossflow membrane filtration over dead-end filtration, which exhibits only perpendicular forces on the filter media.

Two design approaches to minimizing the gel layer in ceramic membranes are explained in the box, p. 49.

Fouling

Two types of fouling are encountered in crossflow ceramic-membrane filtration: reversible fouling, where the flux increases and decreases proportionally to the applied transmembrane pressure, and irreversible fouling, where the flux does not recover with a decrease in pressure. In either case, the rate of fouling is related to the flux rate, and to control fouling there is a critical flux rate that must not be exceeded. This is particularly important during startup, where instantaneous fluxes can be high. Typically, the separation plant needs to operate in the transmembrane pressure range where flux increases proportionally to increasing pressure. At the point where the flux no longer increases proportionally, the critical flux has been exceeded and fouling can be irreversible without cleaning.

When designing the system, it is important to define the critical flux rate through pilot testing. In well-developed applications, experienced engineers have a pretty good idea what the critical flux rate will be. In new applications, on the other hand, particularly within the biotechnology and pharmaceutical area, pilot testing is imperative. Process engineers should focus on "excursions" in order to maximize capacity and minimize the gel layer, changing operating parameters such as temperatures, pressures and flow velocities until reaching the critical point. Once the optimum parameters are defined, they can be set as the operating conditions for the commercial system. ■

Edited by Rebekkah Marshall

Authors

Robert J. Keefe is market manager for the Biotech/Pharma business at Niro, Inc.'s GEA Filtration div. (1600 O'Keefe Rd., Hudson, WI USA; Phone: 715-386-0176; Fax: 715-386-9376; E-Mail: rjk@geafiltration.com). Keefe has worked in the field of membrane filtration for over 25 years. He joined Niro in 1986 as a senior sales engineer selling membrane filtration systems with a specialty in the pharmaceutical industry. From 1991 through 2002, Keefe served as Sales Manager of GEA Filtration. He holds a bachelor's degree in Environmental Studies from Colby College, Waterville, Maine.

David M. Dubbin is sales director for Niro Ltd, U.K.'s GEA Process Engineering div. (1 The Quadrant, Abingdon Science Park; Barton Lane, Abingdon OX14 3YS, Oxfordshire, U.K.; Phone: +44 (0) 1235-557812; Fax: +44 (0) 1235-554140, E-mail: dmd-nuk@niro.co.uk). He has been involved with membrane filtration for more than 30 years. Initially he worked as a process engineer for a manufacturer of synthetic rubber, where membrane filtration was used to recover product from waste water — one of the first occasions in which the technology was used outside of the dairy industry. Dubbin joined Niro Ltd. in 1985 initially to develop the sales of membrane filtration equipment. In 2001, he was promoted to sales director, with special responsibility for membrane and spray drying plant sales to the pharmaceutical industry.

GEA Filtration

GEA Filtration • Niro, Inc. • 1600 O'Keefe Road • Hudson, WI 54016, USA
TEL 1-715-386-9371 • FAX 1-715-386-9376 • E-MAIL info@geafiltration.com

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