Factors Influencing Ultrafiltration Scale-Up

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An ultrafiltration feed stream flows parallel to the surface of the membrane. A fraction of the feed stream permeates that membrane; the remaining fraction is retained and exits as retentate. In the absence of solute, flow through the membrane is accurately modeled by the Hagen-Poiseulle equation, which describes the flow of liquid through cylindrical pores (**1**) as shown in Equation 1 (see Equations box), where J = liquid flux, ε = membrane porosity, r = mean pore radius, Δp = transmembrane pressure (TMP), η = kinematic liquid viscosity, and Δx = pore length.

Equation 1 states that liquid flux is proportional to the transmembrane pressure and inversely proportional to the liquid viscosity, which is controlled by the solute concentration and the temperature.

When solute is present in the feed stream, permeating liquid brings solute to the membrane surface by convective flow. Resistance to flow increases as retained solute builds a solute layer on the membrane surface. The thickness of that solute cake depends on a number of factors, including the rate at which permeating liquid brings solute to the membrane surface, the rate at which solute back-diffuses into the feed stream, and the hydrodynamic shear of the tangentially flowing stream.

Successful exploitation of membranes in crossflow filtration therefore largely depends on effective fluid-management techniques (**1**). "By using hydrodynamic considerations, polarized solutes can be sheared from the membrane surface, thereby increasing the back diffusion and reducing the decline in performance" (**2**). Equation 2 has been traditionally used to predict flux for ultrafiltration applications.

As pressure increases, flux becomes independent of it. When TMP increases, a resultant increase in flux causes the solute cake (polarized layer) to thicken proportionally, which prevents further increase in flux. Figure 1A shows this flux-versus-pressure relationship. The mass-transfer coefficient (k) also can be determined from that plot, from the semi log plot of flux vs. protein concentration, where the slope of the line is proportional to k (Figure 1B). Figure 2 shows that k is a function of the crossflow (recirculation flow) velocity, with k increasing as crossflow velocity (flow rate) and shear rate increases.

Dependence of the mass-transfer coefficient on crossflow velocity has been accurately correlated (**2**,**3**). For laminar flow the correlation is as shown in Equation 3, where γ is shear rate, and $\gamma = 8v/d$ for flow through tubes and $6v/h$ for flow through rectangular channels (v is solution velocity, d is tube diameter, h is channel height); L is length of the membrane

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Equation 1:

$$J = \frac{\varepsilon \cdot r^2 \cdot \Delta p}{8 \cdot \eta \cdot \Delta x}$$

Equation 2:

$$J_w = k \ln\left[\frac{C_g}{C_f}\right]$$

Equation 3:

$$k = 0.816\left[\frac{\gamma}{L} D^2\right]^{0.33}$$

Equation 4:

$$k = 0.023\left(\frac{1}{dh}\right)^{0.20}\left(\frac{p}{u}\right)^{0.47}(D)^{0.67}(v)^{0.80}$$

Equation 5:

$$\Delta P \propto f(Q)^n$$

Product Focus: Proteins, antibodies, parenteral products

Process Focus: Filtration (downstream processing)

Who Should Read: Process development and manufacturing, formulation development

Keywords: Ultrafiltration, flux, transmembrane pressure, scale-up

Level: Intermediate

flow path; and D is solute diffusivity. When flow is turbulent, the mass-transfer coefficient is proportional to velocity raised to the 0.80 power instead of to the 0.33 power as in laminar flow, as shown in Equation 4, where d_h is the hydraulic diameter and equals four times the cross-sectional area divided by the wetted perimeter, ρ is liquid density, and μ is the liquid's kinematic viscosity. Because of the greater dependence on velocity when flow is turbulent, improved benefits in flux can be realized when flow is increased. Figure 2 shows the relationship between flux and velocity for both laminar and turbulent flow.

This shear-dependent flux relationship is particularly true for PES-based (polyethersulfone) membranes, which are subject to considerable membrane fouling. The consequence of protein fouling is the formation of a protein gel that is irreversibly stuck to the membrane surface. Such gels become secondary membranes with protein rejection characteristics that mask the intrinsic properties of the membrane. Additionally, the gels are highly resistant to flow. Once formed, they cannot be adjusted through the control of process hydraulics, but if initial recirculation rates are sufficiently high, the initial flux values will be higher. When proteins do not foul on a membrane surface, dependence on recirculation velocity becomes markedly diminished, as has been reported for regenerated and modified regenerated cellulose membranes (**4**). This is true because the polarized protein layer does not have as great a resistance to flow. The interstitial spaces between native proteins are greater than for those of denatured protein gels. However, dependence on surface shear remains proportional to protein concentration.

Because those parameters are flux dependent (recirculation rates and pressure profiles), controlling and understanding them is clearly important in the scale-up of any crossflow process.

Ultrafiltration and diafiltration processes are developed at laboratory or process-development scale. Their successful implementation is the result of careful analysis of process hydraulics: recirculation flow rates, pressure profiles, retentate flow channel, permeate flux values, and membrane surface area. As the processes are scaled up from research to pilot scale and again to commercial production, process engineers are often faced with limited data that at first glance seem adequate for straightforward scale-up, but in fact lack critical information. Failing to recognize critical parameters may result in inaccurate scale-up performance predictions. Shortfalls in performance can have serious economic consequences, not the least of which are added labor costs and yield losses.

For successful scale-up from small clinical-scale volumes to pilot or commercial production scale, the EMEA (the European Agency for the Evaluation of Medical Products) recommends the following: "It is expected that during the development stage, the manufacturer of the product should gain sufficient information about the behavior and the physical and chemical properties of the drug substance, the composition of the product in terms of active ingredient(s) and key excipients, and the manufacturing process clearly define the critical steps in the manufacturing process (**5**)."

Small-scale experiments conducted in the laboratory generate data, including data from equipment (elbows, valves, and pumps) that may skew performance expectations because of the inherent nature of the system's plumbing. Those effects cannot be minimized or disregarded.

Elucidating a process allows decision making based on selecting optimal parameters. Experiments must be conducted looking at flux versus TMP and log flux versus log recirculation rate, identifying the optimal pressures and flows (**6–8**). Such experiments also provide reference values for the scaling process.

Materials and Methods

All experiments reported here were conducted on Sartorius Sartoflow Alpha and Beta Crossflow systems. The systems include a positive displacement pump, three pressure transducers, flow meters, data recorder, jacketed vessel, sanitary diaphragm valves, and a Sartocon Slice or Sartocon 3 filter holder, respectively. Filter cassettes used are Hydrosart 30,000 kd (part numbers 3021445906E-SG, 3051445901E-SG, and 3081445902E-SG).

Flux measurements were made at controlled crossflow velocities and TMP values. TMP studies were conducted using 15, 25, 35, and 45 psi with filtered water or bovine serum. Cassettes were cleaned with 1N NaOH after exposure to serum and then rinsed with water according to the manufacturer's recommended procedures. Membranes were equilibrated with 0.9% saline before each experimental run in which testing included exposure to serum. All experiments were conducted at 15 °C ± 0.5 °C.

System Hydraulics

Scale-up process piping is typically designed around the desired flow rate, pressure, and fluid flow velocity. Elbows, valves, and other process components within the fluid path have calculatable effects on both pressure and flow rate. Scaling-up a crossflow system, on the other hand, offers an additional hurdle: that of the hydrodynamics of the fluid flow through a cassette's feed and retentate's screened flow paths (**9**). The two components to a cassette's feed and retentate flow path are the feed and retentate flow manifolds internal to the cassettes. They feed and receive flow from the membrane flow channels and the flow channel itself. Crossflow cassettes have screens interleaved between each membrane pair on both the feed and permeate flow channels.

Those screens serve three purposes: They provide structural support for the membranes; they serve as a substrate into which the potting compounds may adhere; and the screen in the feed-flow path serves as a static mixer. Depending on a screen's designation, the gap between membranes can vary, and with it the pressure drop through that channel

Table 1: Reynolds numbers for water in a 1-inch tube (1 inch is the combined hydraulic diameter of the feed ports of a cassette); these values are used as a relative gauge to understand the magnitude of the turbulence (Reynolds value) in the manifold. Values are not corrected for the physical nature of the manifold.

Recirculation Flow Rate per Cassette	Fluid Velocity in Manifold m/sec versus Number of Cassettes			Nominal Reynolds Number in Manifold versus Number of Cassettes for Water		
cm^3/min	1	5	10	1	5	10
5,000	0.15	0.76	1.5	3,870	19,355	38,709
10,000	0.30	1.5	3.1	7,742	38,709	77,419
15,000	0.46	2.3	4.6	11,613	58,000	116,128

Table 2: Normalized experimental water flux calculated surface areas in comparison with published areas

Filter/ Cassette	Flux [L/min] at a TMP of 30 psi at t (5 min)	Published Area (m^2)	Flux Based on Published Areas (L/hm^2)	Calculated Surface Areas (m^2)	Flux Norm. (L/hm^2)
47 mm disk	0.0067	0.00145	277.2	0.00145	277.2
Slice 200	0.0981	0.02	294.3	0.0212	277.2
Slice	0.548	0.1	328.9	0.1186	277.2
Sartocon 2	2.389	0.6	238.9	0.517	277.2

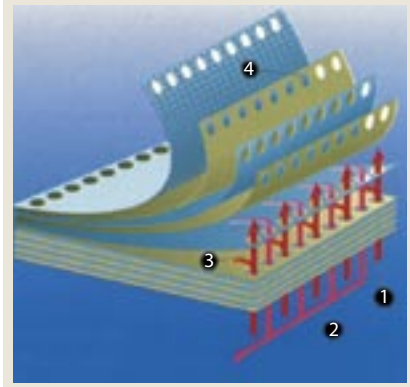
Table 3: Cassette scale-up factors determined experimentally, using published values and QC lot release data

Filter/Cassette	Mean Factor Based on Experimental Water Flux	Factor Based on Published Area	Factor Based on Experimental Serum Flux	Factor Based on QC Water Flux
Slice 200 (200 cm^2)	1	1	1	1
Slice (1000 cm^2)	5.6	5	7.5	7.5
Sartocon 2 (6000 cm^2)	4.4	6	4.4	4.8

Table 4: Flux values for bovine serum on a variety of cassettes from 200 cm^2 to 6 m^2 (lines 3–8)

		Flux (L/min) Compared with Transmembrane Pressure				
1						
2	Cassette/TMP (bar)	1	1.5	2	2.5	3
3	1 × Slice 200	0.02349	0.0249	0.0253	0.0254	0.0255
4	1 × Slice	0.1761	0.186	0.19	0.1915	0.1905
5	1 × Sartocon 2	0.8	0.832	0.856	0.861	0.860
6	2 × Sartocon 2	1.63	1.74	1.76	1.78	1.78
7	5 × Sartocon 2	3.68	3.84	3.89	3.91	3.89
8	10 × Sartocon 2	7.78	8.08	8.25	8.34	8.35
9	Predicted Flux for 10 Sartocon Cassettes	8.4564	8.964	9.108	9.144	9.18
10	Error % = 1 – (Actual Flux ÷ Predicted Flux)	8%	10%	9%	9%	9%

Figure 3: Diagram of a cassette, where 1 is the feed flow through the feed ports of the cassette, 2 is the retentate flow, 3 is the feed flow through the membrane flow channel, and 4 is the membrane



varies. As part of the cassette's construction, the screens and membranes make up the wall of the manifold feeding the membrane feed channel (Figure 3). The cassette's internal manifold is therefore not smooth like process tubing, so wall drag increases resistance to flow to a much greater extent than that observed for process tubing. Flow rate through the feed manifold increases with surface area (adding cassettes) because recirculating flow rate per square meter of membrane is generally kept constant as the process is scaled up. Drag at the edges of the manifold can cause the feed solution to transition from laminar to turbulent flow especially at the proximal cassette(s). As that happens, pressure drop develops in this channel. Pressure drop is directly tied to fluid viscosity in the flow path. Figures 4 and 5 show the effect of viscosity on pressure drop. Pressure drop is measured with water and with bovine serum and then plotted against surface area. Sartorius 30,000 MWCO cassettes with 200-, 1000-, and 6000-cm^2 cassettes were used in this study.

Regardless of the TMP and inlet and outlet pressures, the pressure differentials remained constant at any one flow rate (data not shown). Reynolds numbers increased as viscosity decreased. Pressure drop likewise increased as the flow through the manifold transitioned into turbulent flow. This transition occurs at lower flow rates when the viscosity

Figure 1A: Bovine serum flux through a Sartorius Sartocon 0.7m² 100k PES ultrafilter cassette at three recirculation flow rates

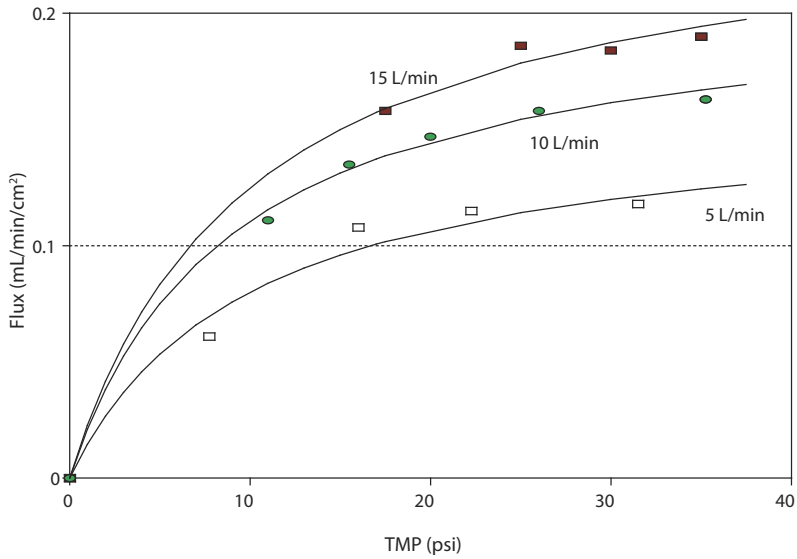


Figure 1B: Flux vs. protein concentration at two different recirculation rates for skim milk diluted to about 0.2% protein (Sartorius Hydrosart 30kd Membrane Area = 6000 cm²).

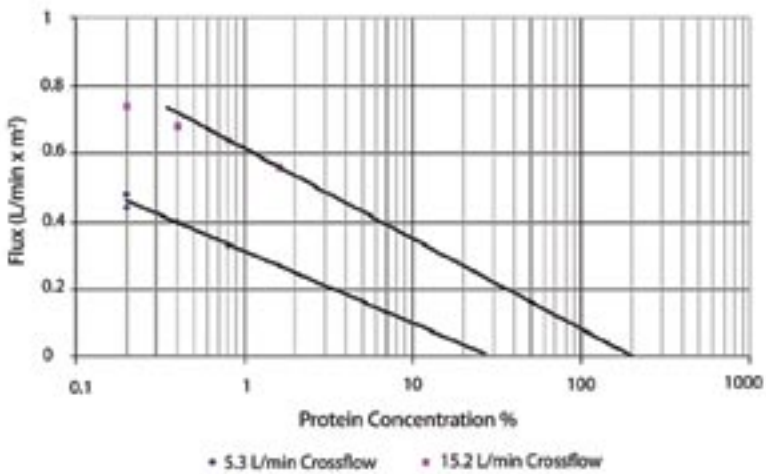
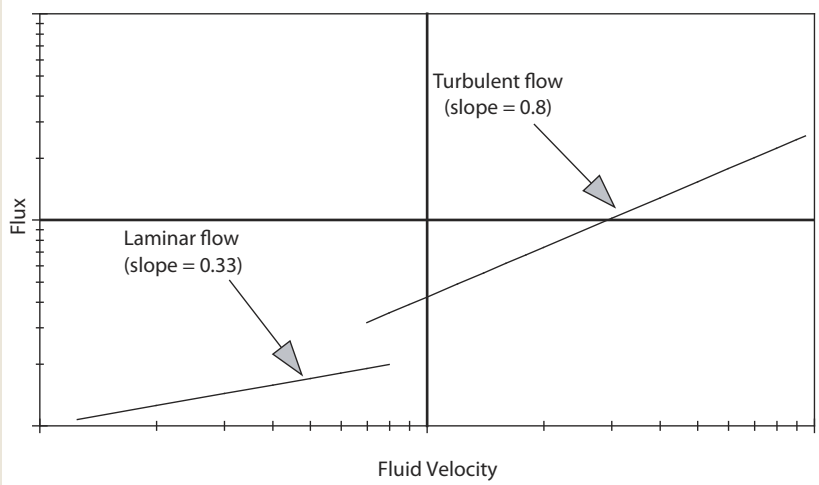


Figure 2: Flux as a function of fluid velocity



is low. Cheryan shows the general relationship of pressure drop (ΔP) being directly proportional to flow rate (Q) (4). This relationship determines whether flow rate is laminar or turbulent using Equation 5, where for values of n = 1, flow is laminar and where for values of n > 1.4, flow becomes turbulent (Table 1).

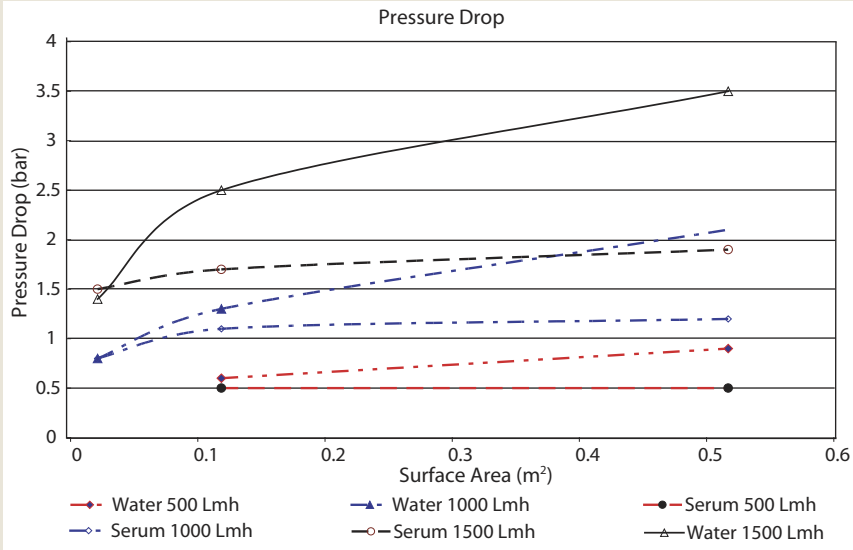
At similar recirculation velocities the pressure drops associated with those two flow paths make it more difficult to predict scale-up data using the standard conventional engineering procedures. As cassettes are added to a system, the pressure required to maintain a constant recirculation rate per square meter must increase. This increase may not be linear; it can vary as a function of the screen designation and the width of the flow channel gap. In short, each membrane flow path creates a resistance to flow. As flow paths are added, additional pressure is required to overcome the additive effect of pressure drops.

Turbulence Induced Pressure Drop

The pressure drop data shown in Figure 5 implies that with water, a significant pressure drop happens at high flow rates as a result of turbulence. This turbulence occurs at the proximal entrance into the first cassette's feed port where two "elbow" effects are created by the change in fluid path direction. Flow enters the holder and exits at a 90° angle into the cassette. A part of the flow then changes direction a second time, entering the membrane flow channel. Depending on the rate of flow and those abrupt changes in flow direction, a region of turbulence can be created when the flow rate is sufficiently high. As cassettes are added, the effect is eliminated (Figure 6) because the solution can change back into laminar flow. As more cassettes are added, additional flow is required to maintain a constant flow per cassette, and turbulent flow can once again be reinitiated if the flow rate is sufficiently high.

The flow rate for small surface area cassettes <200 cm² relative to both the inflection distances and the port size assures smooth flow throughout,

Figure 4: Observed pressure drop with water and bovine serum using Sartocon Slice 200 (200 cm^2), Slice (1000 cm^2), and Cassette (5200 cm^2) at recirculation rates of 500, 1000, and 1500 Lmh (liters per square meter per hour)



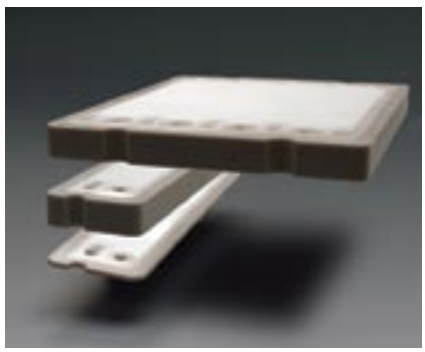


Photo 1: Sartocon Cassette; the patented integrated framework leads to the elimination of silicone gaskets between each individual cassette.

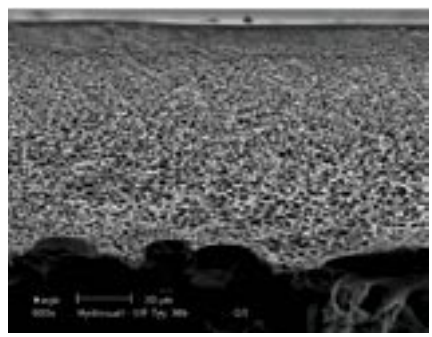


Photo 2: SEM of a void free 30k Sartorius Hydrosart ultrafilter membrane

resulting in no turbulence-induced drop in pressure. At 1000 cm^2, turbulence-induced pressure drops can be inferred at high recirculation rates.

Because turbulence and viscosity are inextricably linked, the pressure drops seen with water are not observed with product feed streams. Depending on the nature of a product's viscosity at the start, middle, and end of a concentration run, turbulence-induced pressure drops should be accounted for and controlled.

Pressure Drop–Induced Flux Loss

When turbulence induced pressure drops occur, the consequence is a drop in permeate flux due to loss of motive force. At low recirculation flow rates, solvent flow is greater than at higher rates at the same calculated TMP. This is due to the pressure drop in the feed ports. When the pressure drop occurs before entering the membrane flow channel, the actual pressure available for permeation is reduced even though the apparent TMP's are the same (Figure 7).

Surface Area

Surface area is the amount of effective membrane in a system. Commercially available "scalable" cassettes are available in surface areas from about 50 cm^2 to 2.5 m^2. Cassettes from a variety of manufactures all claim to maintain common geometries within their respective product lines, making them suitable for scale-up and scale-down studies.

Sources for Variation in Flux

Surface Area: Cassette surface areas reported by most cassette manufactures come in whole-number increments. Rounding errors can therefore contribute considerably to errors in scaling (Table 2).

Available Surface Area: Filter cassettes are an assembly of components (Figure 3) held together by a potting compound, which is either a silicone (Photo 1) or an epoxy resin.

The potting compound penetrates to a certain depth around the margin of the cassette, sealing its components together. Minor variations affect the available surface area. Cassettes come in two different but similar geometries over the range of available surface areas: 0.1 m^2 and smaller cassettes have a single feed or retentate and one permeate port at each end, compared with larger cassettes that have five feed or retentate and four permeate ports at each end. The rectangular shape of these different formats results in a greater perimeter and membrane area for the smaller format. Variations in potting depth, therefore, have a bigger influence on the smaller format than on the larger format.

Membrane Casting and Cassette Lot-to-Lot Consistency

Additional sources of flux variance arise from flux variations across a manufactured lot and minor lot-to-lot variances. For ultrafilters, the primary release criterion is the membranes' rejection coefficient. The window for flux can be rather broad in comparison, with acceptance based on rejection and possibly varying over a twofold range (**10**). Within any casting of membrane, variation can be seen in samples from the center of the casting belt to its edge. Membrane QC procedures will include looking at a pattern of samples from different parts of the casting lot.

Although casting processes are very well controlled, minor variations in the thickness of the active layer also affect flux. A typical membrane is 100 to
200 µm thick. But the active portion of an ultrafilter 1–200 µm thick is somewhere between 1 µm and 10 µm depending on the polymer. The slightest variation in this layer consequently affects flux (Photo 2).

Cassettes with small amounts of

surface area are subject to variance in the actual available membrane surface area, which can significantly influence the observed flux. As the area increases, these variances become less and less noticeable.

Analysis of multiple membrane lots (data not shown) support the supposition that cassettes with smaller surface areas (1000 cm^2 or less membrane) may have statistically greater flux variation than those with greater surface areas. The primary reason can be attributed to the observation that cassettes with 1000 cm^2 or less have a far greater edge surface-to-membrane ratio than the larger cassettes (Photo 1) and can therefore have greater variations in membrane flux rates.

The average standard deviation as a percent of the mean normalized water flux was used to compare the different sized cassettes. As expected, the values increase as the cassette surface area decreases. In the analysis of eight membrane casting lots from which 104 lots of cassettes were made of various sizes, flux range/standard deviation increased from ±6% of mean flux for a 0.7m^2 cassette to ±8% for 1000-cm^2 cassettes and to ±22% for 200-cm^2 cassettes (Table 3).

Predicted flux for 10 cassettes (line 9) is calculated by taking the measured flux from a Slice 200 (200 cm^2) cassette and multiplying it by 10 times the product of the QC-based data scale up factors from Table 3 for the Slice 200 to Slice (7.5) and the Slice to Sartocon (4.8) (Table 4). The % error (line 10) is 1–(actual flux for 10 cassettes on line 8 divided by the predicted flux for 10 cassettes on line 9).

Figure 5: Pressure Drop in 1, 5, and 10 cassettes with water and serum

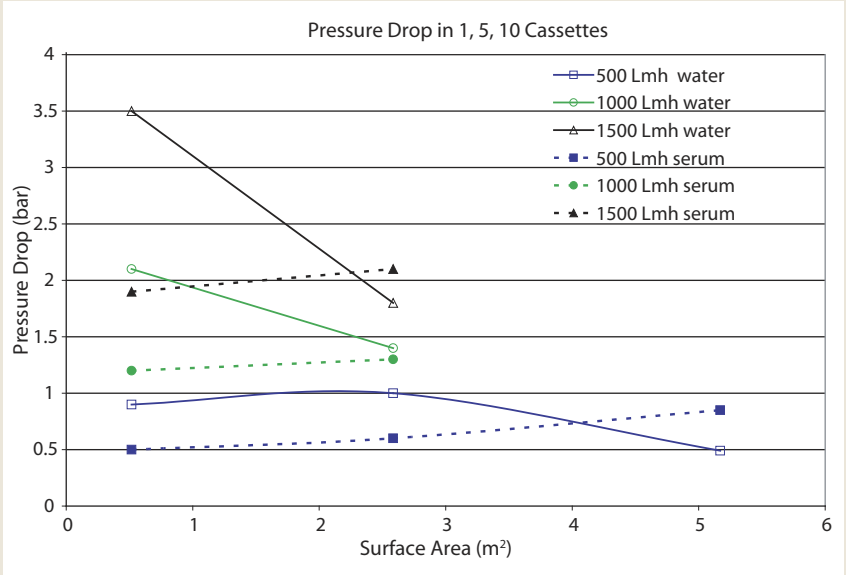
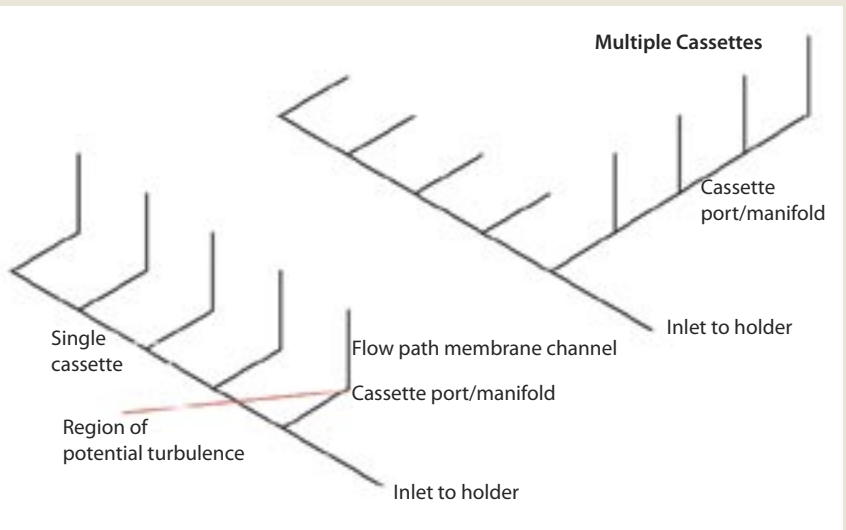


Figure 6: Diagram of flow path into a filter holder and cassettes



Single-Lot versus Mixed-Lot Cassette Manufacturing

The strategies for manufacturing cassettes in single or mixed lots can significantly affect the statistical analysis of water flux per inter- and intracassette lots. Although mixing membrane casting lots in a cassette lot will result in increased uniformity of both flux and rejection performance, it robs a user's ability to select cassette/membrane lots based on rejection, and it blurs regulatory issues regarding traceability. Our company's current strategy is to use only a single lot of membrane for any lot of cassettes. Although this approach widens the flux range, it complies with the cGMP concept of lot specificity and component traceability.

Improving Scale-up Predictions

With the availability of caustic-stable-modified regenerated cellulose membranes, you can establish lower recirculation rates at higher TMPs for a given desired flux (**6,11**). The diminished requirement for high shear on regenerated cellulose membranes notwithstanding, flux still shows a dependence on pressure and recirculation velocities, especially at higher protein concentration levels. Careful analysis of pressures and scaling factors allows scientists and engineers to more accurately predict scale-up performance using regenerated cellulose membranes compared with PES-based membrane polymers, which require higher circulation rates. Scaling predictions using average water flux from multiple membrane lots allows users to take a single scaling step from 200 cm^2 to 6 m^2 or more. This scale-up approach predicts performance that falls well within the standard accepted scientific error of ±10%.

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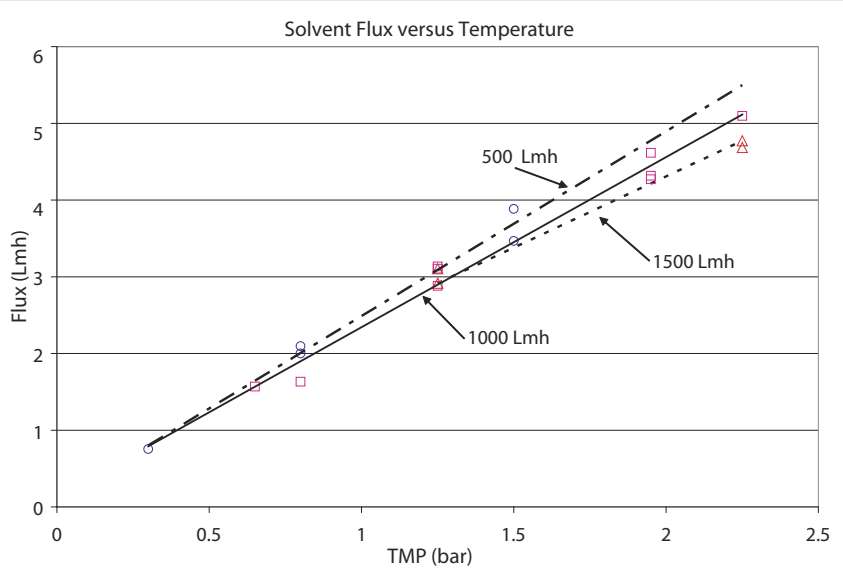
Figure 7: Solvent flux (water) is measured at recirculation flux values of 500, 1000, and 1500 Lmh on a Slice 200 (200 cm^2), Slice (1180 cm^2), and on 1, 5, 10, and 20 Sartocon Cassettes (5200 cm^2 each). All values are plotted together, making no distinction between the devices and relative surface areas. Trend lines are automatically drawn by Excel through the data sets.



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