

Filtration is an operation that has found an important place in the processing of biotechnology products. In general, filtration is used to separate particulate or solute components in a fluid suspension or solution according to size by flowing under a pressure differential through a porous medium. There are two broad categories of filtration, which differ according to the direction of the fluid feed in relation to the filter medium. In *conventional* or *dead-end filtration*, the fluid flows perpendicular to the medium, which generally results in a cake of solids depositing on the filter medium. In *crossflow filtration* (which is also called *tangential flow filtration*), the fluid flows parallel to the medium to minimize buildup of solids on the medium. Conventional and crossflow filtration are illustrated schematically in Figure 4.1.

Conventional filtration is typically used when a product has been secreted from cells, and the cells must be removed to obtain the product that is dissolved in the liquid. Antibiotics and steroids are often processed by using conventional filtration to remove the cells. Conventional filtration is also commonly used for sterile filtration in biopharmaceutical production. Crossflow filtration has been used in a wide variety of applications, including the separation of cells from a product that has been secreted, the concentration of cells, the removal of cell debris from cells that have been lysed, the concentration of protein solutions, the exchange or removal of a salt or salts in a protein solution, and the removal of viruses from protein solutions.

Filtration often occurs in the early stages of bioproduct purification, in keeping with the process design heuristic “remove the most plentiful impurities first” (see Chapter 12, Bioprocess Design and Economics). At the start of purification, the desired bioproduct is usually present in a large volume of aqueous solution, and it is desirable to reduce the volume as soon as possible to reduce the scale and thus the cost of subsequent processing operations. Filtration, along with sedimentation and extraction (see Chapters 5 and 6), is an effective means of accomplishing volume reduction.

In this chapter, conventional and crossflow filtration are first described mathematically as a basis for understanding how these filters perform. Next, filter media

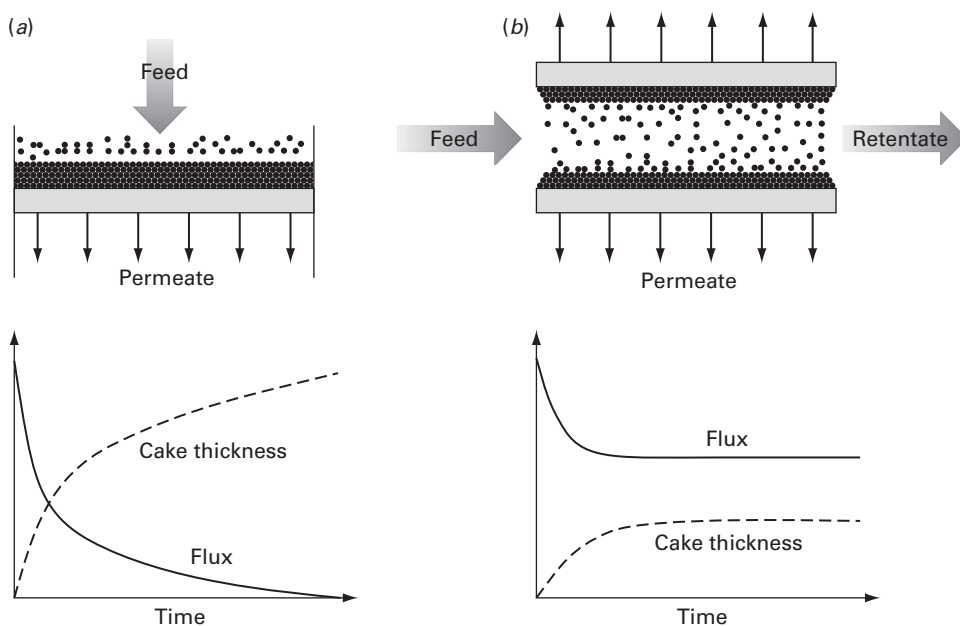


FIGURE 4.1 Schematic diagrams for (a) dead-end or conventional filtration and (b) crossflow filtration. For dead-end filtration, the thickness of the solids buildup increases and the permeate flux decreases with time, ultimately reaching zero. In crossflow filtration, the feed can contain either a soluble or a solid solute, which becomes concentrated at the membrane surface; the permeate flux reaches a constant value at steady state.

and equipment of various types are described, and mechanisms of membrane fouling are presented. The chapter concludes with a discussion of the scale-up and design of the various filtration systems.

4.1 INSTRUCTIONAL OBJECTIVES

After completing this chapter, the reader should be able to do the following:

- Calculate solvent fluxes and filtration times for conventional filtration using Darcy's law.
- Use washing theory to calculate the removal of solutes from a filter cake.
- Estimate the extent of concentration polarization in crossflow filtration.
- Select filtration media and equipment to meet bioproduct processing requirements.
- Explain and identify the mechanisms of membrane fouling.
- Select filtration unit operations to meet product requirements, consistent with product properties.
- Perform scaling calculations on conventional and crossflow filters.
- Perform process calculations for the four basic modes of operations for cross-flow filters.

4.2 FILTRATION PRINCIPLES

The theory of filtration has been extensively developed. The goal of this section is to describe the fundamental filtration theory that is important to an understanding of how conventional and crossflow filters operate, which can then be used as a basis for design and scale-up of the unit operations.

4.2.1 Conventional Filtration

When a slurry containing suspended solids flows towards and through a filter medium by the application of a pressure gradient across that medium, the solids begin to build up on the filter medium as shown in Figure 4.1a. The accumulation of solids on the filter medium is called a cake. If the solids load in the slurry is high, the cake quickly comes to dominate the performance of the filtration. Darcy's law describes the flow of liquid through a porous bed of solids and can be written as follows:

$$(4.2.1) \quad \frac{1}{A} \frac{dV}{dt} = \frac{\Delta p}{\mu_0 R}$$

where V is the volume of filtrate, t is time, A is the filtration cross-sectional area, Δp is the pressure drop through the cake and filter medium, μ_0 is the viscosity of the filtrate, and R is the resistance of the cake and the filter medium. These resistances can be treated separately; thus, for R_m as the resistance of the filter medium and R_c as the resistance of the cake solids,

$$(4.2.2) \quad R = R_m + R_c$$

It is convenient to write the cake resistance R_c in terms of a specific cake resistance α as follows:

$$(4.2.3) \quad R_c = \alpha \rho_c \left(\frac{V}{A} \right)$$

where ρ_c is the mass of dry cake solids per volume of filtrate. Thus, the resistance increases with the volume filtered. Combining Equations (4.2.1), (4.2.2), and (4.2.3), we obtain

$$(4.2.4) \quad \frac{1}{A} \frac{dV}{dt} = \frac{\Delta p}{\mu_0 [\alpha \rho_c (V/A) + R_m]}$$

For the case of zero filtrate at time zero, integration of this equation yields

$$(4.2.5) \quad \frac{t}{V/A} = \frac{\mu_0 \alpha \rho_c}{2 \Delta p} \left(\frac{V}{A} \right) + \frac{\mu_0 R_m}{\Delta p}$$

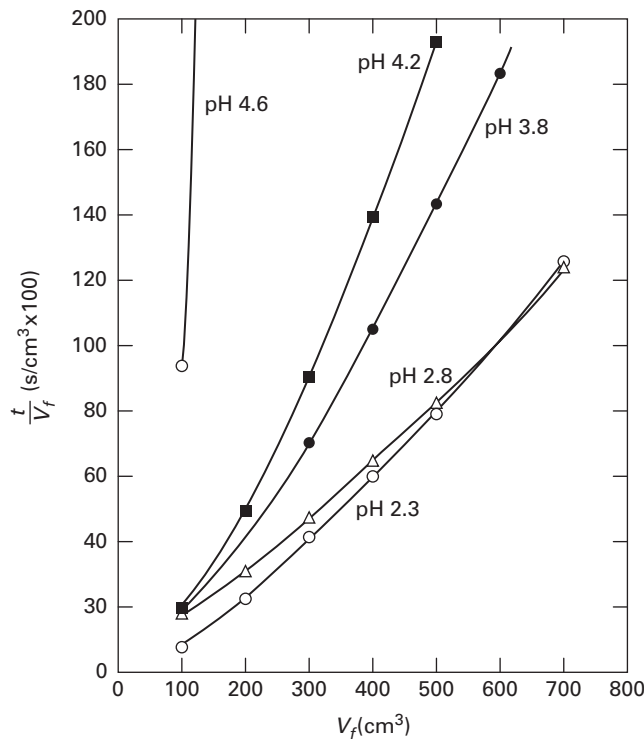


FIGURE 4.2 Filtration data for *Streptomyces griseus* broth with $\Delta p = 2.0$ bar. The filter medium was cotton cloth, and a diatomaceous earth filter aid was added to the broth. (Data from S. Shirato and S. Esumi, "Filtration of a culture broth of *Streptomyces griseus*" J. Ferment. Technol. (Japan), vol. 41, p. 87, 1963.)

This is a convenient form of the integrated equation, since a plot of $t/(V/A)$ versus V/A should give a straight line. Filtration data plotted in this manner for *Streptomyces griseus* fermentation broth are shown in Figure 4.2. One noteworthy feature of the plots in Figure 4.2 is that most of the lines connecting the data at given pH values are not perfectly straight. Of the variables constituting the slope in Equation (4.2.5), the only one that could change appreciably with Δp is α , the specific cake resistance. The slopes are increasing with the volume filtered, indicating that α is increasing. This implies that α is a function of V/A . At constant pressure, α can increase as the cake is compressed. Cakes are typically compressible when cells and other biological materials are being filtered. For soft or amorphous solids, at constant pressure, some consolidation is expected as the filtration volume increases, leading to the dependence of α on V/A .

EXAMPLE 4.1

Batch Filtration A Büchner funnel 8 cm in diameter is available for testing the filtration of a cell culture suspension, which has a viscosity of 3.0 cp. The data in

Table E4.1 were obtained with a vacuum pressure of 600 mm Hg applied to the Büchner funnel.

The cell solids on the filter at the end of filtration were dried and found to weigh 14.0 g. Determine the specific cake resistance α and the medium resistance R_m . Then estimate how long it would take to obtain 10,000 liters of filtrate from this cell broth on a filter with a surface area of 10 m² and vacuum pressure of 500 mm Hg.

TABLE E4.1

Time (s)	Volume of filtrate (ml)
26	100
96	200
197	300
342	400
537	500
692	600
989	690 (end)

Solution

According to Equation (4.2.5), we can plot $t/(V/A)$ versus V/A and obtain α from the slope and R_m from the intercept. We see that the data are reasonably close to a straight line. A linear regression of the data in this plot gives the following results (Figure E4.1):

$$\text{Slope} = 4.81 \frac{\text{s}}{\text{cm}^2}$$

$$\text{Intercept} = 4.26 \frac{\text{s}}{\text{cm}}$$

From these values, we can calculate α and R_m :

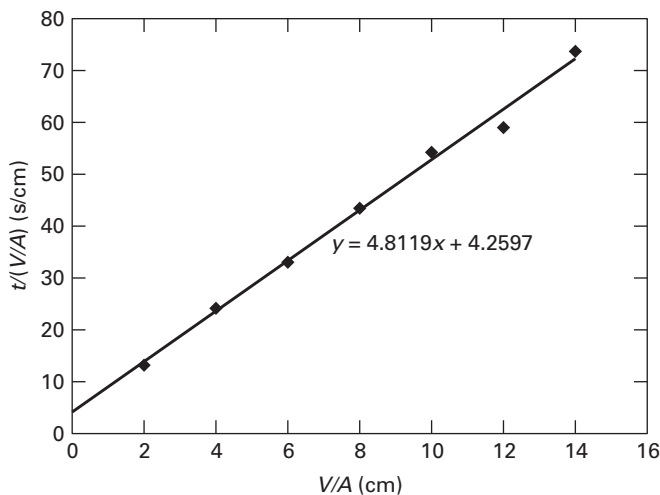


FIGURE E4.1 Plot of batch filtration data for the determination of α and R_m .

$$\begin{aligned}
\alpha &= (\text{slope}) \left(\frac{2\Delta p}{\mu_0 \rho_c} \right) \\
&= \left(4.81 \frac{\text{s}}{\text{cm}^2} \right) \left(\frac{2 \times 600 \text{ mm Hg} \times \frac{1.33 \times 10^3 \text{ g}}{\text{cm s}^2 \text{ mm Hg}}}{\frac{0.03 \text{ g}}{\text{cm s}} \times \frac{14 \text{ g}}{690 \text{ ml}}} \right) \\
&= 1.26 \times 10^{10} \frac{\text{cm}}{\text{g}} \\
R_m &= (\text{Intercept}) \left(\frac{\Delta p}{\mu_0} \right) \\
&= \left(4.26 \frac{\text{s}}{\text{cm}} \right) \times \left(\frac{600 \text{ mm Hg} \times \frac{1.33 \times 10^3 \text{ g}}{\text{cm s}^2 \text{ mm Hg}}}{\frac{0.03 \text{ g}}{\text{cm s}}} \right) \\
&= 1.13 \times 10^8 \text{ cm}^{-1}
\end{aligned}$$

This is a typical value of R_m for a large-pore (micrometer-sized) filter.

To determine the time required to obtain 10,000 liters of filtrate using a filter with an area of 10 m^2 , we must make the assumption that α does not change at the new pressure drop of 500 mm Hg. We use Equation (4.2.5) and solve for time:

$$t = \frac{\mu_0 V}{\Delta p A} \left(\frac{\alpha \rho_c V}{2A} + R_m \right)$$

We calculate the two components of this equation as follows:

$$\begin{aligned}
\frac{\mu_0 V}{\Delta p A} &= \frac{\frac{0.03 \text{ g}}{\text{cm s}} \times 10^4 \text{ liters} \times \frac{1 \text{ m}^3}{10^3 \text{ liter}} \times \frac{100 \text{ cm}}{1 \text{ m}} \times \frac{1 \text{ h}}{3600 \text{ s}}}{500 \text{ mm Hg} \times \frac{1.33 \times 10^3 \text{ g}}{\text{cm s}^2 \text{ mm Hg}} \times 10 \text{ m}^2} = 1.25 \times 10^{-9} \text{ cm h} \\
\frac{\alpha \rho_c V}{2A} + R_m &= \frac{1.26 \times 10^{10} \frac{\text{cm}}{\text{g}} \times \frac{14 \text{ g}}{0.69 \text{ liter}} \times 10^4 \text{ liters}}{2 \times 10 \text{ m}^2 \left(\frac{100 \text{ cm}}{\text{m}} \right)^2} + 1.36 \times 10^8 \text{ cm}^{-1} \\
&= 12.8 \times 10^9 \text{ cm}^{-1} + 0.14 \times 10^9 \text{ cm}^{-1} = 12.9 \times 10^9 \text{ cm}^{-1}
\end{aligned}$$

and finally

$$t = (1.25 \times 10^{-9} \text{ cm h})(12.9 \times 10^9 \text{ cm}^{-1}) = 16.1 \text{ h}$$

Thus, this filter is probably undersized for the volume to be filtered. In addition, from this calculation we see that at the end of the filtration,

$$\frac{R_m}{R_c + R_m} = \frac{0.14}{2(12.8) + 0.14} = 0.005$$

Therefore, the filter medium is contributing very little of the resistance to filtration, a typical situation in a lengthy dead-end filtration. Also, it should be noted that 10 m^2 is a large surface area for a filter. To accommodate areas this large (and larger), filters are typically three dimensional, that is, through the use of filter press or filter leaf systems in which multiple filters are stacked atop one another, the surface area is contained in an efficient volume for manufacturing (see Section 4.3.1).

The specific resistance of the cake is directly affected by Δp_c , the pressure drop across the cake. Studies have shown that the relationship between specific resistance and pressure drop commonly takes the form [1]:

$$(4.2.6) \quad \alpha = \alpha' (\Delta p_c)^s$$

where α' and s are empirical constants. The power s has been called the “cake compressibility factor” and has been found to range from zero for incompressible cakes such as sand and diatomite (see Section 4.3.1, Conventional Filtration) to near unity for highly compressible cakes.

For products that are recovered in the filtrate, it is often necessary to wash the filter cake with water or a salt solution to maximize the removal of dissolved product from the cake. Frequently, the wash must be done with more than the volume of liquid in the cake to obtain the recovery desired. This is because some of the product is in stagnant zones of the cake, and transfer into the wash liquid from these zones occurs by diffusion, which takes place at a slower rate than the convective flow of wash through the cake. Data for the washing of filter cakes have been correlated by Choudhury and Dahlstrom [2] using the following equation:

$$(4.2.7) \quad R' = \left(1 - \frac{E}{100}\right)^n$$

where R' is the weight fraction of solute remaining in the cake after washing (on the basis that $R' = 1.0$ prior to washing), E is the percentage wash efficiency, and n is the volume of wash liquid per volume of liquid in the unwashed cake. The percentage

wash efficiency E is therefore 100% minus the percentage solute remaining in the cake after 1.0 volume of wash liquid per volume of liquid in the unwashed cake (or $n = 1.0$). Choudhury and Dahlstrom found the wash efficiency E to vary from a minimum of 35% to a maximum of 86%, with the lower values applying to cakes through which the wash liquid flows relatively rapidly.

Assuming that the liquid viscosity and the pressure drop through the bed of solids are the same during washing as during the filtration of the solids, the washing rate per cross-sectional area can be found from the filtrate flow rate per unit area given in Equation (4.2.4) at the end of the filtration. Thus, for negligible filter medium resistance for filtrate volume V_f at the end of time t_f to form the cake, this yields

$$(4.2.8) \text{ Washing rate per cross-sectional area} = \left(\frac{1}{A} \frac{dV}{dt} \right)_{V=V_f} = \frac{\Delta p}{\mu_0 \alpha \rho_c (V_f/A)}$$

If V_w is the volume of wash liquid applied in time t_w , then

$$(4.2.9) \quad V_w = t_w \left(\frac{dV}{dt} \right)_{V=V_f}$$

Using the definition of $(dV/dt)_{V=V_f}$ from Equation (4.2.8), we obtain

$$(4.2.10) \quad \frac{V_w}{A} = t_w \left(\frac{1}{A} \frac{dV}{dt} \right)_{V=V_f} = \frac{t_w \Delta p}{\mu_0 \alpha \rho_c (V_f/A)}$$

At the end of the filtration, the integrated form of the filtration equation [Equation (4.2.5)], with R_m neglected, can be written

$$(4.2.11) \quad \frac{V_f}{A} = \left(\frac{2 \Delta p t_f}{\mu_0 \alpha \rho_c} \right)^{1/2}$$

Substituting this expression for V_f/A in Equation (4.2.10) and simplifying gives

$$(4.2.12) \quad \frac{V_w}{A} = \left(\frac{\Delta p}{2 \mu_0 \alpha \rho_c t_f} \right)^{1/2} t_w$$

From Equations (4.2.11) and (4.2.12), the ratio of t_w to t_f is

$$(4.2.13) \quad \frac{t_w}{t_f} = \frac{2 V_w}{V_f}$$

It is helpful to write t_w/t_f in terms of n , the ratio of the volume V_w of wash liquid to the volume V_r of residual liquid in the cake:

$$(4.2.14) \quad \frac{t_w}{t_f} = 2 \frac{V_w}{V_r} \frac{V_r}{V_f} = 2n f$$

where f is the ratio of V_r to the volume V_f of filtrate at the end of filtration. The ratio f can be determined by a material balance. Thus, for a given cake formation time t_f , a plot of wash time t_w versus the wash ratio n will be a straight line.

4.2.2 Crossflow Filtration

As illustrated in Figure 4.1b, the fluid in crossflow filtration flows parallel to the membrane surface, resulting in constant permeate flux at steady state. Crossflow filtration can be divided into two categories depending on whether the component being filtered is soluble or insoluble. When dissolved species such as proteins are being filtered, ultrafiltration membranes are generally used. The ultrafiltration membrane is selected so that the species of interest will not pass through these membranes. The retained species is carried to the surface of the membrane by the convective flow of fluid, and the concentration of the species builds up next to the membrane surface. The concentration of the species can be so high that it precipitates on the membrane surface, further impeding the flow of fluid through the membrane. The resulting layer of solids on the membrane surface has been called a “gel layer.” In addition, even without precipitation, the increased osmolarity near the membrane surface creates a solvent gradient that opposes the applied transmembrane pressure Δp . On the other hand, when suspended particles are present, these particles are carried to the membrane surface and may form a cake at the surface. In this situation, microfiltration membranes are generally utilized. These membranes let dissolved components pass through but retain particles above a certain size. There are instances, such as in the crossflow filtration of cells that have been ruptured, where the layer at the membrane surface contains both suspended particles and precipitated solutes. More complete information about ultrafiltration and microfiltration membranes is given in Section 4.3.

Dissolved Species

In crossflow filtration, a solution under pressure flows across the surface of a membrane. As a result of this pressure, fluid is forced through the membrane. This flow toward the surface of the membrane causes species dissolved in the solution also to be carried toward the membrane's surface. For a solute that is rejected by the membrane, there will be a concentration gradient of this solute across a stagnant boundary

layer next to the surface of the membrane, as indicated in Figure 4.3. The elevation of the solute concentration at the membrane surface (c_w) compared to that in the bulk solution (c_b) is known as *concentration polarization*.

At steady state, the rate of convective mass transfer of solute toward the membrane surface must be equal to the rate of mass transfer of solute by diffusion away from the membrane surface, which is described by [3]:

$$(4.2.15) \quad Jc = -\mathcal{D} \frac{dc}{dx}$$

where J is the transmembrane fluid flux, c is the concentration of the solute, and $\mathcal{D}$ is the diffusion coefficient of the solute. For a boundary layer thickness of δ , the solution of Equation (4.2.15) is

$$(4.2.16) \quad J = \frac{\mathcal{D}}{\delta} \ln \frac{c_w}{c_b}$$

which can be also written as

$$(4.2.17) \quad \frac{c_w}{c_b} = \exp\left(\frac{J\delta}{\mathcal{D}}\right)$$

The term $\mathcal{D}/\delta$ can also be defined as a mass transfer coefficient k . The ratio c_w/c_b is sometimes called the *polarization modulus* and indicates the extent of concentration polarization. From Equation (4.2.17), it can be seen that the polarization modulus is

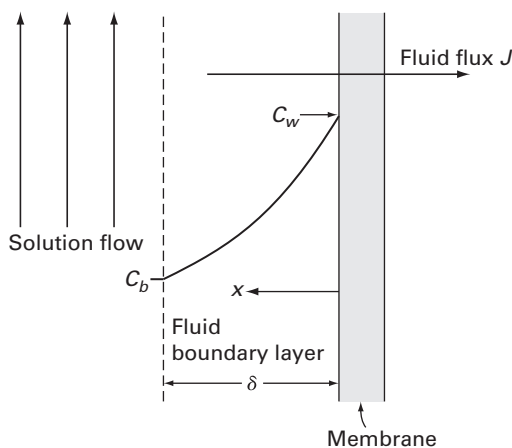


FIGURE 4.3 Schematic representation of the boundary layer in crossflow filtration with a dissolved solute in the feed. A solution flows parallel to the membrane surface, and fluid flows through the membrane under the influence of pressure. A fluid boundary layer forms next to the membrane surface, creating a gradient in the concentration c of solute.

particularly sensitive to changes in J , δ , and $\mathcal{D}$ because of the exponential functionality involved. For high molecular weight solutes (small $\mathcal{D}$) and membranes with high solvent permeability (high J), concentration polarization can become severe, with $c_w/c_b > 10$. At high concentration polarization levels, the solubility of the solute can be exceeded, resulting in the precipitation of the solute and the formation of a solids or gel layer on the membrane surface.

Experimental data have been obtained to support this simple model of concentration polarization. Figure 4.4 shows data for the ultrafiltration of the protein casein and dextran with a molecular weight of 110,000. For both species, a plot of ultrafiltration flux versus log of bulk concentration gives a straight line for bulk concentration varying by an order of magnitude. Estimates of the concentration of solute at the membrane surface can be obtained from the intercept of the straight line in Figure 4.4 at zero flux. These estimates of c_w appear to be physically reasonable.

Correlations have been developed for the mass transfer coefficient k . For laminar flow, boundary layer theory has been applied to yield analytical solutions (known as the Leveque or Graetz solutions) for k [4]:

$$(4.2.18) \quad k = 0.816 \left(\gamma_w \frac{\mathcal{D}^2}{L} \right)^{\frac{1}{3}}$$

where γ_w is the fluid shear rate at the membrane surface and L is the length of the flow channel over the membrane. The constant 0.816 is applicable for the

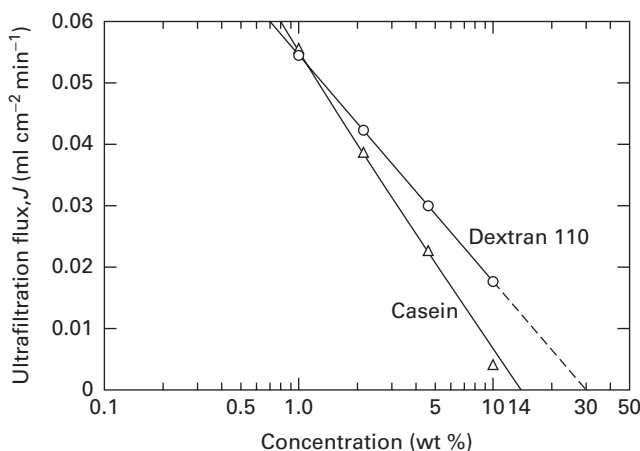


FIGURE 4.4 Decline in ultrafiltration flux with increasing concentration for solutions of casein and Dextran (MW 110,000). Data were obtained in thin-channel recirculating flow cells. (Data from W. F. Blatt, A. David, A. S. Michaels, and L. Nelsen, "Solute polarization and cake formation in membrane ultrafiltration: Causes, consequences, and control techniques," in *Membrane Science and Technology*, J. E. Flinn, ed., p. 63, Plenum Press, New York, 1970.)

gel-polarized condition of concentration polarization where the solute concentration at the wall is constant. For a rectangular slit of height $2h$ and bulk stream velocity u_b ,

$$(4.2.19) \quad \gamma_w = \frac{3u_b}{h}$$

and the equation for a circular tube of diameter D is

$$(4.2.20) \quad \gamma_w = \frac{8u_b}{D}$$

For turbulent flow, empirical correlations have been developed for the mass transfer coefficient. These correlations are based upon dimensional analysis of the equations of change for forced convection mass transfer in a closed channel, which gives [5]:

$$(4.2.21) \quad \text{Sh} = \frac{kD_h}{\mathcal{D}} = f(\text{Re}, \text{Sc}, L/D_h)$$

where $\text{Re} = D_h u_b \rho / \mu = \text{Reynolds number}$

$\text{Sc} = \mu / \rho \mathcal{D} = \text{Schmidt number}$

$D_h = \text{equivalent diameter of the channel}$

$= 4 (\text{cross-sectional area/wetted perimeter})$

$u_b = \text{bulk stream velocity}$

$\rho = \text{density of fluid}$

$\mu = \text{viscosity of fluid}$

A typical correlation that has been developed for this Sherwood number is [6]:

$$(4.2.22) \quad \text{Sh} = 0.082 \text{Re}^{0.69} \text{Sc}^{0.33}$$

Note that the L/D_h term in the generalized dimensionless analysis solution is left out of the empirical correlation in Equation (4.2.22).

EXAMPLE 4.2

Concentration Polarization in Ultrafiltration Equipment is available for ultrafiltration of a protein solution at constant volume to remove low molecular weight species (achieved by the addition of water or buffer to the feed in an operation called diafiltration—see Example 4.6). The flow channels for this system

are tubes 0.1 cm in diameter and 100 cm long. The protein has a diffusion coefficient of $9 \times 10^{-7} \text{ cm}^2/\text{s}$. The solution has a viscosity of 1.2 cp and a density of 1.1 g/cm^3 . The system is capable of operating at a bulk stream velocity of 300 cm/s. At this velocity, determine the polarization modulus for a transmembrane flux of 45 liters $\text{m}^{-2} \text{ h}^{-1}$.

Solution

We see from Equation (4.2.17) that we can determine c_w/c_b if we know $J \delta/\mathcal{D} = J/k$, where J is as given in the problem statement. We can determine k from either Equation (4.2.18) or Equations (4.2.21) and (4.2.22), depending on whether the flow is laminar or turbulent. We first need to calculate the Reynolds number to characterize the flow regime:

$$\text{Re} = \frac{D_h u_b \rho}{\mu} = \frac{0.1 \text{ cm} \times \frac{300 \text{ cm}}{\text{s}} \times 1.1 \frac{\text{g}}{\text{cm}^3}}{\frac{0.012 \text{ g}}{\text{cm s}}} = 2750$$

In the calculation of the Reynolds number, we see that the equivalent diameter of the channel, D_h , is the same as the diameter of the tubes. The flow is turbulent, since the Reynolds number is greater than 2000. For turbulent flow, we need to know Sc , the Schmidt number:

$$\text{Sc} = \frac{\mu}{\rho \mathcal{D}} = \frac{\frac{0.012 \text{ g}}{\text{cm s}}}{1.1 \frac{\text{g}}{\text{cm}^3} \times 9 \times 10^{-7} \frac{\text{cm}^2}{\text{s}}} = 1.21 \times 10^4$$

From Equations (4.2.21) and (4.2.22),

$$\begin{aligned} k &= \frac{\mathcal{D} \text{Sh}}{D_h} \\ &= \frac{\mathcal{D}}{D_h} (0.082) \text{Re}^{0.69} \text{Sc}^{0.33} \\ &= \left(\frac{9 \times 10^{-7} \frac{\text{cm}^2}{\text{s}}}{0.1 \text{ cm}} \right) (0.082) (2750)^{0.69} (12,100)^{0.33} = 3.88 \times 10^{-3} \frac{\text{cm}}{\text{s}} \end{aligned}$$

From Equation (4.2.17), the polarization modulus can be estimated:

$$\frac{c_w}{c_b} = \exp\left(\frac{J\delta}{\mathcal{D}}\right) = \exp\left(\frac{J}{k}\right)$$

$$= \exp\left(\frac{45 \frac{\text{liters}}{\text{m}^2\text{h}} \times \frac{10^3 \text{cm}^3}{\text{liter}} \times \frac{1 \text{m}^2}{10^4 \text{cm}^2} \times \frac{1 \text{h}}{3600 \text{s}}}{3.88 \times 10^{-3} \frac{\text{cm}}{\text{s}}}\right) = 1.38$$

Thus, the concentration polarization is not severe.

Concentration polarization at the surface of the membrane can become great enough that it creates a significant resistance to fluid flow. This effect on the transmembrane fluid flux J can be modeled by using Darcy's law [Equation (4.2.1)] with the flow resistance made up of the sum of the membrane resistance R_m and the resistance R_p of the polarized boundary layer and any gel layer next to the surface of the membrane. For membranes, a correction needs to be made for the osmotic pressure $\Delta\pi$ of the solute that is being filtered, which results in the following equation:

$$(4.2.23) \quad J = \frac{\Delta p - \sigma \Delta \pi}{\mu_0 (R_m + R_p)}$$

where Δp is the pressure difference between the bulk fluid and the permeate, μ_0 is the viscosity of the permeate, and σ is the reflection coefficient for the solute. A reflection coefficient of 1.0 indicates no passage of solute through the membrane, while a coefficient of zero indicates free passage of the solute with the solvent through the membrane. For an ideal dilute solution,

$$(4.2.24) \quad \Delta \pi = RTc_w$$

where R is the ideal gas constant, T is the absolute temperature, and c_w is the solute concentration at the surface of the membrane.

Data for J versus Δp for the ultrafiltration of serum albumin in a stirred filtration cell are shown in Figure 4.5 as a function of both cell stirrer speed and protein concentration. At high values of Δp for 3.9 and 6.5% protein concentrations, the ultrafiltration flux J is constant with increasing Δp . Constant flux as Δp increases can be interpreted as a condition in which the solute concentration at the membrane surface c_w has reached a solubility limit; this behavior is supported by Equation (4.2.16), where J becomes constant when c_w reaches a constant.

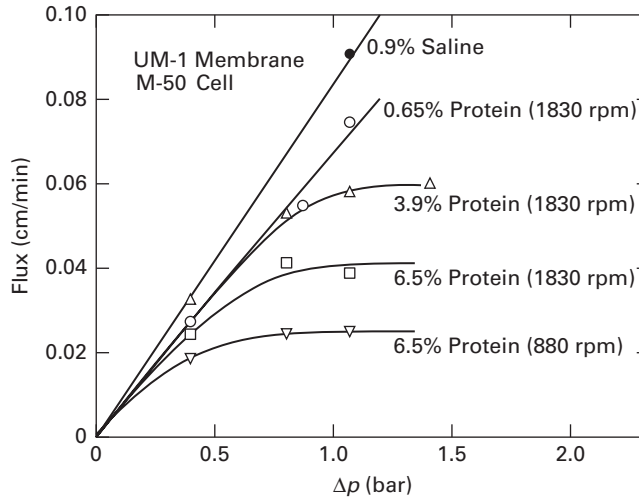


FIGURE 4.5 Ultrafiltration flux as a function of pressure drop in a stirred cell with varying protein concentration and stirring rate. (Data from E. S. Perry, ed., *Progress in Separation and Purification*, vol. 1, p. 318, Wiley, New York, 1968.)

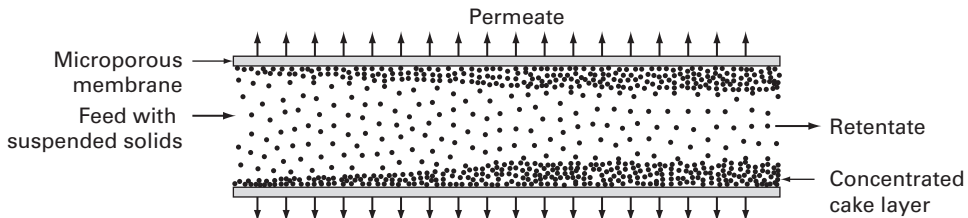


FIGURE 4.6 Illustration of the buildup of a cake layer at the membrane surface in crossflow filtration with suspended solids in the feed.

Suspended Particles

In the crossflow filtration of mixtures with suspended particles, the fluid flux toward the membrane carries particles to the membrane surface, where they are rejected and form a cake layer that is analogous to the gel layer in the ultrafiltration of dissolved species. As indicated in Figure 4.6 for crossflow filtration with microporous filtration membranes, the cake layer initially grows with time, thus reducing the permeate flux and constricting the channel. At steady state conditions, the layer reaches a constant thickness, which is relatively thin if the shear exerted by the fluid flowing tangentially to the membrane surface is high enough.

The theory for the crossflow filtration of dissolved species has been found to hold only for very small suspended particles up to approximately $1\ \mu\text{m}$ in size [7]. Beyond this size, experimental membrane flux values are often one to two orders of magnitude higher than those obtained from the Leveque or Graetz theory given by Equation (4.2.18) [8]. Two different theories have been developed to more accurately predict membrane fluxes for particles larger than $1\ \mu\text{m}$, depending on the size of

the particles: a shear-induced diffusion theory for small particles and an inertial lift theory for larger particles.

The shear-induced diffusion theory was developed by Zydney and Colton [9], who proposed that the concentration polarization model could be applied to the crossflow filtration of suspended particles if the Brownian diffusivity was replaced by a shear-induced hydrodynamic diffusivity. In shear-induced hydrodynamic diffusion, the particles are randomly displaced from the streamlines in a shear flow and collide with other particles. In their model, Zydney and Colton employed an approximate relationship for the shear-induced diffusion $\mathcal{D}_s$ of spherical particles measured by Eckstein et al. [10] for $0.2 < \phi < 0.45$

$$(4.2.25) \quad \mathcal{D}_s = 0.3\gamma_w a^2$$

where ϕ is the particle volume fraction in the bulk suspension, a is the particle radius, and γ_w is the fluid shear rate at the membrane surface. Substituting for the diffusivity in the equation for the laminar flow mass transfer coefficient in the concentration polarization model [Equation (4.2.18)], we obtain

$$(4.2.26) \quad k = 0.366\gamma_w \left(\frac{a^4}{L} \right)^{1/3}$$

where L is the tube or channel length. Comparing this equation for k with the one for dissolved species in laminar flow, we see that the mass transfer coefficient is much more strongly dependent on the shear rate at the wall. Shear-induced diffusion has been found to dominate for particles up to 30 to 40 μm in size, while inertial lift dominates for larger particles [7].

Inertial lift arises when the Reynolds number based on the particle size is not negligible. Inertial lift produces a velocity that carries particles away from the membrane surface. For fast laminar flow of dilute suspensions with thin fouling layers, the steady state transmembrane flux predicted by the inertial lift theory is [7]:

$$(4.2.27) \quad J = \frac{0.036\rho_0 a^3 \gamma_w^2}{\mu_0}$$

where ρ_0 and μ_0 are the density and viscosity, respectively, of the permeate. Thus, for transport by inertial lift, the flux is strongly dependent on the particle size and shear rate at the membrane surface and not dependent at all on the length of the filter or on the concentration of particles in the bulk suspension.

EXAMPLE 4.3

Comparison of Mass Transfer Coefficient Calculated by Boundary Layer Theory Versus by Shear-Induced Diffusion Theory Cells that are 5 μm in diameter

are being concentrated by crossflow filtration using hollow fibers that are 1.1 mm in diameter (inside) and 20 cm long. The velocity of the fluid in the hollow fibers is 100 cm/s. The fluid can be assumed to have the same density and viscosity as water. The temperature is 4°C.

Compare the mass transfer coefficient k calculated using boundary layer theory with that using shear-induced diffusion theory.

Solution

Boundary layer theory

We first calculate the Reynolds number in order to determine the flow regime. At 4°C for water, $\rho = 1.00 \text{ g/cm}^3$ and $\mu = 1.56 \text{ cp}$ from a handbook of physical properties. Therefore,

$$\text{Re} = \frac{D u_b \rho}{\mu} = \frac{0.11 \text{ cm} \times \frac{100 \text{ cm}}{\text{s}} \times 1.00 \frac{\text{g}}{\text{cm}^3}}{0.0156 \frac{\text{g}}{\text{cm s}}} = 705$$

The upper limit of the Reynolds number for laminar flow in tubes is about 2100. Therefore, the flow is laminar in our case. For laminar flow in tubes, we can calculate k using Equations (4.2.18) and (4.2.20). Equation (4.2.18) requires the diffusion coefficient for the cells, which can be estimated from the Stokes-Einstein equation for spheres, Equation (1.8.9):

$$\mathcal{D} = \frac{kT}{6\pi\mu a} = \frac{\left(1.38 \times 10^{-23} \frac{\text{J}}{\text{K}}\right)(277 \text{ K}) \left(\frac{10^7 \text{ g cm}^2 \text{ s}^{-3}}{\text{J s}^{-1}}\right)}{6\pi \left(0.0156 \frac{\text{g}}{\text{cm s}}\right) (2.5 \times 10^{-4} \text{ cm})} = 5.20 \times 10^{-10} \text{ cm}^2 \text{ s}^{-1}$$

From Equations (4.2.20) and (4.2.18), respectively,

$$\gamma_w = \frac{8u_b}{D} = \frac{8 \times 100 \frac{\text{cm}}{\text{s}}}{0.11 \text{ cm}} = 7273 \text{ s}^{-1}$$

$$k = 0.816 \left(\gamma_w \frac{\mathcal{D}^3}{L} \right)^{1/3} = 0.816 \left(\frac{7273 \frac{1}{\text{s}} \times \left(5.20 \times 10^{-10} \frac{\text{cm}^2}{\text{s}} \right)^2}{20 \text{ cm}} \right)^{1/3} = 3.77 \times 10^{-6} \text{ cm s}^{-1}$$

Shear-induced diffusion

For laminar flow with shear-induced diffusion, Equation (4.2.26) applies:

$$k = 0.366 \gamma_w \left(\frac{a^4}{L} \right)^{1/3} = 0.366 \left(7273 \frac{1}{s} \right) \left(\frac{(2.5 \times 10^{-4})^4 \text{ cm}^4}{20 \text{ cm}} \right)^{1/3} = 1.54 \times 10^{-2} \text{ cm s}^{-1}$$

Therefore, k is more than 4000 times greater when calculated using shear-induced diffusion theory than when calculated using Fickian diffusion theory.

4.3 FILTER MEDIA AND EQUIPMENT

In the development of a filtration process, much effort is often devoted to the evaluation of the filter media and equipment that are available. The filter media and equipment selected can have a large impact on the process economics, both in terms of the capital outlay required and the operating expenses. Filter media and equipment considerations are discussed in this section for both conventional and crossflow filtration.

4.3.1 Conventional Filtration

Filter Media

There are many different filter media [11, 12], so the choice of the type to use can be difficult. The choice, however, is heavily governed by the type of filtration equipment being used. The filter media most commonly used in the conventional filtration of biotechnology products are woven fabrics, metal fabrics or screens, and rigid porous media. Sterile filtration in biopharmaceutical production is usually carried out in the conventional mode, and the medium is either a membrane filter or a depth filter, depending on whether a liquid solution or air is being filtered.

Woven fabrics are available in a wide variety of materials. The chemical resistance of the fabric is a primary consideration for the filtration of biotechnology products. There should be minimal or no leaching of components from the fabric during filtration, and the fabric should be able to withstand any chemicals used during cleaning. For filtration involving a filter cake, woven fabrics are the most common type of filter medium. The minimum size of particles trapped in woven fabrics is 10 μm .

Metal fabrics or screens are available in several types of weave in nickel, copper, brass, aluminum, steel, stainless steel, Monel, and other alloys. Metal media are especially desirable when good resistance to leaching and corrosion is required. The smallest size of particles trapped in woven wire media is 5 μm .

Rigid porous media are available in sheets and tubes. A wide variety of materials is available for rigid porous media, including sintered stainless steel and other metals, silica, porcelain and other ceramics, and some plastics.

For the sterile filtration of solutions, an asymmetric membrane filter (see Section 4.3.2) is used in cartridge style. Typically, these membranes are made of cellulose esters or other polymers and have pore sizes of 0.22 or 0.45 μm . In the sterile filtration of air, two types of filters are typically found. High-efficiency particulate air (HEPA) filters are large, high-throughput ventilation filters used to reduce the particulate load in a room. HEPA filters are typically depth-type filters that can collect microbes and other airborne particulates at high flow rates. Depth filters consist of compacted beds of pads of fibrous material such as glass wool. The other type of filter for the sterile filtration of air is a vent filter, installed on all equipment that needs to be filled or drained, such as product tanks. Vent filters are typically hydrophobic asymmetric membrane filters, rated at 0.22 μm .

Filter Aids

It is possible to significantly improve the filtration operation by adding a powdered solid, called a filter aid, to a feed that is to be filtered. The filter aid can be either added directly to the feed or applied to the filtration equipment. The objectives of the first approach, the admixture of the filter aid powder to the suspension, are to keep the pores in the filter cake open, to make the cake less compressible, and to provide faster filtration. In the second approach, the filter medium is precoated with a layer of the filter aid. Rotary vacuum filters can be operated with “precoat” (see the next section).

A successful filter aid must be highly permeable. Other important properties of filter aids that should be considered are surface properties, chemical resistance, and compatibility with the product.

Two of the most widely used types of filter aid are diatomite (kieselguhr or diatomaceous earth) and perlite. Diatomite is the skeletal remain of diatoms, which are a type of algae. The skeletal structure of diatomite particles gives them a high intrinsic permeability. Diatomite consists mostly of silica and thus is insoluble in both strong acids and strong alkalies. Perlite, a glassy volcanic material consisting mainly of aluminum silicate with some combined water, expands on heating during processing to give highly porous particles. Perlite is sometimes used for rough filtrations where high flow rates are desirable and less significance is given to filtrate clarity.

Equipment

A large variety of conventional filtration equipment is available. This equipment can be classified according to the driving force for filtration, whether by pressure, vacuum, or gravity. Conventional filtration equipment may be designed for batch, semicontinuous, and continuous operation.

One of the most common types of batch filter is the plate-and-frame filter press (Figure 4.7). This filter consists of a varying number of filter chambers with either

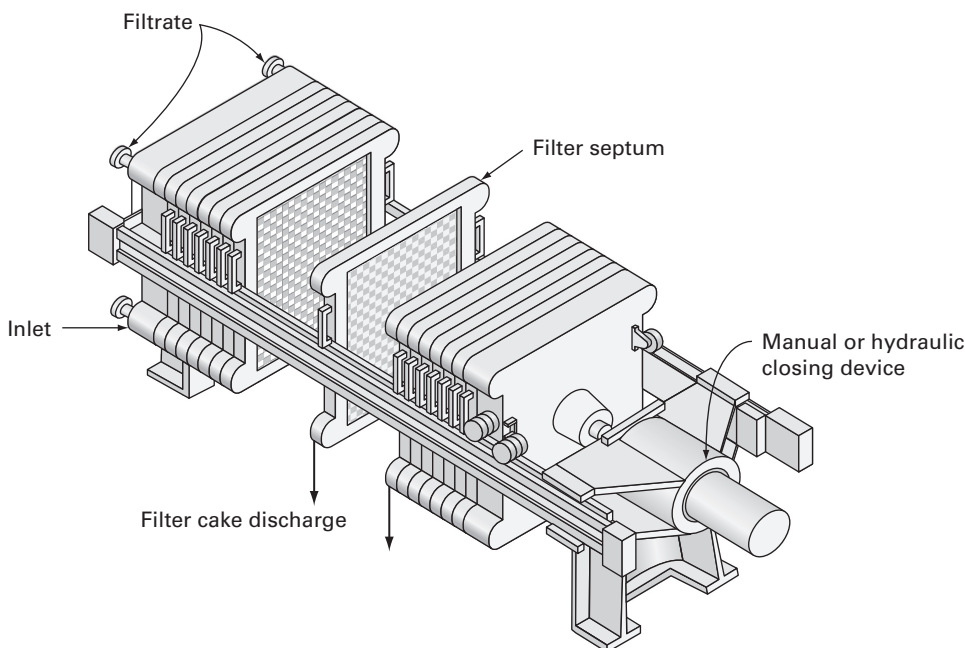


FIGURE 4.7 Plate-and-frame filter press.

medium-covered recessed filter plates, or medium-covered plates alternated with frames that provide space for the cake. The chambers are closed and tightened by a hydraulic ram or screw that pushes the plates and frames together. The feed to be filtered enters the filter press under pressure and fills each chamber simultaneously. The liquid passes through the filter medium, and the solids are retained on the medium. The clear filtrate is taken off at a discharge outlet. Mechanized systems are available for opening and closing of the filter press at the end and commencement of each filtration cycle. Because the filter cake is open to the atmosphere at the end of each cycle, this filter should not be used when the filter cake poses a biohazard.

Other types of batch filter are the horizontal or vertical leaf filter, plate filter, tray filter, tube or candle filter, and Nutsche filter. These devices are similar in that they are all pressure filters, with the filter medium being enclosed within a pressure vessel. Because these filters are enclosed, they are advantageous when one is working with materials that must be contained. A vertical leaf filter is shown as an example in Figure 4.8. The filter leaves are covered with the filter medium on either side, and the filtrate passing into the inside of each filter leaf flows into a filtrate manifold. The Nutsche filter, consisting of one horizontal medium-covered filter plate dividing half of a tank, is the simplest type of pressure filter.

The most common type of semicontinuous or continuous filter for biotechnology products is the rotary vacuum filter. The operation of a rotary vacuum filter is

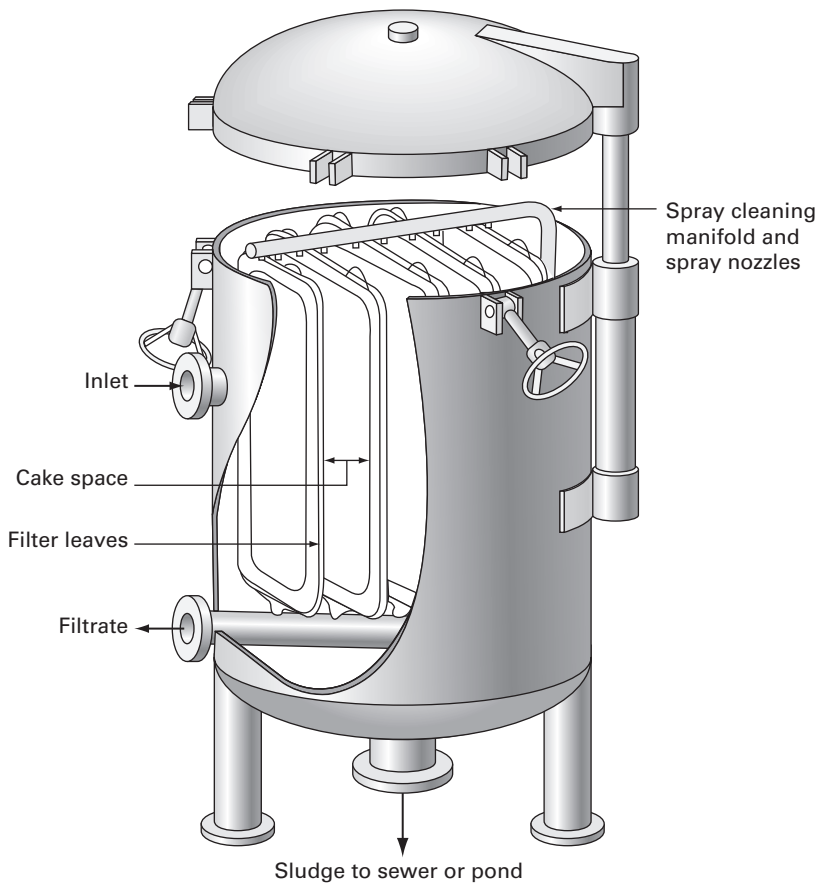


FIGURE 4.8 Vertical leaf filter.

illustrated in Figure 4.9. The drum rotates slowly about its horizontal axis and is partially submerged in a slurry reservoir. The surface of the drum is covered with the filter medium, and a vacuum is maintained below the medium on the inside of the drum. Liquid is sucked through the filter medium, and solids in the feed are retained on the medium. Filtration is followed by washing and dewatering. Several different types of cake discharge can be used: simple knife discharge, advancing knife discharge (with precoat filtration), belt or string discharge, and roller discharge. Because the feeds for biotechnology applications tend to be slimy and non-granular, precoat filtration is commonly used during rotary vacuum filtration. In precoat filtration, the filter medium is coated with a thick layer of diatomaceous earth or other type of filter aid. The solids being filtered penetrate a small distance into the precoat. The knife is adjusted to remove all the feed solids on the filter, including any precoat penetrated with feed solids to give a fresh surface of precoat. When the thickness of the precoat becomes small, a fresh batch of precoat is applied to the drum.

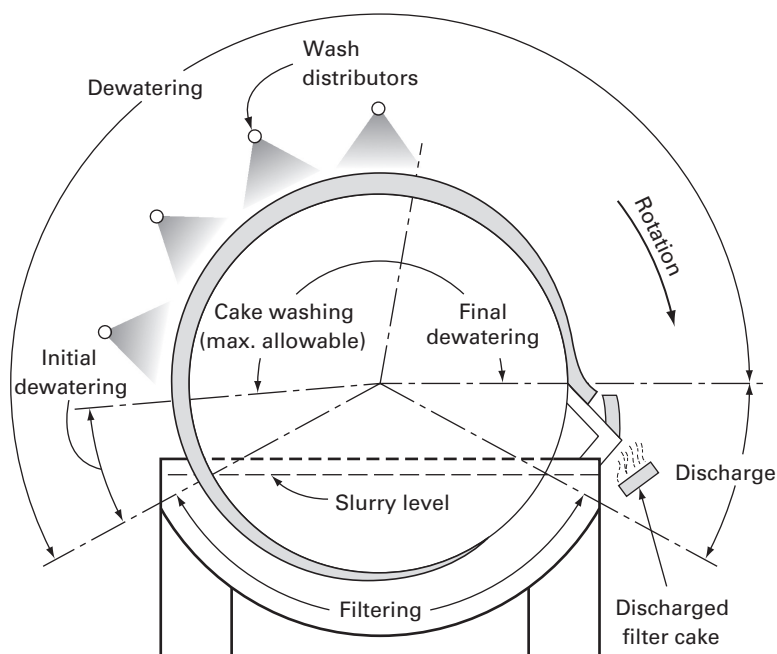


FIGURE 4.9 Rotary vacuum filter.

4.3.2 Crossflow Filtration

Filter Media (Membranes)

Filter media for crossflow filtration are generally referred to as membranes. There are two general categories of membranes: ultrafiltration membranes and microporous membranes. The separation between ultrafiltration (UF) and microfiltration (MF) is based on the pore size of the membrane, with membranes having pores $0.1\ \mu\text{m}$ and larger considered to be microporous. The pore sizes of UF membranes are in the range of 0.001 to $0.1\ \mu\text{m}$ [13], although these membranes are usually classified by their molecular weight cutoff (MWCO), which is the molecular weight of a globular solute at which the solute is rejected by the membrane. Typically, a 90% rejection level is used for establishing the MWCO. Ultrafiltration membranes can be obtained down to a MWCO level of 1000 Daltons (Da) and up to as high as 1,000,000 Da. There is also a category of membranes called reverse osmosis (RO) or hyperfiltration membranes that pass only water and a very low flux of solutes. A very good RO membrane rejects 99.7% or more of sodium chloride [11].

Three basic structures are commonly used for membranes: homogeneous, asymmetric, and composite. These three types are illustrated in Figure 4.10. The homogeneous structure has no significant variation in pore diameter from the feed side to the filtrate side. In the asymmetric structure, there is a thin layer on the feed side of the filter that has very small pores. Below this layer is a much thicker layer that has much larger pores and serves as structural support for the membrane. The composite membrane is similar to the asymmetric membrane in having a thin layer containing



FIGURE 4.10 Three commonly used membrane structures: (a) homogeneous: uniform pore profile through filter; (b) asymmetric: finer filtering surface faces feed suspension; and (c) composite: two types of materials used.

very small pores next to the filtering surface; however, the thin and thick layers of this membrane are made of two different types of material.

Backflushing composite filters is generally not recommended. The major element in pressure drop across the filter is due to the thin layer with very small pores, and so significantly more mechanical force is applied to the area of the thin layer, compared to the support layer. When operated in the intended direction, the thin layer is forced towards the support layer. But when operated in the opposite direction, the thin layer is forced away from the support layer, which can lead to delamination.

Filtration membranes are made from a wide variety of polymers and inorganic materials. The polymers that are used include cellulose acetate, polyamide, polyether, polycarbonate, polyester, polypropylene, polyethylene, regenerated cellulose, poly(vinyl chloride), poly(vinylidene fluoride) (PVDF), poly(tetrafluoroethylene) (PTFE), acrylonitrile copolymers, and polyethersulfones. The inorganic materials used include ceramics, zirconium oxide, borosilicate glass, stainless steel, and silver.

Equipment

Crossflow filtration membranes are available in a variety of configurations. The membranes are housed in a physical unit called a *module*. The membrane module must satisfy a number of mechanical, hydrodynamic, and economic requirements, the most important of which are the following [13]:

Mechanical: obtain effective (physical) separation of the feed and permeate streams; provide the necessary physical support for the membrane (including the ability of the module to endure the required pressure drops and any backflushing).

Hydrodynamic: minimize pressure drops through the module (to reduce pumping costs); optimize solute mass transfer (reduce concentration polarization); minimize particulate plugging or fouling; avoid dead spots (for sanitary design); allow for or promote turbulence (for sanitary design and to reduce boundary layer thickness).

Economic: maximize membrane packing density (ratio of membrane area to module volume); minimize manufacturing costs; permit easy access for cleaning and/or membrane replacement; provide sufficient chemical resistance and operational lifetime; incorporate modularity of design for easy scaleup, staging, or cascading.

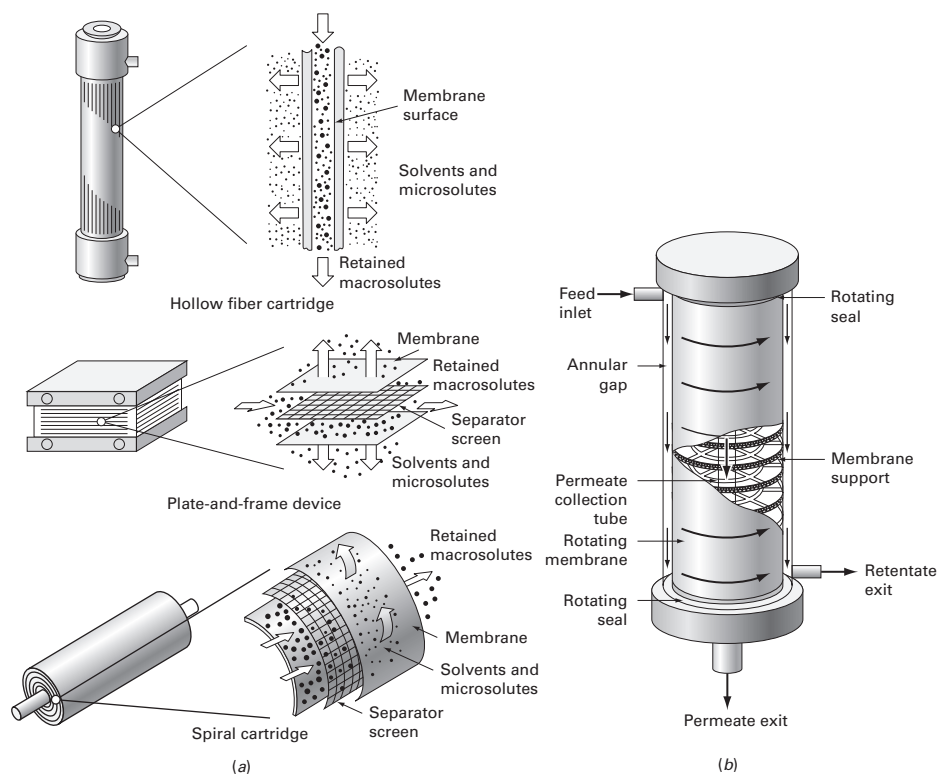


FIGURE 4.11 Schematic representations of filter modules. (a) Hollow-fiber, plate-and-frame, and spiral-wound membrane modules. (b) A rotating cylinder module.

Several of these criteria are in mutual opposition: for example, modules with high membrane packing density tend to be highly susceptible to plugging with particulates. Therefore, the choice of a particular module involves balancing these criteria to arrive at the most economic system for each particular application.

There are five types of module configuration for crossflow filtration (Figure 4.11): hollow fiber, tubular, flat plate, spiral wound, and rotating. The tubular module has the same general configuration as the hollow-fiber module, but the tubes have much larger diameters than the fibers. Some key characteristics of these modules are compared in Table 4.1.

Hollow-fiber modules consist of an array of narrow-bore, self-supporting fibers that generally have an asymmetric membrane structure. The dense skin layer is usually on the lumen side of the fiber, but it can be placed on the outside. The feed flows through the lumen of the fibers when the dense skin layer is on the lumen side, and the flow is typically laminar, although hollow-fiber systems by some manufacturers can be operated in turbulent flow. Since the hollow fibers are self-supporting, they can be cleaned by backflushing, that is, by reversing the direction of the permeate flow. One disadvantage of hollow-fiber modules is that the entire module usually needs to be replaced upon the rupture of even a single fiber. Also, to avoid plugging of the small-diameter fibers, feed streams generally need to be prefiltered.

TABLE 4.1 Comparison of Key Characteristics of Crossflow Membrane Modules^a

Module type	Channel spacing (cm)	Packing density (m ² /m ³)	Energy costs	Particulate plugging	Ease of cleaning
Hollow fiber	0.02–0.25	1200	Low	High	Fair
Tubular	1.0–2.5	60	High	Low	Excellent
Flat plate	0.03–0.25	300	Moderate	Moderate	Good
Spiral wound	0.03–0.1	600	Low	Very high	Poor–fair
Rotating	0.05–0.1	10	Very high	Moderate	Fair

^aSee reference [13].

Except for some inorganic membranes, tubular membranes are not self-supporting and are usually cast in place within a porous support tube made of fiberglass, ceramic, plastic, or stainless steel. The feed flows through the inside of the tubes, while the permeate flows radially outward across the membrane and support tube. Inorganic membranes are usually constructed in a honeycomb monolith unit in which the membranes are arranged in a parallel array. Tubular systems are typically operated in the turbulent flow regime. Because of the large diameter of the tubes in these systems, the pumping costs are relatively high compared to other module configurations operated in turbulent flow. In addition, large diameter tubes decrease the filter surface area to module volume ratio, leading to bigger equipment footprints. The chief advantages of tubular modules are that they are highly resistant to plugging by particulates, and they can be cleaned by backflushing. The diameter of the tubes can be selected to avoid prefiltration of the feed.

Most flat-plate systems are in a rectangular configuration. The flow channels can be open or can have separator screens to improve the mass transfer characteristics. Units with open channels are usually operated in laminar flow, while those with separator screens are often operated with flow in the turbulent regime. One disadvantage of these modules is that backflushing is often impractical because the membranes are effectively supported only on one side.

Spiral-wound modules are constructed from flat sheet membranes separated by spacer screens. The feed solution is fed into one end of the module and flows through the separator screens along the surface of the membranes. The retentate is then collected on the other end of the module. The permeate spirals radially inward, eventually to be collected through a central tube. The flow in these systems tends to be turbulent. The main disadvantage of spiral-wound modules is that they are susceptible to fouling by particulates because of the narrow and irregular flow through the spacers.

One effective rotating-type module is the rotating cylinder device originally proposed by Hallstrom and Lopez-Leiva [14]. The feed flows into a thin annular region between two concentric cylinders (Fig. 4.11b). Either cylinder or both can be porous and can have a membrane bound to the surface. With the membrane on the inner cylinder, permeate is collected in the central chamber. When the membrane is on the

outer cylinder, permeate is collected in a separate annular permeate region adjacent to the outer porous cylinder. The inner cylinder is rotated at high speed (typically > 3000 rpm) to induce the formation of Taylor vortices, which effectively mix the fluid near the surface of the membrane and thereby increase the mass transfer coefficient for the solutes/particles in the feed. The vortices also help reduce the thickness of the cake or gel layer at the membrane surface. One advantage of this system is that the rate of mass transfer is determined almost entirely by the rate of rotation of the inner cylinder, which effectively decouples the mass transfer characteristics from the feed flow rate. As a result, the rotating devices can be operated at very low flow rates and with minimal pumping costs. Since, however, the energy requirements for rotating the device are usually very high, capital costs are high, and scaleup is very difficult, these systems have been limited to small-scale operation.

4.4 MEMBRANE FOULING

Fouling of membranes results from physical and/or chemical interactions between the membrane and various components that are present in the process stream. Fouling leads to a decline in the permeate flux and a change in the membrane selectivity. Because of the high affinity of proteins for solid surfaces, proteins are the leading contributor to fouling in bioseparations by UF and MF. The flux decrease caused by proteins can be attributed to one or more of the following processes [7]:

- Protein adsorption, which involves the interaction of the proteins and the membrane and occurs with no convective flow through the membrane
- Protein deposition, which is the addition of more protein that is associated with the membrane, over and above the protein that would be adsorbed in a nonflowing system
- Protein accumulation on the membrane surface exposed to the flowing process stream as a result of concentration polarization, which can lead to formation of a gel layer

This last effect is governed by the mass transfer coefficient [see Equations (4.2.18) and (4.2.22)], and thus can be minimized by increasing the fluid shear rate at the filtering surface of the membrane. These three processes can lead to pores in membranes that are constricted and even completely blocked, as illustrated in Figure 4.12.

Protein adsorption studies have been performed for both MF and UF membranes to determine the extent to which the pores are constricted by adsorbed protein. To eliminate concentration polarization effects, these studies were done in the absence of flow. The work with MF membranes and a variety of proteins showed that there was approximately monolayer adsorption throughout the internal pores [7]. Protein adsorption was reduced on the more hydrophilic membranes such as the hydrophilic PVDF type, with only a fraction of monolayer adsorption. A study of the adsorption

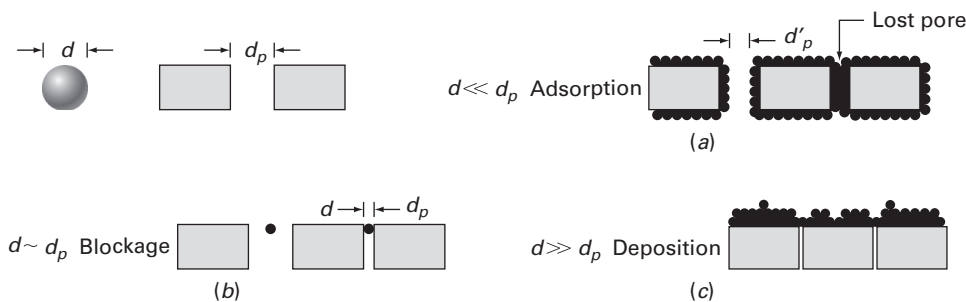


FIGURE 4.12 Mechanisms of membrane fouling. (a) Pore narrowing and constriction. (b) Pore plugging. (c) Solute deposition and formation of a gel or cake layer. Dimensions: d , protein or particle diameter; d_p , clean pore diameter; and d'_p , effective pore diameter in the presence of adsorbed proteins or particles.

of bovine serum albumin (molecular weight 69,000 Da) on UF membranes indicated the following extents of protein coverage within the ultrathin skin portion of the membrane: monolayer adsorption for the 300,000 Da MWCO membrane, only about half a monolayer for the 100,000 Da MWCO membrane, and no measurable protein adsorption for the 50,000 Da MWCO membrane [15]. Thus, protein fouling within the membrane can be completely eliminated by making the pore size small enough.

To account for fouling caused by irreversible adsorption and deposition of proteins and other biological molecules to the membrane surface, it is useful to write Darcy's law (Equation 4.2.23) for the transmembrane flux in terms of the clean membrane resistance (R_m), the resistance due to concentration polarization and a gel layer on the membrane surface (R_p), and the resistance caused by irreversible fouling (R_{if}) [16]:

$$(4.4.1) \quad J = \frac{\Delta p - \sigma \Delta \pi}{\mu_0 (R_m + R_p + R_{if})}$$

In this model, irreversible fouling is considered the fouling that can only be removed by cleaning agents such as acids, bases, enzymes, surfactants, and disinfectants; and the resistance caused by concentration polarization and any gel layer is that which can be removed by physical means, such as circulation of feed through the system at zero transmembrane pressure and relatively high shear rate, or by backflushing using negative transmembrane pressure to remove foulants from the membrane surface [13]. A comprehensive review of methods to control fouling in microfiltration and ultrafiltration membranes has been given by Hilal et al. [17].

A study of protein ultrafiltration by Rajabzadeh et al. has given insight into the relative contributions of the three resistances in Equation (4.4.1). Soy protein extract was ultrafiltered using polysulfone hollow fibers with a molecular weight cutoff of 100 kDa, and the three resistances were measured after a short (2 minutes)

filtration period [16]. As shown in Figure 4.13, the resistance R_p from concentration polarization and a gel layer increased with average transmembrane pressure (TMP, or average Δp) and was greater than the membrane and irreversible fouling resistances (R_m and R_{if}). Increasing TMP causes J to increase, thus causing greater convection of proteins to the membrane surface, leading to more concentration polarization. Computational fluid dynamics modeling was used to estimate R_p and R_{if} as a function of volume concentration ratio (VCR) and membrane length (Figure 4.14), where

$$(4.4.2) \text{VCR} = \frac{V_{\text{feed}}}{V_{\text{feed}} - V_{\text{permeate}}}$$

Both R_p and R_{if} increased as the concentration progressed (i.e., as VCR increased). The transmembrane flux was both measured and modeled as a function of VCR, as shown in Figure 4.15. The decrease in flux with VCR is consistent with the increase in both R_p and R_{if} with VCR. The model showed that increasing the axial velocity caused an increase in permeate flux J , but the increase is relatively small.

4.5 SCALE-UP AND DESIGN OF FILTRATION SYSTEMS

Experimental testing is generally needed in the scale-up and design of conventional and crossflow filtration systems. This is especially true for bioprocesses because of the unique features of each bioprocess that is being considered. For example, in the filtration of ruptured cells, there can be great differences in the filtration characteristics of ruptured cells of different types; these differences can even exist for cells of the same class (e.g., yeasts). Some of the more common small-scale tests are described, as well as considerations in the design of filtration systems.

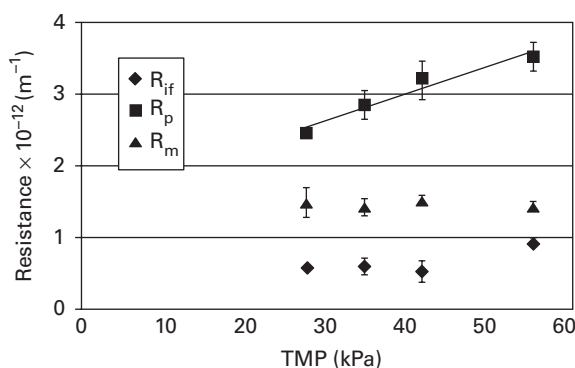


FIGURE 4.13 Effect of transmembrane pressure (TMP) on resistances in the ultrafiltration of soy protein extract at an axial velocity of 1 m s^{-1} using polysulfone hollow fibers with a molecular cutoff of 100 kDa. R_{if} , irreversible fouling resistance; R_p , concentration polarization and gel layer resistance; and R_m , membrane resistance. (Data from A. Rajabzadeh, C. Moresoli, and B. Marcos, "Fouling behavior of electroacidified soy protein extracts during cross-flow ultrafiltration using dynamic reversible-irreversible fouling resistance and CFD modeling," J. Membr. Sci., vol. 361, p. 191, 2010.)

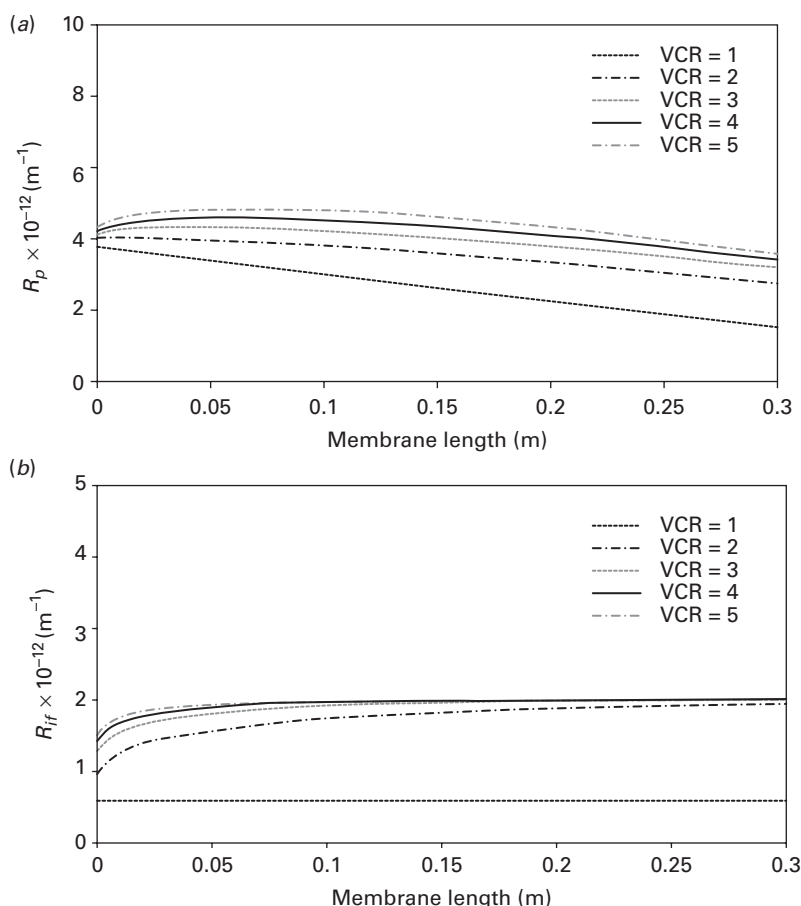


FIGURE 4.14 Computational fluid mechanics modeling results for the effect of membrane length and volume concentration ratio (VCR) on estimated concentration polarization resistance (a) and irreversible fouling resistance (b) for the ultrafiltration of soy protein extract at an axial velocity of 1 m s^{-1} and TMP of 34.5 kPa using polysulfone hollow fibers with a molecular cutoff of 100 kDa. (Data from A. Rajabzadeh, C. Moresoli, and B. Marcos, "Fouling behavior of electroacidified soy protein extracts during cross-flow ultrafiltration using dynamic reversible-irreversible fouling resistance and CFD modeling," *J. Membr. Sci.*, vol. 361, p. 191, 2010.)

4.5.1 Conventional Filtration

Small-scale testing procedures are described for the two basic types of conventional filtration, vacuum filtration and pressure filtration. A large majority of all continuous filters use vacuum as the driving force for filtration. Occasionally, however, an enclosed pressure filter is needed in a bioprocess because of the presence of biohazards. The design of sterile filtration systems is also discussed.

Vacuum and Pressure Filtration

To develop data for scaling up the rotary vacuum filter (Figure 4.9), tests with a filter leaf are usually performed. The objective is to simulate the operation of a large-scale rotary vacuum filter (see the stages of operation indicated in Figure 4.9). A laboratory

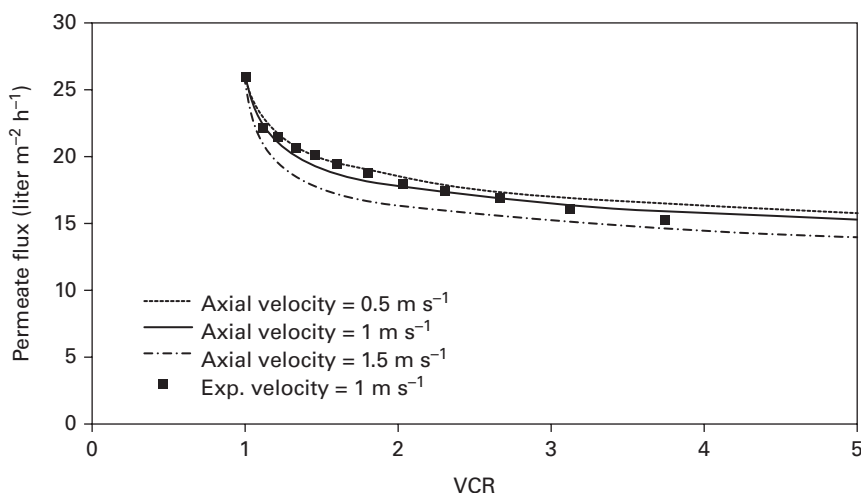


FIGURE 4.15 Comparison of model and experimental results for the effect of volume concentration ratio (VCR) and axial velocity on permeate flux for the ultrafiltration of soy protein extract at a TMP of 34.5 kPa using polysulfone hollow fibers with a molecular cutoff of 100 kDa. (Data from A. Rajabzadeh, C. Moresoli, and B. Marcos, "Fouling behavior of electroacidified soy protein extracts during cross-flow ultrafiltration using dynamic reversible-irreversible fouling resistance and CFD modeling," J. Membr. Sci., vol. 361, p. 191, 2010.)

system for doing vacuum filter leaf tests with a precoat is shown schematically in Figure 4.16; filter leaves that do not use a precoat are similar. To do a filter leaf test with the leaf shown in Figure 4.16, the leaf should first be precoated with a filter aid. The precoat is trimmed off until it is flat with the top of the cake ring of the leaf. The leaf is then submerged in the broth being filtered for the amount of time that the rotating drum will be submerged. To simulate the washing segment of the rotating drum, the leaf is submerged in water or other wash liquid for the amount of time of washing for the rotating drum. The leaf is removed from the wash liquid, and air is allowed to be pulled through the cake to dewater it. The cake ring is then screwed down to expose precoat that has not been penetrated by the broth solids, and the solids above the top of the ring are cut off with a knife. The leaf now has a fresh surface of precoat and is ready for another cycle of filtration, washing, and dewatering. This procedure can be repeated for as many cycles as desired. The volume of filtrate and weight of the cake can be measured, and analyses can be performed on the filtrate and cake. For example, if it were desired to recover a protein in the filtrate, the cake solids and the filtrate (plus wash) should be analyzed for the protein.

EXAMPLE 4.4

Rotary Vacuum Filtration It is desired to filter a cell broth at a rate of 2000 liters/h on a rotary vacuum filter (see Figure 4.9) at a vacuum pressure of 70 kPa. The cycle time for the drum will be 60 s, and the cake formation time (filtering time) will be 15 s. The broth to be filtered has a viscosity of 2.0 cp and a cake solids (dry basis) per

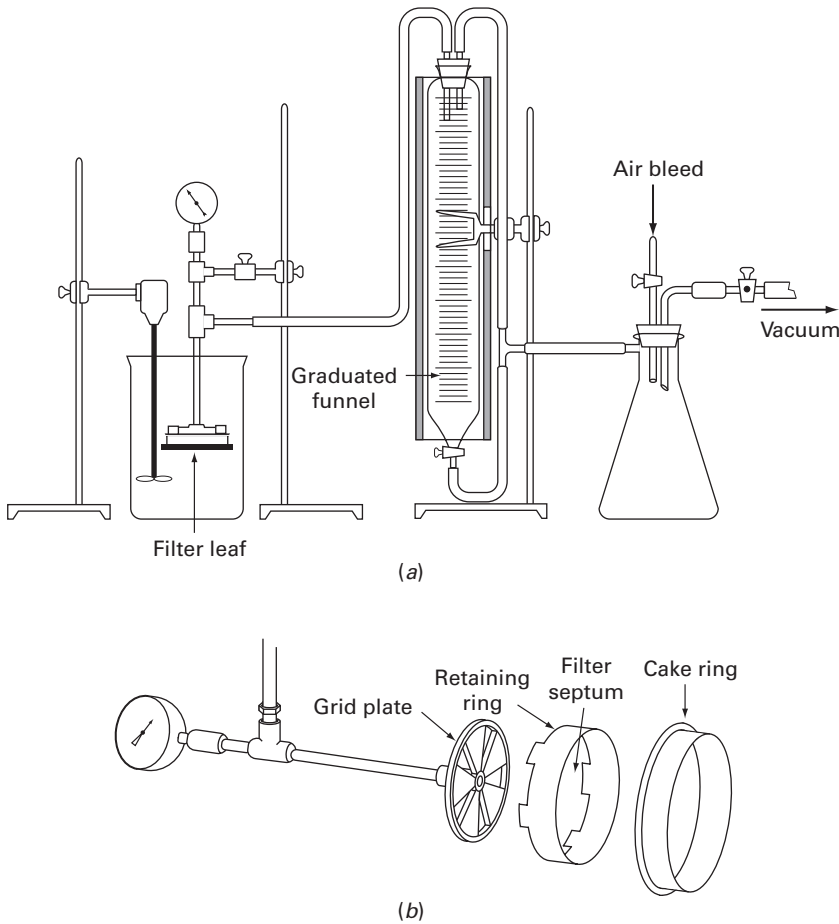


FIGURE 4.16 (a) Filter leaf apparatus, and (b) detail of a precoat filter leaf.

volume of filtrate of 10 g/liter. From laboratory tests, the specific cake resistance has been determined to be 9×10^{10} cm/g. Determine the area of the filter that is required. The resistance of the filter medium can be neglected.

Solution

We can use the integrated form of the filtration equation, Equation (4.2.5), with $R_m = 0$:

$$\frac{t}{V/A} = \frac{\mu_0 \alpha \rho_c}{2\Delta p} \left(\frac{V}{A} \right)$$

We solve for A^2 to obtain

$$A^2 = \frac{\mu_0 \alpha \rho_c V^2}{2\Delta p t}$$

In applying this equation, it is helpful to focus on the area of the drum that is submerged, which is where the cake is being formed and where filtrate is being obtained. Thus, A is the area of that part of the drum that is submerged. We can calculate the volume of filtrate that needs to be collected during the cake formation time of 15 s:

$$V_{15s} = \frac{2000 \text{ liters}}{h} \times 15 \text{ s} \times \frac{1 \text{ h}}{3600 \text{ s}} = 8.33 \text{ liters}$$

We use this volume of filtrate with $t = 15 \text{ s}$ in the equation for A^2 to obtain

$$A^2 = \frac{\frac{0.02 \text{ g}}{\text{cm s}} \times 9 \times 10^{10} \frac{\text{cm}}{\text{g}} \times 10 \frac{\text{g}}{\text{liter}} \times (8.33 \text{ liters})^2 \times \frac{\text{cm s}^2 \text{ kPa}}{10^4 \text{ g}} \times \frac{10^3 \text{ cm}^3}{\text{liter}} \times \left(\frac{\text{m}}{10^2 \text{ cm}} \right)^4}{2 \times 70 \text{ kPa} \times 15 \text{ s}}$$

$$= 0.595 \text{ m}^4$$

$$A = 0.771 \text{ m}^2$$

The area A' of the entire rotary vacuum filter can be calculated from the cake formation time and the total cycle time as

$$A' = \left(\frac{60 \text{ s}}{15 \text{ s}} \right) \times 0.771 \text{ m}^2 = 3.08 \text{ m}^2$$

This is a medium-sized rotary vacuum filter, with possible dimensions of 1.0 m diameter by 1.0 m long.

EXAMPLE 4.5

Washing of a Rotary Vacuum Filter Cake For the filtration in Example 4.4, it is desired to wash a product antibiotic out of the cake so that only 5% of the antibiotic in the cake is left after washing. We expect the washing efficiency to be 50%. The filter cake can be assumed to contain 70 wt% water. Estimate the washing time per cycle that would be required.

Solution

From Equation (4.2.7) for the washing efficiency of a filter cake

$$R' = \left(1 - \frac{E}{100} \right)^n$$

where R' is the weight fraction of solute remaining in the cake after washing (on the basis of $R' = 1.0$ before washing), E is the percentage wash efficiency, and n is

the volume of wash liquid per volume of liquid in the unwashed cake. Substituting $R' = 0.05$ and $E = 50\%$ into this equation gives

$$n = 4.32$$

From Equation (4.2.14), the relationship between the washing time t_w and the cake formation time t_f is given by

$$t_w = 2nf t_f$$

where f is the ratio of volume V_r of residual liquid in the cake to the volume of filtrate V_f after time t_f . Thus, we need to estimate the volume of residual liquid in the filter cake to determine t_w . At the end of the 15 s cake formation time,

$$\text{Weight of dry cake solids filtered} = 10 \frac{\text{g}}{\text{liter}} \times 8.33 \text{ liters} = 83.3 \text{ g}$$

Since the filter cake contains 70 wt% water, we find

$$\text{Weight of water in the filter cake} = \frac{70}{30} \times 83.3 = 194 \text{ g}$$

Thus,

$$f = \frac{V_r}{V_f} = \frac{0.194}{8.33} = 0.0233$$

$$t_w = 2nf t_f = 2(4.32)(0.0233)(15 \text{ s}) = 3.0 \text{ s}$$

From this result, the estimated washing time is 20% of the cake formation time.

For small-scale tests of pressure filtration, a bomb filter may be used (Figure 4.17). The bomb filter contains a filter leaf, typically 2 in. by 2 in., that is covered with an appropriate filter medium. Enough slurry is placed in the bomb to cover the filter leaf. Air may be sparged into the slurry to provide gentle agitation. After the filtration has been started at a given pressure, the filtrate volume is recorded as a function of time. After a given time for filtration of the slurry, the cake can be washed with a wash liquid and dewatered by flowing air through the cake. Analyses can be performed on the cake and filtrate plus wash.

The data obtained from small-scale filtration tests can be used to calculate the filtration rate and area of the large-scale unit. For units in which the filter medium is continuously washed, it is recommended that filtration rates calculated from small-scale filtration data be multiplied by a factor of 0.9 [11]. For units in which the filter medium is not continuously washed, this factor should be reduced to 0.8.

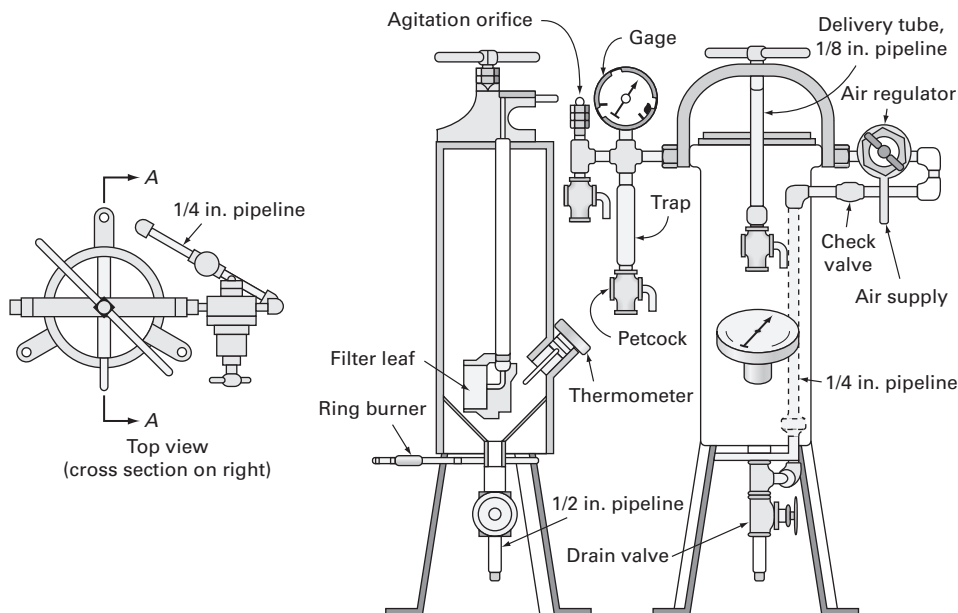


FIGURE 4.17 Bomb filter for small-scale pressure filtration tests.

Before scaling up the filtration area, the relationship between the nominal filtration area and the active filtration area should be determined. The nominal filtration area is based on the overall dimensions of the filtering surface. The active filtration area may be less than the nominal area because part of the filtration surface may be blinded by mechanical dividers or by painting.

Considerations for the Design of Sterile Filters

Sterile filtration is an important application of conventional filters in the pharmaceutical industry, where many products are sold in sterile form. It is sometimes desirable that other processing steps besides the final one be carried out under sterile conditions, which requires the filtration of both liquids and air.

Liquid Sterile Filtration

In typical sterile liquid filtration applications, there is no appreciable filter load, no cake buildup, and no contribution to filtration resistance from the filtrate that is reliable or reproducible. Further, there is no opportunity to add filter aids to form a cake, since this is usually the last step in a clean process.

Sizing of the filter is almost always based on the maximum allowable load in the solution to be filtered, and the desired sterility assurance limit. The sterility assurance limit is the calculated probability of a single unit of product containing a single microorganism. This is expected to be a maximum of 10^{-3} for aseptic processes, and one usually designs in an extra order of magnitude at least. One determines the maximum load on the filter by knowing the bioburden or viral load specification of the purified pool from the preceding step, or by knowing the acceptable microbial or viral levels in the raw materials that make up that pool. The retentive requirement

for the filter is then divided by the retention capability (per area) of the filter to be used. The resulting filter area is the minimum required to meet the sterility goal of fewer than one unit dose contaminated with one organism per thousand doses manufactured. The next step is to ensure that the filter is large enough to allow reasonable processing times. Typically, one does not want to filter for more than one shift (8 h). At 24 h, questions will be raised about “grow-through” (where retained microbes will have colonized the filter and “grown through” to the other side). The filtration time for the filter sized is determined by finding the clean water flow rate for the filter, either through laboratory experiment or through the vendor’s published materials, and adjusting for the viscosity of the solution to be filtered relative to water (a correction for the effect of temperature on viscosity may be necessary). Once the flow rate is known, the time to filter a given size batch can be determined. The area of the filter can be adjusted up to reduce the filtration time, but cannot be adjusted down without jeopardizing the sterility assurance.

For the ultimate filtration step, in which the product is rendered sterile, a depth filter is often added upstream of the membrane filter. This protects the sterile filter from fouling during use. It is very risky to replace a sterile filter once in place, with all the connections downstream sterilized. Depth filters with high “dirt loads” can keep particulate matter from reaching the membrane surface, keeping it clean for the removal of microbes. Two sterile filters are sometimes used in series, for added sterility assurance. This gives very high probability that dosage units will not be contaminated, but the arrangement sometimes becomes difficult to manage in other respects. For instance, multiple sterility-assurance tests must be performed, a requirement that adds manipulations and increases chances for breeches in sterility.

Filters used for the purpose of sterilizing pharmaceutical products must be tested to ensure that they have been properly installed and have no defects that could allow sterility to be compromised. The two most common tests for a sterile filter for an aqueous product are the “bubble point” and the “pressure hold” or “diffusion” test. In both tests, a wetted, sterilized filter is pressurized with air or nitrogen. In the bubble point test, this pressure is increased until the lowest pressure is found at which air passes freely through the filter. It is assumed that this is the pressure required to overcome the surface tension and viscosity of water in the largest membrane pore (where the forces are the weakest). As the pore size of the membrane decreases, the bubble point increases. This test will also detect a sliced or unseated O-ring or other seal failure. The pressure hold test pressurizes a wetted filter to a pressure lower than the bubble point and measures either the total flow of gas through the membrane (by diffusion) or the rate of pressure decay. Both should be low, and both should meet the manufacturer’s specifications for an intact, properly installed sterile filter.

Compatibility and extractable tests need to be performed on each filter type, in addition to testing each installed filter for sterility assurance. Compatibility means that the filter does not adsorb an active ingredient or any other type of active excipient, such as an antibiotic or preservative. Such adsorption to the filter medium can change the strength (or biological potency) of the solution after the filtration step.

Extractables are chemicals that can leach out of the filter medium, such as monomers from the membrane or support medium, filter coatings or mold-release agents, and storage solutions, such as ethanol. These chemicals would be considered impurities in the final product and should be removed. When the filter is used in the final sterilization step, impurities leaching into the product cannot be allowed. Compatibility and extractables should be tested in a sample of the product solution. When this is not possible, because product or excipients would interfere with the analysis of the impurities, a placebo or similar solution should be used.

Viral filtration is an emerging technology in the manufacture of biopharmaceuticals, specifically those manufactured from mammalian cell culture. Viral filters have pore sizes on the order of 10 nm, so that they exclude virus particles as small as 20 nm. These filters are qualified in viral clearance studies, in which high titers of model viruses are spiked into a sample product stream, and their recovery measured downstream of the filter. Clearance is typically measured in logs, and 5 logs are typical removal rates for viral filters. The sizing of viral filters is typically based on amount of protein filtered per unit area. Many virus filters are constructed using hollow fibers and require using the crossflow mode. For these filters, R_m is very high, but the pressure the filter can support is very low, sometimes only around 1 atm. For this reason, virus filtration can take extremely long times. The technology is still not standardized and several platforms exist. More research is needed in the application and scale-up of virus filters.

Air Sterile Filtration

Air filters are also sized based on the anticipated flow rate. Airflows are specified with one or more of the following criteria: pressure differential between areas, air changes per hour, or linear flow rate. Pressure differentials are usually measured between rooms, or between rooms and corridors. These are specified when it is important for air to flow from a “cleaner” area to a “dirtier” area when doors, windows, or pass-throughs are opened between them. Pressure differentials are typically 50 to 150 Pa (= 0.5–1.5 cm of water, or 0.4–1.1 mm Hg (torr)). Air changes per hour are often specified for rooms based on hazardous materials or operations the room is designed for. Air changeover is the airflow rate divided by the volume of the room. Air changeovers are different from “makeup rate,” which is the fraction of fresh air injected in the room’s air handler.

Clean rooms often have very high changeover rates but low makeup rates. Rooms handling solvents or hazardous materials have high makeup rates (also called “once-through air”) but low air cleanliness requirements. The changeover rate varies with the hazard of the material. Linear flow rate is usually specified in hoods and smaller spaces. Linear flow rates of 5 to 20 ft/s (= 1.5–6.1 m/s) are found in laminar flow hoods, in aseptic areas where pharmaceuticals are sterile processed, and in clean rooms where microelectronics are manufactured. Linear flow rates are established to prevent airborne microbes and particulate matter from settling in or on the materials being processed. The flow rate required for the

room or area being ventilated can be determined by one or more of the specifications just cited.

The air quality of a room or area is typically classified according to the number of airborne particles that can be measured in a cubic meter. Increasingly, rooms are being classified according to the International Organization for Standardization (ISO), which has published a series of documents numbered 14644 (volumes 1–5). These standards classify clean room space as 1 (cleanest) through 9 (dirtiest), with each classification allowing approximately one log more particles in a cubic meter of air than the previous. For biotechnology and pharmaceuticals, the most commonly used grades are ISO Class 5 (similar to the military standard Class 100) to ISO Class 8 (similar to the military standard class 100,000). ISO Class 5 is used for aseptic processing where products may be briefly exposed to the environment, and ISO Class 8 is used for areas containing primarily closed operations. High-efficiency particulate air (HEPA) filters are routinely tested for integrity by spraying a polyalphaolefin (PAO) aerosol on the feed side of the filters. The typical specification for a PAO test is a 10^3 reduction in aerosol particles.

Vent filters filter air on tanks and drainable equipment. Vent filters typically follow the same specification as the liquid filters used in the process. Vent filters are also sized based on the maximum airflow rate anticipated. The maximum flow rate is often encountered when the tanks are being filled or cleaned. Vent filters must allow flow in both directions, which is a unique requirement among filters discussed in this chapter.

Integrity testing of vent filters is an evolving technology. These filters are typically hydrophobic, so bubble points and pressure holds are not appropriate. The PAO tests will not work because vent filters are typically membrane filters (which are the most compact), while HEPA filters are depth filters. Testing bubble points in solvents is feasible, and often performed, but is considered a destructive form of measurement.

4.5.2 Crossflow Filtration

As for conventional filtration, scale-up of crossflow filtration requires data from laboratory or pilot scale units. There are, however, more different types of designs possible for crossflow filtration compared to conventional filtration because of the various modes of operation that can be used for crossflow filtration and because there is often a choice between batch and continuous operation for crossflow filtration.

Crossflow filtration modules are available from manufacturers for carrying out laboratory or pilot plant tests. The size of a plant unit can be determined by a direct scale-up of the filtration area based on the feed or permeate flow rate. For this scale-up, however, it is important that the following variables be kept constant [18]:

- Inlet and outlet pressures
- Crossflow (or tangential) velocity

- Flow channel sizes (height and width)
- Feed stream properties—test slurries should be representative of the actual process streams
- Membrane type and configuration—test data from one design cannot directly be used to design another geometry

Maintaining the inlet and outlet pressures, the crossflow velocity, and the flow channel size means that the length of the flow path is constant as well. It is also important to make an assessment of the rate of fouling of the membranes. Tests should be performed for several cycles of operation to estimate the fouling rate and to determine how fouling can be kept to a minimum.

There are four basic modes of operation of crossflow filtration (Figure 4.18): batch concentration, diafiltration, purification, and complete recycle. In the batch concentration mode, the retained stream containing the product suspended particles or dissolved macromolecules is reduced in volume. In diafiltration, the volume of the retained stream is maintained constant by the continuous addition of water or buffer, which results in the removal of low molecular weight solutes into the permeate. Diafiltration is commonly used when salt removal or exchange is desired. In the purification mode, a low molecular weight product passes into the permeate and is thus separated from higher molecular weight impurities; or, the product can be retained and impurities removed in the filtrate. In the complete recycle mode, both the retained stream and the permeate are returned to the feed tank. Systems may be operated in complete recycle at start-up to reach

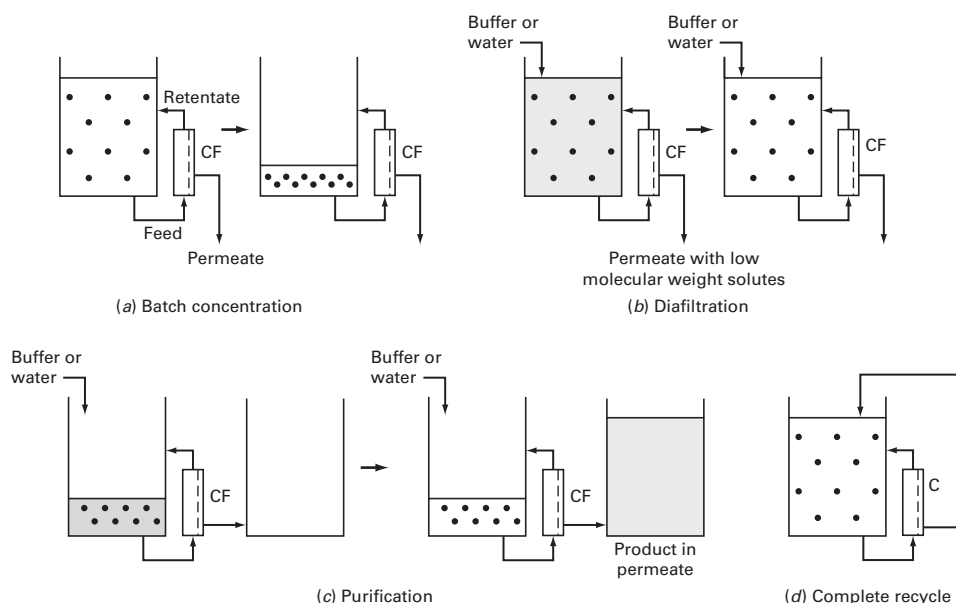


FIGURE 4.18 The four basic modes of operation of crossflow filtration (CF = crossflow filter): before the arrow, start of the operation; after the arrow, end of the operation.

steady state, saturate the membranes, test for leaks and blockage, and adjust the feed rate.

Diafiltration is similar to dialysis in that salts are exchanged or removed in both modes. Dialysis is a laboratory method that involves placing the feed in a bag made with an ultrafiltration membrane. The bag is placed in a large volume of the new solvent desired, and the new solvent is mixed until the system comes to equilibrium or near equilibrium. Complete equilibrium takes 3 to 5 h, while 90% equilibrium can be reached in 2 to 3 h [19]. For a complete change of solvent, it is necessary to do the dialysis at least twice. It is frequently the job of the engineer to scale up a dialysis done in the laboratory to a diafiltration in the pilot plant or plant. For scaling and planning, it is customary to perform material balances on solids mass and liquid volume around any component of the operation.

EXAMPLE 4.6

Diafiltration Mode in Crossflow Filtration It is desired to use a crossflow filtration system to desalt 1000 liters of a protein solution containing NaCl. The system is capable of operating at a transmembrane flux of $30 \text{ liters m}^{-2} \text{ h}^{-1}$. To remove 99.99% of the salt, determine the time required and the volume of water required using a crossflow filtration unit with a membrane area of 100 m^2 .

Solution

We operate the system in the diafiltration mode, which means that the volume of the solution being desalted is maintained constant. A material balance on the salt in the retained volume gives

$$V \frac{dc_s}{dt} = -QC_s(1 - r_s)$$

where V = volume of solution being desalted

c_s = concentration of salt in volume V

r_s = fraction of salt rejected by the membrane

Q = filtration rate (volume/time)

For this case we assume that there is no rejection of salt by the membrane, so that $r_s = 0$. Integrating the differential equation with the initial time equal to zero gives

$$\ln \frac{c_s}{c_{s0}} = -\frac{Qt}{V}$$

where c_{s0} = initial salt concentration. Solving for t , we obtain

$$t = -\frac{V \ln \frac{c_s}{c_{s0}}}{Q} = -\frac{(1000 \text{ liters})(\ln 0.0001)}{\left(30 \frac{\text{liters}}{\text{m}^2 \text{ h}}\right)(100 \text{ m}^2)} = 3.07 \text{ h}$$

$$\text{Volume of water required} = (3.07 \text{ h}) \left(30 \frac{\text{liters}}{\text{m}^2 \text{ h}}\right) (100 \text{ m}^2) = 9210 \text{ liters}$$

Thus, a relatively large volume of wastewater will be generated by this process.

In designing a diafiltration process, a decision must be made about the concentration of retained product at which to operate. As this concentration is increased, the filtration flux will decrease according to Equation (4.2.16), and the total volume of filtrate will decrease for the removal of a given percentage of a low molecular weight solute. This leads to an optimum concentration to minimize the time required, which can be determined mathematically if the relation between filtrate flux and concentration in the bulk fluid (c_b) is known [20].

The basic components in the design of a crossflow filtration system are shown in Figure 4.19. A pump flows the feed through the filtration module to give a permeate and a retentate or retained stream. The pump needs to be sized to provide the desired flow velocity and pressure. The transmembrane pressure is controlled by a back-pressure valve on the retentate stream exiting from the filtration module. Thus the transmembrane pressure drop is estimated by

$$(4.5.1) \quad \Delta p_{TM} = \frac{1}{2}(p_i + p_o) - p_p$$

where p_i and p_o are the retentate pressures in and out of the module, respectively, and p_p is the pressure of the outlet permeate. In designing a crossflow filtration system, it is important to minimize the occurrence of gas-liquid interfaces, since bioproduct denaturation, especially of proteins, can occur at these interfaces in the presence of mechanical shear and turbulent flow (see Section 1.4.7).

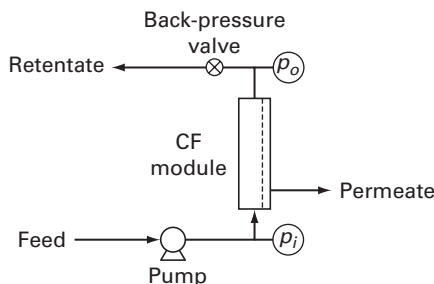


FIGURE 4.19 Basic components of a crossflow filtration system.

Crossflow filtration systems may be designed to operate in the batch or the continuous mode (Figure 4.20). In a batch system, feed is pumped through the filtration module and then back to the feed tank. In a variation of this mode (called semibatch) for diafiltration, fluid is continuously added to the feed tank to keep the feed volume constant (Figure 4.18b).

In the continuous mode of operation, also sometimes called the “feed-and-bleed” mode, or “retentate bleed” mode, feed is added to a recirculation loop by the feed pump, and concentrate exiting in the retained stream is withdrawn from the system so that the concentration factor (i.e., concentration in the retentate divided by the concentration in the feed) is at the desired value. When steady state has been achieved, the concentrate will be at its maximum concentration, which means that the filtration flux will be at a minimum throughout the run [20]. It is generally more economical to use a multistage system in a continuous process (Figure 4.21). As more stages are added, the average filtration flux approaches that for a batch system, and thus the total filtration area decreases as more stages are added. This is illustrated in Table 4.2, where batch ultrafiltration operation is compared with continuous operation using one, two, three, and five stages.

Because of the economic advantages of continuous operation and reduced tankage, this scheme is preferable to batch operation for most large-scale ultrafiltration operations [11]. Another advantage of continuous operation is that it permits the minimization of the residence time of the product in the crossflow filtration unit, which is important for products that are sensitive to heat or shear. Dairy and food

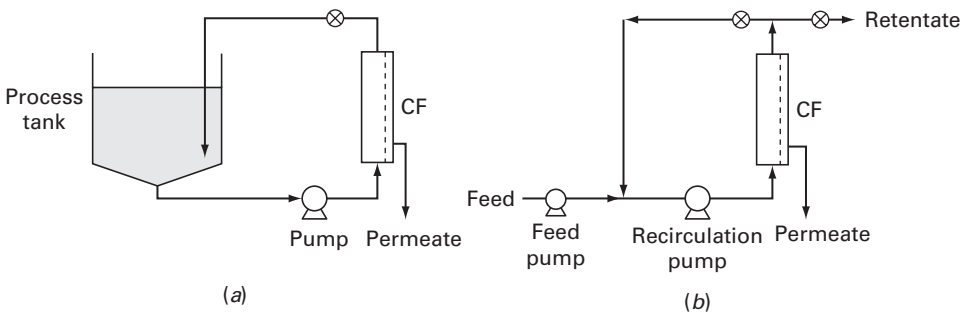


FIGURE 4.20 Comparison of (a) batch and (b) single-stage continuous (feed-and-bleed) crossflow filtration systems.

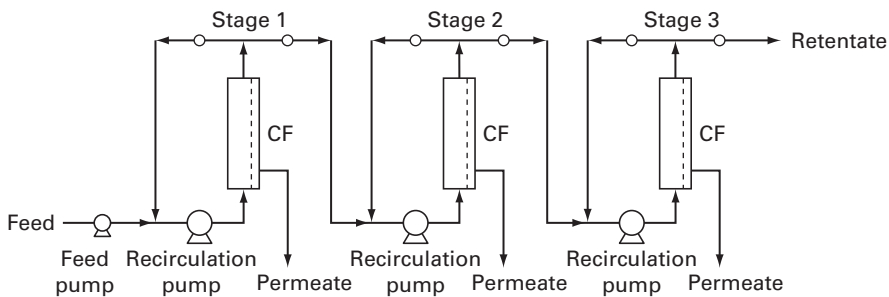


FIGURE 4.21 Multistage crossflow filtration system using the retentate bleed mode.

TABLE 4.2 Comparison of Batch and Continuous Ultrafiltration Systems^a

System ^b	Flux (liters m ⁻² h ⁻¹)	Total area (m ²)
Batch	33.1 (average)	136
Continuous		
One-stage	8.1	555
Two-stage	31.1	243
	8.1	
Three-stage	38.7	194
	23.4	
	8.1	
Five-stage	44.7	165
	35.6	
	26.4	
	17.3	
	8.1	

^aSee reference [20].

^bSystem design for 10× concentration factor and feed rate of 5000 liters/h.
Flux from $J = 20 \ln(30/c_b)$.

proteins are generally processed continuously, while most pharmaceutical and biological products are processed using batch operation [20].

4.6 SUMMARY

Filtration separates particulate or solute components in a fluid suspension or solution according to size by flowing under a pressure differential through a porous medium. The two broad categories of filtration are conventional (or dead-end) filtration and crossflow filtration. Fluid flows perpendicular to the filter medium in conventional filtration and parallel to the membrane in crossflow filtration.

- Filtration can be used to accomplish a number of objectives, including the removal of cells or cell debris, the concentration of cells or protein solutions, and the removal or exchange of salts.
- The calculation of solvent fluxes and filtration times for conventional filtration is accomplished using various forms of Darcy’s law, which states in general that the flux of filtrate is equal to pressure drop divided by viscosity and resistance, $J = \Delta p / \mu_0 R$, where R is a combination of the resistance R_m of the filter medium and the resistance R_c of the cake solids.
- The time to wash a filter cake to remove all but a desired minimal level of solute can be estimated on the basis of the washing efficiency (E), the filtration time and volume of filtrate before washing, and the volume of residual liquid in the cake.

- At steady state during the crossflow filtration of a stream containing a dissolved solute, the fluid flux of permeate through the membrane is given by

$$J = \left(\frac{\mathcal{D}}{\delta} \right) \ln \left(\frac{c_w}{c_b} \right)$$

where $\mathcal{D}$ is the solute diffusion coefficient, δ is the mass transfer boundary layer thickness next to the membrane, and c_w and c_b are the solute concentrations at the wall and in the bulk fluid, respectively. The term $\mathcal{D}/\delta$ is a mass transfer coefficient that can be predicted for both laminar and turbulent flow.

- For suspended particles greater than $1\ \mu\text{m}$ in crossflow filtration, the boundary layer analysis for dissolved solutes gives low predictions of the fluid flux, and a shear-induced diffusion theory and an inertial lift theory have been used to predict fluxes for this situation, depending on the particle size.
- A variety of filter media, membranes, and equipment is available for conventional and crossflow filtration.
- Fouling of membranes adds another resistance to the transmembrane flux in crossflow filtration. Membrane fouling by proteins can be attributed to one or more of the following processes: (1) protein adsorption, which involves the interaction of the proteins and the membrane and occurs with no convective flow through the membrane, (2) protein deposition, which is the addition of more membrane-associated protein over and above the protein that would be adsorbed in a nonflowing system, and (3) protein accumulation on the membrane surface exposed to the flowing process stream as a result of concentration polarization, producing a solids or gel layer on the membrane surface.
- The scale-up of a conventional filtration can be performed with values of the specific cake resistance α and medium resistance R_m determined in laboratory filter leaf tests, assuming that feed stream properties are constant and that α does not change with a change in pressure drop upon scale-up. A crossflow filter can be scaled up directly based on membrane area, provided pressures, crossflow velocity, flow channel sizes, feed stream properties, and membrane type and configuration are held constant.
- There are numerous special considerations for the design and operation of sterile filters for liquids and air.
- There are four basic modes of operation of crossflow filtration: batch concentration, diafiltration, purification, and complete recycle. A multistage continuous process is generally more economical than a batch process in large-scale operations.

NOMENCLATURE

a	radius of spherical particles (cm)
A	filter cross-sectional area (cm ²)
c	concentration of solute (M, or g liter ⁻¹)
D	diameter of tube (cm)
D_h	equivalent diameter of channel (cm)
$\mathcal{D}$	diffusion coefficient of solute (cm ² s ⁻¹)
$\mathcal{D}_s$	shear-induced diffusion coefficient for a suspended particle (cm ² s ⁻¹)
E	washing efficiency for a filter cake (%)
f	ratio of volume of residual liquid in filter cake to volume of filtrate at end of filtration (dimensionless)
h	half-height of rectangular flow channel (cm)
J	transmembrane fluid flux (liter m ⁻² h ⁻¹)
k	mass transfer coefficient ($= \mathcal{D}/\delta$) (cm s ⁻¹)
L	length of flow channel over membrane (cm)
n	volume of wash liquid per volume of liquid in unwashed filter cake (dimensionless)
p	pressure (kPa)
R	overall resistance to filtration (cm ⁻¹)
R	gas constant (0.082058 liter atm mol ⁻¹ K ⁻¹)
R_c	resistance of filter cake (cm ⁻¹)
R_{if}	resistance from irreversible membrane fouling (cm ⁻¹)
R_m	resistance of filter medium or membrane (cm ⁻¹)
R_p	resistance from concentration polarization and a gel layer (cm ⁻¹)
R'	weight fraction of solute remaining in the cake after washing (on the basis that $R' = 1.0$ before washing)
Re	Reynolds number ($= D_h u_b \rho / \mu$) (dimensionless)
Sc	Schmidt number ($= \mu / \rho \mathcal{D}$) (dimensionless)
Sh	Sherwood number ($= k D_h / \mathcal{D}$) (dimensionless)
t	time (s)
T	temperature (K)
TMP	Average transmembrane pressure, or average pressure drop (mm Hg)
u_b	bulk fluid velocity (cm s ⁻¹)
V	volume of filtrate (conventional filtration) or volume of retentate (diafiltration) (liters)
VCR	volume concentration ratio (dimensionless)

Greek Letters

α	specific cake resistance (cm g ⁻¹)
α'	resistance parameter for a compressible cake (cm g ⁻¹ Pa ^{-s})
γ_w	shear rate at membrane surface (s ⁻¹)

δ	boundary layer thickness (cm)
Δp	pressure drop (mm Hg)
$\Delta \pi$	osmotic pressure (mm Hg)
Θ	angle of drum rotation of rotary vacuum filter after entering broth (rad)
μ	viscosity of fluid ($\text{g cm}^{-1} \text{s}^{-1}$)
μ_0	viscosity of filtrate or permeate ($\text{g cm}^{-1} \text{s}^{-1}$)
ρ	density of fluid (g cm^{-3})
ρ_c	mass of dry cake solids per volume of filtrate (g liter^{-1})
σ	membrane reflection coefficient for a solute (dimensionless)
φ	particle volume fraction in bulk suspension (dimensionless)
ω	rate of drum rotation of rotary vacuum filter (rpm)

PROBLEMS

4.1 Conventional Batch Filtration In a laboratory test of the filtration of a cell culture, the following equation was obtained to describe the filtration:

$$\frac{t}{V/A} = K_1 \left(\frac{V}{A} \right) + K_2$$

where $K_1 = 0.18 \text{ min/cm}^2$ and $K_2 = 0.017 \text{ min/cm}$. The cell slurry has a viscosity of 2 cp, and the filter cake solids (dry basis) per volume of filtrate was 13 g/liter. The pressure drop for the filtration was 610 mm Hg (0°C). Determine the specific cake resistance α and the medium resistance R_m . Evaluate the relative significance of the medium resistance after 5 min of filtration.

4.2 Batch Filtration with Change in Pressure In a filtration of suspended cells under full vacuum using a 20 cm Büchner funnel, you collect data for the volume of filtrate as a function of time (see Table P4.2). The concentration of cells was 100 g/liter (mass of dry cake solids per volume of filtrate), and the viscosity of the filtrate was 1.0 cp.

TABLE P4.2

Time (min)	Volume filtered (liters)
0	0
20	4
30	5
40	6.5
50	7
60	7.5
70	7.8

- What is the resistance of the filter medium?
- What is the specific resistance of the cake layer?

- (c) Being disappointed in the amount of time required, you decide to give the vacuum filter a boost by pressurizing the funnel to 1 atm gage pressure. The result is the same. Concerned that you may have done the wrong thing, you then remove the funnel pressure and reduce the vacuum in the flask to 0.5 atm. The result is the same. Determine the dependence of the specific resistance of the cake layer as a function of the pressure drop. Comment on what is happening in the filtration.
- (d) What is the most effective change you can make to decrease the time required to filter a given volume?

4.3 Filtration on a Filter with Uniform Cylindrical Pores A depth filter has a membrane resistance of $R_m = 10^{12} \text{ cm}^{-1}$ and retains all particles greater than $0.4 \mu\text{m}$ in diameter. Design a filter having uniform straight cylindrical pores with identical performance (including identical flux) to that of this depth filter using a polycarbonate film $200 \mu\text{m}$ thick.

- (a) How many pores per square centimeter must the filter with straight cylindrical pores have?
- (b) Is a filter with straight cylindrical pores feasible in this situation?

Hint: Assume that the flow rate Q through each pore can be described by the Hagen–Poiseuille equation for laminar flow

$$Q = \frac{\pi \left(\frac{D}{2} \right)^4 \Delta p}{8 \mu L}$$

where D and L are the pore diameter and the length, respectively.

4.4 Scale-up of a Rotary Vacuum Filter A rotary vacuum filter is available with an area of 200 m^2 and vacuum pressure of 75 kPa. Filter leaf tests have been performed on a cell broth with a viscosity of 5 cp. The leaf tests gave a specific cake resistance of $1 \times 10^{11} \text{ cm/g}$ and a medium resistance of $1 \times 10^8 \text{ cm}^{-1}$. The cake solids (dry basis) per volume of filtrate was 15 g/liter. It is desired to operate the large filter with a cycle time of 45 s and a cake formation time of 10 s. What is the filtration rate expected for the rotary vacuum filter? How significant is the medium resistance?

4.5 Accumulated Cake Solids and Cake Thickness for a Rotary Vacuum Filter For filtration with a rotary vacuum filter, the following variables are known: filtrate viscosity (μ_0), pressure drop (Δp), specific cake resistance (α), mass of cake solids on a dry basis per volume of filtrate (ρ_c), and rate of drum rotation in revolutions/time (ω).

- (a) It is desired to know the mass X of accumulated cake solids on the dry basis per unit area of the filter. For the case of negligible medium resistance, determine X as a function of the foregoing variables and Θ , the angle that the drum has rotated from a given point after entering the broth.
- (b) It is necessary that the thickness of the cake be limited to a value h . Determine h in terms of the same variables in part (a), the bulk density of the cake (ρ_b), and the weight fraction of water in the cake (x_w).

- 4.6 Continuous Crossflow Filtration System Operating at Steady State** It is desired to concentrate a cell slurry continuously at a flow rate Q_f and cell concentration x_f to a concentration x_r in a steady state operation with a crossflow microfilter. The process variables are shown in the system diagram (Figure P4.6). The concentration of cells in the permeate is zero. If the dependence of the permeate rate Q_p on cell concentration x entering the pump is known, describe how you would determine the recycle ratio R and concentration x .

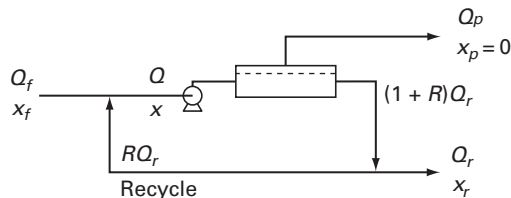


FIGURE P4.6 Process flow diagram for continuous operation of a crossflow filter. Flow rate is denoted by Q and cell concentration by x .

- 4.7 Crossflow Filtration Operating in Complete Recycle Mode** A crossflow filtration unit is operated in the complete recycle mode.
- Sketch the flow diagram for the system, defining flow stream parameters for all flow streams. Write a material balance around the tank.
 - The membrane has a molecular weight cutoff (MWCO) of 50,000 Da. (MWCO refers to the molecular weight of globular solute at which the solute is 90% rejected by the membrane.) Your product is a globular molecule with a molecular weight of 50,000 Da. Write a relationship that gives the mass of product per unit time returning to the tank through the permeate return line in terms of the starting concentration of product and the volumetric flow rates.
 - What are the reasons for operating in the complete recycle mode?
- 4.8 Concentration Polarization during Ultrafiltration** A system is available for the ultrafiltration of protein solutions. On Monday, you filter a globular protein with 12,000 Da molecular weight, and it is fully retained. On Tuesday, you filter a 120,000 Da molecular weight globular protein at the same molar concentration and using the same membrane. The transmembrane flux was the same on both days. Assuming identical boundary layer thicknesses for both filtrations, in which case will the polarization modulus c_w/c_b be greater? What is the relationship between the polarization moduli for the two cases?
- 4.9 Concentration and Diafiltration with an Ultrafiltration System** A 2000-liter volume of a 30 g/liter protein solution needs to be concentrated to 200 g/liter. Also, the initial salt concentration must be reduced one hundredfold. The relationship between the permeation rate and the bulk protein concentration has been determined experimentally as follows:

$$Q = 500 \ln \left(\frac{270}{c_b} \right)$$

where Q = permeation rate (liters/h)

c_b = bulk protein concentration (g/liter)

Determine the operation batch volume that will give the minimum time for diafiltration. Then determine the times required for (a) concentration to the volume at which diafiltration is to be carried out, (b) diafiltration, and (c) concentration to the final concentration desired.

4.10 Time Required for Ultrafiltration A protein solution at a concentration of 0.5 g/liter and volume of 1000 liters must be concentrated on a crossflow ultrafilter to a concentration of 10 g/liter. The ultrafilter has an area of 100 m² and operates at 5°C with an inlet feed pressure of 16.0 bar, outlet feed pressure of 14.0 bar, and back pressure on the permeate of 1.4 bar. The protein has a molecular weight of 20,000 Da and will not pass through the ultrafiltration membranes. The feed has a viscosity of 1.2 cp. The membrane resistance (R_m) of the ultrafilter has been determined to be 2×10^{13} cm⁻¹. The Reynolds number for flow within the ultrafilter is large enough to render concentration polarization negligible. Determine the time required to perform the ultrafiltration.

4.11 Concentration at the Membrane Surface of a Crossflow Filter You operate a crossflow filter at a very low Δp and low flux until the transmembrane solvent flow becomes zero as a result of concentration polarization. Show how you would determine the concentration of solute c_w right at the membrane surface on the feed (retentate) side. Assume that c_w is not high enough to form a precipitate or gel layer.

4.12 Scale-up of Batch Filtration of Protein Precipitate A small test filtration of a protein precipitate in an aqueous suspension uses a conventional filter with an area of 89 cm² at a pressure drop of 0.4 atm to give data for the filtrate volume as a function of time (see Table P4.12). We would like to filter a much larger batch of the precipitate at the same temperature containing 1000 liters of solvent by using a filter of 1.3 m² area having the same filter medium as for the small-scale filtration. However, this larger batch has a concentration of 0.28 g/100 cm³ of solvent, less than in our test filtration, which is 0.34 g/100 cm³ of solvent. How long will it take to filter this new batch at the same pressure drop? What is the error in the calculated time if the resistance of the filter medium is neglected?

TABLE P4.12

Time (s)	Filtrate volume (liters)
10	0.489
20	0.703
30	0.864
40	0.995
50	1.120

4.13 Explanation of Flux Reduction in Microfiltration of an Enzyme A microfiltration membrane system is being used to process a cell lysate (i.e. cells broken) in the continuous mode so that a low molecular weight enzyme is obtained in the filtrate. The filtrate flux across the microfiltration membrane is less than when the membrane was tested using a buffer solution as feed before the cell lysate was processed. Explain how

you could determine if the flux reduction is due to concentration polarization on the membrane surface and/or to fouling within the membrane.

4.14 Crossflow Filtration of Suspended Particles Crossflow filtration is being performed at bulk velocity u_b in tubes of diameter D in a solution containing suspended biological particles of radius a . The flow regime is laminar. The diffusion coefficient in free solution of the biological molecule that makes up the particles is $\mathcal{D}$.

- Determine the ratio of the mass transfer coefficient k for the filtration of the particles to the mass transfer coefficient for the filtration of the dissolved biological molecule as a function of u_b , a , D , and $\mathcal{D}$, assuming the particles are in the 1 to 30 μm size range.
- For the conditions given in Example 4.2 for the ultrafiltration of a protein (except $u_b = 210 \text{ cm/s}$), calculate the value of the ratio in part (a).

4.15 Estimation of Boundary Layer Thickness during Crossflow Filtration Data have been obtained for the concentration of a protein by ultrafiltration (see Table P4.15). The diffusion coefficient of the protein is $8 \times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$. Estimate the thickness of the boundary layer next to the membrane.

TABLE P4.15

Protein concentration (wt. %)	Ultrafiltration flux ($\text{ml cm}^{-2} \text{ min}^{-1}$)
1.0	0.054
2.0	0.039
4.0	0.025
6.0	0.016
10.0	0.006

4.16 Initial Irreversible Fouling and Concentration Polarization Resistance in Ultrafiltration An ultrafiltration system is operated to concentrate a protein solution containing a buffer. The average pressure drop across the membrane is 30 kPa, and the fluid viscosity is $1.5 \times 10^{-6} \text{ kPa s}$. With clean membranes, the transmembrane flux using buffer in the system is $110 \text{ liters m}^{-2} \text{ h}^{-1}$ for this pressure drop. After 2 min of operation with the protein solution, the transmembrane flux is $15 \text{ liters m}^{-2} \text{ h}^{-1}$. At this point, the system is operated with the buffer only in the backflushing mode with negative transmembrane pressure until a constant transmembrane flux is reached. Then, the system is operated with the buffer in the normal mode (positive transmembrane pressure), and the steady-state transmembrane flux is $35 \text{ liters m}^{-2} \text{ h}^{-1}$ at a pressure drop of 30 kPa. It has been determined that the flux due to the osmotic pressure difference is negligible. Estimate the irreversible fouling resistance (R_{fp}) and resistance due to concentration polarization and a gel layer (R_p) for the membrane after 2 min of operation with the protein solution.

REFERENCES

1. Grace, H. P. (1953). Resistance and compressibility of filter cakes. *Chem. Eng. Prog.*, vol. 49, p. 303.
2. Choudhury, A. P. R., and Dahlstrom, D. A. (1957). Prediction of cake-washing results with continuous filtration equipment. *AIChE J.*, vol. 3, p. 433.
3. Michaels, A. S. (1968). New separation technique for the CPI. *Chem. Eng. Prog.*, vol. 64, p. 31.
4. Blatt, W. F., Dravid, A., Michaels, A. S., and Nelsen, L. (1970). Solute polarization and cake formation in membrane filtration: Causes, consequences, and control techniques. In *Membrane Science and Technology*, J. E. Flinn, ed., Plenum Press, New York, p. 47.
5. Bird, R. B., Stewart, W. E., and Lightfoot, E. N. (2002). *Transport Phenomena*, 2nd ed., Wiley, New York.
6. Calderbank, P. H., and Moo-Young, M. B. (1961). The continuous phase heat and mass-transfer properties of dispersions. *Chem. Eng. Sci.*, vol. 16, p. 39.
7. Belfort, G., Davis, R. H., and Zydney, A. J. (1994). The behavior of suspensions and macromolecular solutions in crossflow microfiltration. *J. Membrane Sci.*, vol. 96, p. 1.
8. Porter, M. C. (1972). Concentration polarization with membrane filtration. *Ind. Eng. Chem. Prod. Res. Dev.*, vol. 11, p. 234.
9. Zydney, A. L., and Colton, C. K. (1986). A concentration polarization model for the filtrate flux in cross-flow microfiltration of particulate suspensions. *Chem. Eng. Commun.*, vol. 47, p. 1.
10. Eckstein, E. C., Bailey, P. G., and Shapiro, A. H. (1977). Self-diffusion of particles in shear flow of a suspension. *J. Fluid Mech.*, vol. 79, p. 191.
11. Perry, R. H., Green, D. W., and Maloney, J. O., eds. (1997). Liquid-solid operations and equipment (Section 18) and Membrane separation processes (Section 22). In *Perry's Chemical Engineers' Handbook*, 7th ed., McGraw-Hill, New York.
12. Rushton, A. (1996). Filter media. In *Solid-Liquid Filtration and Separation Technology*, A. Rushton, A. S. Ward, and R. G. Holdich, eds., VCH Publishers, Weinheim, Germany, p. 107.
13. Zeman, L. J., and Zydney, A. L. (1996). *Microfiltration and Ultrafiltration*, Dekker, New York.
14. Hallstrom, B., and Lopez-Leiva, M. (1978). Description of a rotating ultrafiltration module. *Desalination*, vol. 24, p. 273.
15. Robertson, B. C., and Zydney, A. L. (1990). Protein adsorption in asymmetric ultrafiltration membranes with highly constricted pores. *J. Colloid Interface Sci.*, vol. 134, p. 563.
16. Rajabzadeh, A. R., Moresoli, C., and Marcos, B. (2010). Fouling behavior of electroacidified soy protein extracts during cross-flow ultrafiltration using dynamic reversible-irreversible fouling resistances and CFD modeling. *J. Membr. Sci.*, vol. 361, p. 191.
17. Hilal, N., Ogunbiyi, O. O., Miles, N. J., and Nigmatullin, R. (2005). Methods employed for control of fouling in MF and UF membranes: a comprehensive review. *Sep. Sci. Tech.*, vol. 40, p. 1957.
18. Datar, R. V., and Rosen, C.-G. (1993). Cell and cell debris removal: Centrifugation and cross-flow filtration. In *Biotechnology*, vol. 3, *Bioprocessing*, H.-J. Rehm and G. Reed, eds., VCH Publishers, Weinheim, p. 486.
19. Scopes, R. K. (1994). *Protein Purification*, 3rd ed., Springer-Verlag, New York.
20. Tutunjian, R. S. (1985). Ultrafiltration processes in biotechnology. In *Comprehensive Biotechnology*, vol. 2, *The Principles of Biotechnology: Engineering Considerations*, M. Moo-Young, ed., Pergamon Press, Oxford, p. 411.