Recovery Optimization of Process Scale Ultrafiltration/ Diafiltration Systems

Quantitative assessment of performance of common recovery procedures

Introduction

An important performance parameter in any biopharmaceutical process is process yield. Low process yields in one or more process steps can not only result in loss of high-value protein product, but can also impact production capacity and availability to the patient. Ultrafiltration process steps are often located at the end of the downstream process, where the bulk drug substance represents the full cost of production. Therefore, it is important to have optimum process recovery procedures (Table 1).

In recovery operations for ultrafiltration systems, there is a trade-off between recovery and product dilution. Generally, the yield can be improved by increasing chase or flush buffer volumes. However, the bulk drug substance concentration specification limits the amount of flush volumes that can be used to increase recovery.

Ultrafiltration process yields are affected by the system design and the recovery procedure. To ensure high yields, an ultrafiltration system hardware design should be consistent with “best practice” principles such as drain ability and minimum hold-up volume (Table 2). Hold-up is defined here as the flooded volume of the feed line from the pump, the feed retentate volume of the membranes and the retentate line to the vessel.

The recovery procedure should be designed to provide optimal yield values. A variety of different methods and flowpaths are used, some with air, buffer or gravity assist.

Bench scale recovery studies are useful for assessing membrane device/process performance. However, they do not adequately predict product recovery at the process scale. Close resemblance between the small scale equipment and the process scale installation can result in a more predictive and relevant study. Our recovery study was executed at the 20 m^2 scale. The 20 m^2 scale represents a fully loaded, 1 level high Pellicon® Cassette UF/DF process scale holder. Larger systems are configured by adding (stacking) additional holders in parallel. The 20 m^2 system size represents the best compromise between relevant configuration and practical limitations of scale (cost of membrane, protein, hardware, etc.).

A Case for Optimized Recovery for Ultrafiltration/ Diafiltration Systems
Cell culture harvest every 14 days
25 batches/year
2% recovery increase (93% to 95%)
Additional 1/2 batch of product/year

Table 1.

“Best Practice” UF/DF System Design Principles for Recovery
System drain located at a clearly defined low point in the feed/ retentate piping.
Feed/retentate piping sloped towards the system piping low point for good drainage. Minimum slope should be at least 0.12-in. of gradation/ft of pipe run.[1]
Recovery assist fluids (buffer, compressed gas) are introduced to the system at a clearly defined high point in the feed/retentate piping.
Correct sizing of the process piping (5–12 ft/sec) where possible.
Orient system components to take advantage of gravity drain where possible.
Minimize the length of piping runs.
Minimize the number of pipe connections (pulls) on the feed/ retentate recirculation loop.

Table 2.

Objective

The objective of this study was to quantitatively assess the performance of common recovery procedures used in the biopharmaceutical industry. Two recovery procedures were evaluated:

Method 1: Reverse Plug Flow Buffer Displacement

Method 2: Air Blowdown from High Point to Low Point

Air blowdown is often used to displace residual "held-up" product after product recovery. An air blowdown can increase recovery without a dilution effect. However, the low viscosity of air can force a path of least resistance, leaving behind significant amounts of protein product. Additionally, an air blowdown can result in foaming (potentially impacting product quality). A reverse plug flow buffer displacement strategy displaces the protein without foaming effects at the potential cost of protein product dilution. It was decided to assess these two recovery flowpaths to determine the effectiveness of each method.

The study was performed using a representative protein solution on a single system. Yield was calculated for each recovery procedure test run as a quantitative measure of the procedure's performance. This work was extended with an additional experiment to observe a Method 1 recovery of a high concentration protein solution.

Methods & Materials

Equipment and materials

- 20 x 1.14 m² Pellicon® 3 cassettes, 10 kD Ultracel® membrane
- 10g/L BSA solution, 15–16 L (diluted from 30% BSA solution SeraCare with 0.9% NaCl saline buffer)
- Cogent® process scale TFF system automated with Common Control Platform® CCP® v.6 tangential flow filtration system
- Flexible biocontainers for recovered product (20 L)
- 0.2 N NaOH for cleaning and 0.1 N NaOH for storage between cycles
- UV meter for product recovery port on Cogent® process scale TFF system, 0 to 2 AU
- Sample vials 15 mL
- UV spectrophotometer for sample analysis
- Floor scale

Equipment description and setup

Product recovery from a UF/DF system is a function of system design as well as flow path. The system that was used was a Cogent® process-scale tangential flow filtration system. The system design was optimized for low minimum working volume and high drain ability.

The basic system configuration is shown in Figure 1.

System Nomenclature	
C	Conductivity
CWR	Chilled Water Return
CWS	Chilled Water Supply
FE	Flow Element
HX	Heat Exchanger
LE	Level Element
M	Mass (floor scale)
PF	Filtrate Pressure
PF	Feed Pressure
Pr	Retentate Pressure
Tb	Turbidity
TT	Temperature Transmitter
UV	Ultraviolet Absorbance Meter

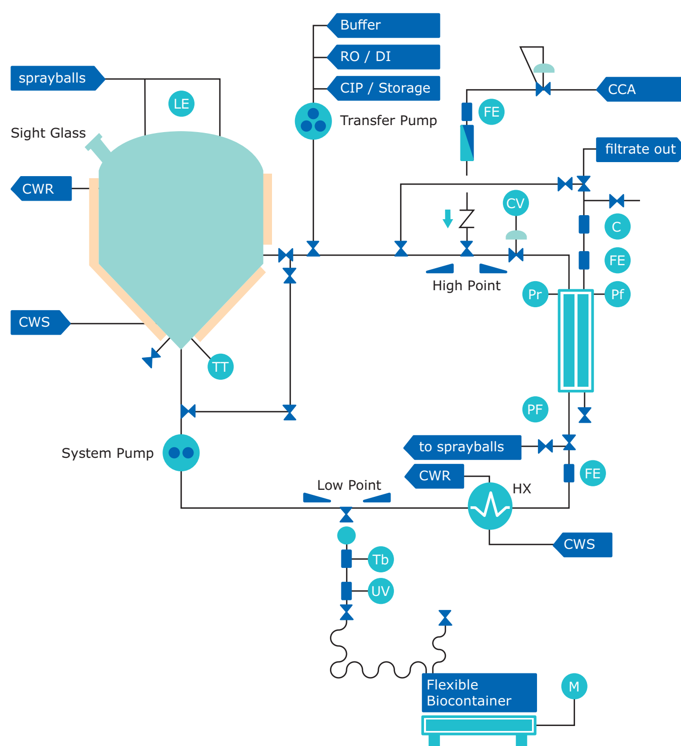

Figure 1.

UF/DF Recovery Study Equipment Configuration

Methods

The overall order of process steps was:

Prepare System: The prepare system step is designed to remove the storage buffer (0.1 N NaOH) from the system and to equilibrate the system into 0.9% NaCl buffer. A series of rinses and recirculations were used to achieve this goal, as shown in Table 3.

Load Product: The load product step in an actual UF/DF run consists of a concentration and diafiltration step. During this step, the membrane becomes "conditioned" (filtrate flux declines due to the dynamics of the protein concentration gradient against the membrane wall and non-specific binding of protein to the membrane). The first effect is hydrodynamic and can be monitored by observing pressures and the filtrate flow. The second effect is likely to be both hydrodynamic and kinetic or time-based. However, since non-specific binding to regenerated cellulose membrane is known to be very low, it was decided that the exposure time parameter could be minimized. Therefore, 1 minimum working volume of the protein test solution was added to the system through the vessel sight glass. The test solution was slowly added to minimize foaming after being sampled. Finally, the test solution was re-circulated at ~4.4 lpm/M^2 in the total recycle mode with the filtrate open for 30 minutes. This re-circulation rate was sufficient to reach stable pressures and filtrate flowrates.

Recover Product: The product recovery methods are described in detail below.

Clean-in-place: The clean-in-place step is designed to remove proteinaceous residues from the system and membrane surfaces. A series of rinses and recirculations of 0.2N NaOH at ambient temperature were used to achieve this goal, as shown in Table 4.

Store: After cleaning, the system was flushed and normalized water permeability (NWP) was measured. Next, the system was placed in 0.1N NaOH storage buffer to prevent microbial growth. The storage steps are outlined in Table 5.

System Preparation Steps

Operation	Control	Vol (L/M^2)	Time (min)	Comments
Gravity Drain	time, level </= 0.5 L	-	2	All valves open - drains storage buffer
System Blowdown	time	-	5	Blowdown by sequential flowpaths/3–5 psig air
Vessel Rinse	~126 lpm	-	5	50 L RO/DI recycle via sprayballs
System Flush	level <2 L stop	8.8	-	RO/DI single pass filtrate open @ 4.4 Lpm/M^2 feed flowrate
Gravity Drain	time, level </= 0.5 L	-	2	All valves open - drains storage remainder of flush
System Rinse	level <2 L stop	4.4	-	Total recycle filtrate open (pulsing across drain valves)
Gravity Drain	time, level </= 0.5 L	-	2	All valves open - drains remainder of rinse
System Blowdown	time	-	5	Blowdown by sequential flowpaths/3–5 psig air
Buffer Equilibration	time	2	10	Total recycle filtrate open - 0.9% NaCL buffer
Gravity Drain	time, level </= 0.5 L	-	2	All valves open - drains storage buffer
System Blowdown	time	-	5	Blowdown by sequential flowpaths/3–5 psig air

Table 3.

System Clean-in-Place Steps

Step	Control	Vol (L/M^2)	Time (sec)	Comments
Vessel Rinse	100 lpm	-	300	50 L 0.2 N NaOH recycle via sprayballs
System Flush	level <2 L stop	2.2	-	0.2 N NaOH single pass filtrate open @ 4.4 Lpm/M^2 feed flowrate
Gravity Drain	time	-	120	All valves open - drains remainder of rinse
System Rinse	level <2 L stop	3.5	600	0.2 N NaOH total recycle filtrate open vessel bypass
Gravity Drain	time	-	120	All valves open - drains remainder of rinse
System Rinse	level <2 L stop	2.2	1800	0.2 N NaOH total recycle filtrate open back to vessel
Gravity Drain	time	-	120	All valves open - drains CIP solution

Table 4.

System NWP, Integrity Test & Storage

Step	Control	Vol (L/M^2)	Time (sec)	Comments
Vessel Rinse	~126 lpm	-	5	50 L RO/DI recycle via sprayballs
System Flush	level <2 L stop	8.8	-	RO/DI single pass filtrate open @ 4.4 lpm/M^2
Gravity Drain	time, level </= 0.5 L	-	2	All valves open - drains storage remainder of flush
NWP Measurement	level <2 L stop	4.4	-	Total recycle filtrate open (pulsing across drain valves)
Gravity Drain	time, level </= 0.5 L	-	2	All valves open - drains storage remainder of rinse
System Blowdown	time	-	5	Blowdown by sequential flowpaths/3–5 psig air
Integrity Test	feed/ret press = 30 psi			</= 1200 cc/min @30 psid
System Rinse	time	0.88	600	0.1 N NaOH total recycle filtrate open back to vessel @ 4.4 lpm/M^2. NWP measured and recorded

Table 5.

Method 1: Reverse Plug Flow Buffer Displacement

After the 30-minute loading step, the system was stopped and the feed vessel sampled. The system was recirculated at 0.79 lpm/M^2 (feed flux) for 10 minutes with the filtrate closed to de-polarize the membrane.

After the depolarization step, the test solution was recovered using Method 1 as described below:

1. **Vessel Recovery:** The sample tap was purged and the feed vessel was sampled again to assess the depolarization effect. The content of the feed vessel was pumped through the system pump at ~3.6 lpm to the recovery container, as shown in Figure 2.
2. **Retentate Line Recovery:** Once the vessel recovery was completed, the feed/retentate line was recovered by pumping 0.9% NaCl buffer back through the line, feed/retentate side of the membranes and out into a second recovery container at approximately 10 lpm by using the transfer pump. The buffer recovery was stopped when the A280 UV signal dropped to 0.2-0.1 absorbance units (AU). The flow path is shown in Figure 2.
3. **Retentate Line Stub Recovery:** The last two steps of the recovery for Method 1 are shown in Figure 2. The retentate line stub (the portion of the retentate line that runs from the entry point of the buffer line to where the retentate line enters the vessel) working volume was calculated to be ~600 mL. A fixed volume of buffer (~1000 mL or 1.5 x 600 mL) was pumped through this line and recovered into the system vessel. The retentate diptube stub line recovery volume was then was pumped at ~3.6 lpm using the system pump to the recovery container.
4. **Mass Balance Recovery:** A mass balance recovery was performed next to quantify the unrecovered protein product. One minimum working volume (~15 L) of buffer was added to the vessel through the transfer pump and re-circulated through the feed/retentate side of the system at ~1 lpm/M^2 with the filtrate valves closed for 10 minutes. After 10 minutes, the content of the feed vessel was pumped at ~3.6 lpm to a third recovery container. The system clean compressed air supply was set to ~5 psig. The system was then blown down to the recovery container for 30 seconds, then allowed to drain to the recovery container until the mass readout from the floor balance was stable.

Table 6 is a list of the sample types that were obtained during the Method 1 recovery test runs. Each sample was assigned a unique consecutive sample ID number.

Method 1 – Flowpath for Reverse Plug Flow Buffer Flush Recovery

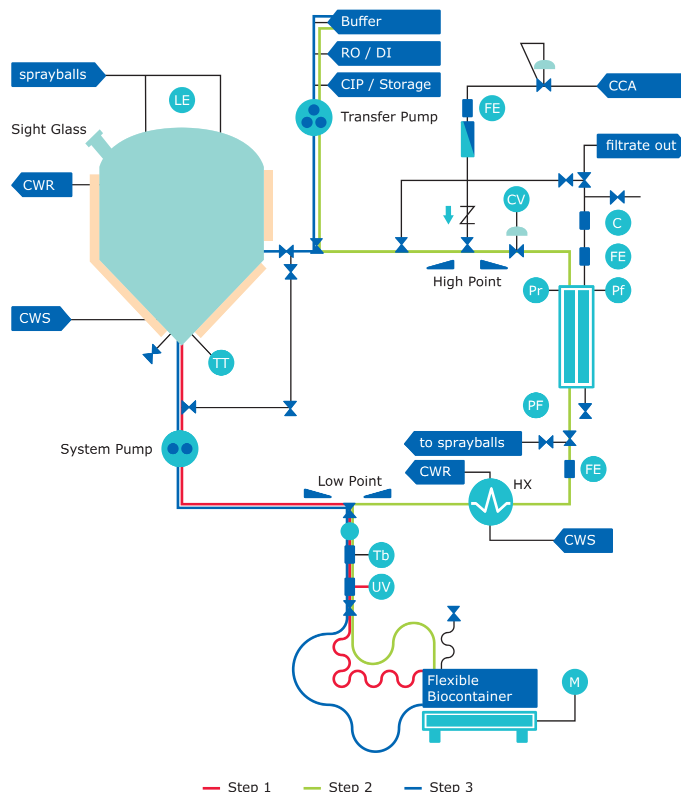

Figure 2.

Recovery Method 1 Sample List	
Step	**Description**
Feed	Feed sample was taken from the well-mixed charge of protein as it was introduced to the system. The mass of this sample was also noted for use in the subsequent yield calculations.
Pre-depolarization	Pre-depolarization sample was taken from the feed vessel at the end of the membrane conditioning step.
Drained from Sample Valve	Drained from the sample valve. This was actually a reminder to displace held-up protein from the sample valve after the depolarization step so as to obtain a representative sample. This sample was only a few mLs and was not analyzed.
Post-depolarization	Post-depolarization sample was taken from the feed vessel after the depolarization recirculation. It was compared to the pre-depolarization step to assess how useful the de-polarization step was at recovering protein from the membrane wall.
Vessel Recovery	Vessel recovery sample was taken from the recovery pool obtained from the system vessel.
Retentate Line Buffer Displacement	The retentate line buffer displacement sample was taken from the recovery pool obtained from the reverse plug flow buffer displacement of the feed line and retentate line.
Mass Balance Buffer Recirculation	The mass balance buffer recirculation sample was taken from the buffer recirculation done after the recovery to capture any remaining protein from the system and close mass balance.

Table 6.

Method 2: Air Blowdown from High Point to Low Point

After the 30-minute loading step, the system feed pump was stopped and the feed vessel sampled. The system was then recirculated at 0.79 lpm/M² (feed flux) for 10 minutes with the filtrate closed to depolarize the membrane.

After the depolarization step, the test solution was recovered using Method 2 as described below:

1. **Vessel Recovery:** The sample tap was purged and the feed vessel sampled again to assess the depolarization effect. The content of the feed vessel was pumped at ~3.6 lpm to the recovery container, as shown in Figure 3.
2. **Retentate Line Air Blowdown:** The feedline was recovered using a clean compressed air blowdown from the system high point to the low point recovery ports, as shown in Figure 6. The system regulator was set for ~5 psig and then the recovery was started. The air supply was shut off when 2 phase flow was seen. The feedline was allowed to drain for 1-2 minutes until the sight glass at the recovery port was clear.
3. **Retentate Line Stub Air Blowdown:** A new biocontainer was connected to the system and then the retentate line stub was recovered with an air blowdown to the vessel, as shown in Table 7. The system regulator was set for ~5 psig and then the recovery was started. The air supply was shut off when 2 phase flow was seen. The feedline was allowed to drain for 1-2 minutes until the sight glass at the recovery port was clear.
4. **Mass Balance Recovery:** A mass balance recovery was performed next. About 19 L of buffer was added to the vessel and re-circulated through the feed/retentate side of the system at ~1 lpm/M² with the filtrate valve closed for 10 minutes. After it was discovered that air was being entrained in the vessel pool during recirculation at lower volumes, 19 L was chosen. The larger volume requires the use of two recovery containers, given that the maximum span of the floor balance is only 20 L and the recovery containers will not physically hold the entire pool volume because of air trapped in the bag. After 10 minutes, the content of the feed vessel was pumped at ~3.6 lpm to a third recovery container. The system clean compressed air supply was set to ~5 psig. The system was then blown down to the recovery container for 30 seconds, then allowed to drain to the recovery container until the mass readout from the floor balance was stable.

Table 7 is a list of the sample types that were obtained during the Method 2 recovery studies. Each sample was assigned a unique consecutive sample ID number.

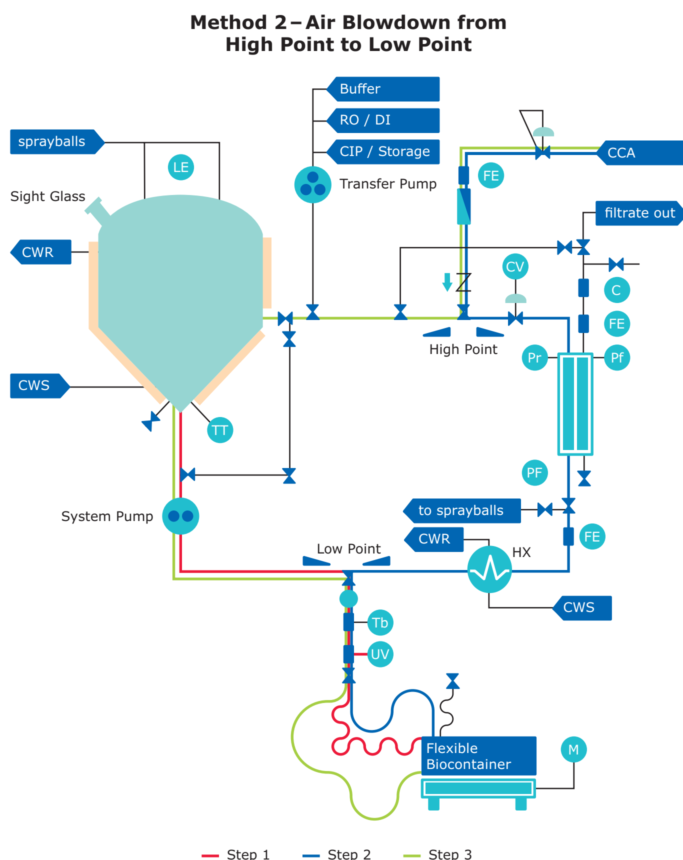

Figure 3.

Recovery Method 2 Sample List	
Step	**Description**
Feed	Feed sample was taken from the well-mixed charge of protein as it was introduced to the system. The mass of this sample was also noted for use in the subsequent yield calculations.
Pre-depolarization	Pre-depolarization sample was taken from the feed vessel at the end of the membrane conditioning step.
Drained from Sample Valve	Drained from the sample valve. This was actually a reminder to displace held-up protein from the sample valve after the depolarization step so as to obtain a representative sample. This sample was only a few mLs and was not analyzed.
Post-depolarization	Post-depolarization sample was taken from the feed vessel after the depolarization recirculation. It was compared to the pre-depolarization step to assess how useful the de-polarization step was at recovering protein from the membrane wall.
Vessel Recovery	Vessel recovery sample was taken from the recovery pool obtained from the system vessel.
Retentate Line Buffer Displacement	The retentate line buffer displacement sample was taken from the recovery pool obtained from the reverse plug flow buffer displacement of the feed line and retentate line.
Mass Balance Buffer Recirculation 1 and 2	The mass balance buffer recirculation sample was taken from the buffer recirculation done after the recovery to capture any remaining protein from the system and close mass balance.

Table 7.

Results

Figure 4 shows the recovery profiles for Method 1. Both the tank drain and the buffer displacement portions of the recovery method are shown. Figure 5 and Figure 6 show the % recovery by step (vessel recovery, buffer displacement/air blowdown and mass balance buffer recirculation) for Methods 1 and 2, respectively.

High Concentration Recovery

A general trend in the industry is increasing final protein concentration. It was desired to attempt a recovery of high concentration protein. Method 1 (reverse plug flow buffer displacement) was chosen as the recovery method to observe the dilution effect of a buffer push on recovery. We wanted to understand how much mixing would occur between the buffer and the protein. In other words, is a plug flow buffer push truly plug flow or does mixing occur at the interface of the protein and buffer solutions during recovery?

Figure 7 shows the relationship between concentration and viscosity of Bovine Serum Albumin.[2]

Work in the previous section utilized a protein solution that was 10 g/L (1%) and that had a water-like viscosity (~1 cp). It was decided that a viscosity of 10 cp (~280 g/L BSA) would have greater relevance to higher concentration biotech processes in development and emerging into manufacturing. The first two attempts at this experiment failed to achieve closure on the mass balance.

It was discovered that a great deal of foam was being created during the recirculation. It was hypothesized that this foam was not recoverable with conventional flushing methods, resulting in a mass balance loss. Additionally, high viscosity protein sample analysis with micropipettes proved to be challenging, leading to assay error. Because of these issues, the procedures used in the previous work were adapted before the third run was made.

- Minimum working volume for a UF system is defined as the minimum feed volume where the system can recirculate at process crossflow rate without entraining air into the batch. Observation though the sight glass on the vessel revealed that a 15 L feed volume was entraining air into the batch. Therefore, the feed volume was increased in 1 L increments until air no longer was entrained in the batch. The minimum working feed volume for this specific system is actually 19 L instead of 15 L.
- In the earlier work, the drained system was filled with the protein feed volume. This led to large amounts of foam generation upon startup of the recirculation for the high concentration experiment. Therefore, the loading procedure was amended to flood the system by recirculating 1 minimum working volume of buffer in the total recycle mode before charging the vessel with the protein feed. This extra step required the additional buffer to be removed from the system through the permeate in a concentration step before the system was put into the 30-minute total recycle conditioning mode. These two changes eliminated the foaming issue and improved the bass balance recovery of the system to 99%.

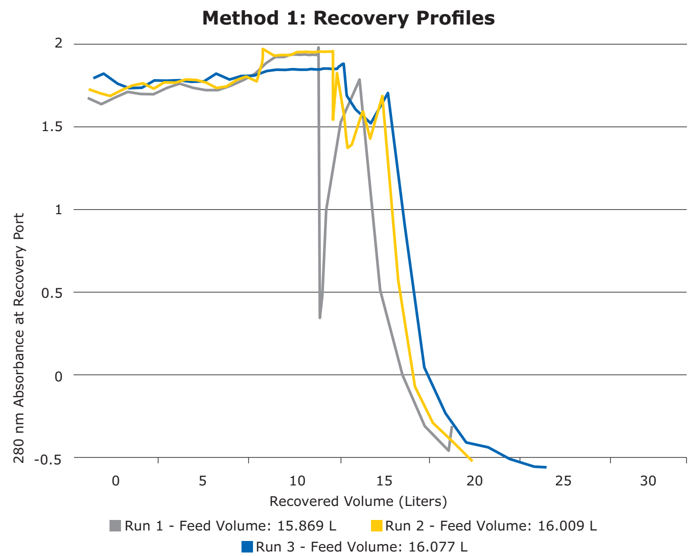

Figure 4.

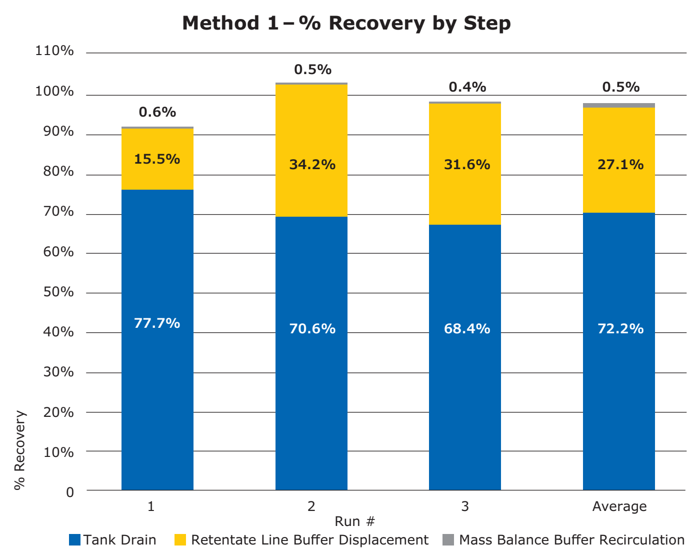

Figure 5.

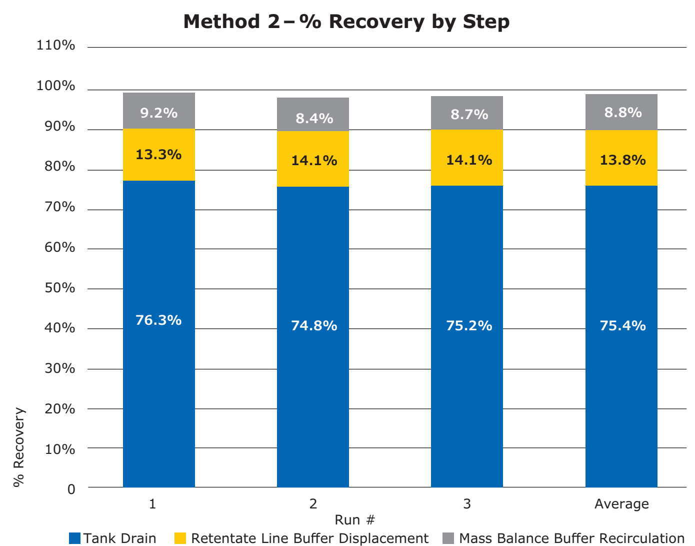

Figure 6.

- The flexible container and the UV meter were eliminated from the reverse plug flow buffer displacement portion of the test. This portion of the recovery was captured in 1 L aliquots to improve the resolution on the changing protein concentration of this stream during the recovery. Analysis of the aliquots (see image below) was still performed by UV Spectrophotometer at 280 nm. The flexible container was retained for the tank drain portion of the recovery.

During the high concentration work, we were limited on the available mass of protein and the feed concentration at the minimum working volume was 230 g/L instead of the target 280 g/L. Given that we were operating on the steep portion of the BSA Viscosity curve, the viscosity of the recovery pool was reduced to ~5 cp instead of the target 10 cp.

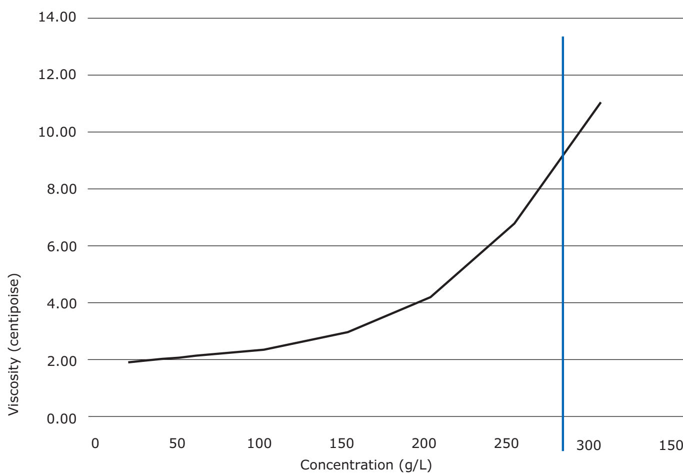

Figure 7.

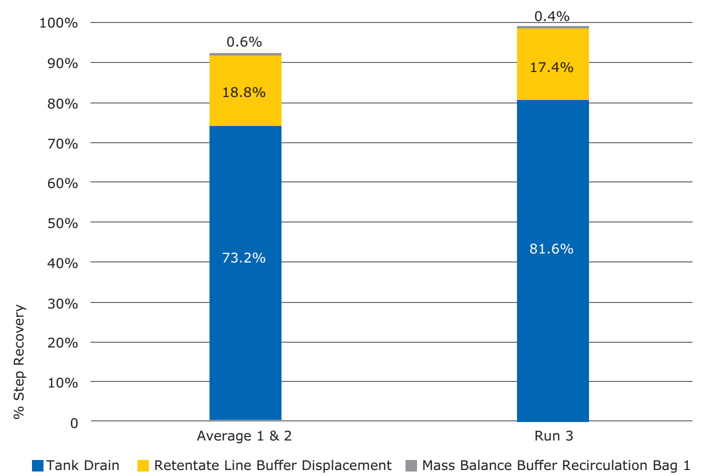

Figure 8.

Figure 9 shows the point concentrations measured from the 1 L aliquots that were recovered during the reverse plug flow buffer push of the retentate line and cassettes.

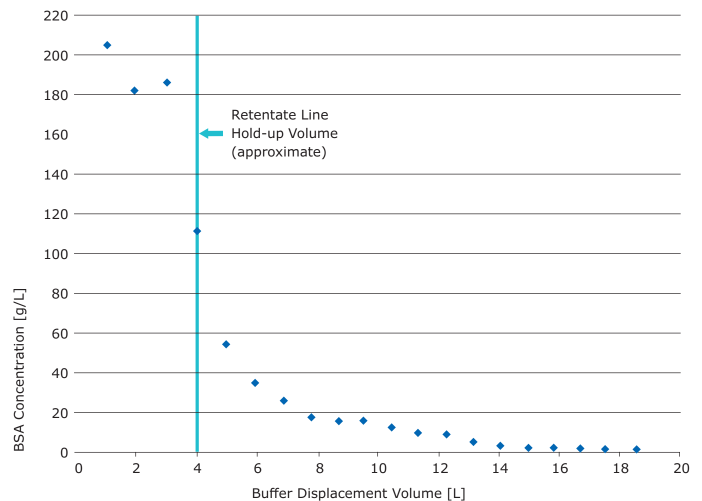

Figure 9.

High Concentration Recovery (continued)

Figure 10 shows the progress of recovery of protein from the retentate line and devices.

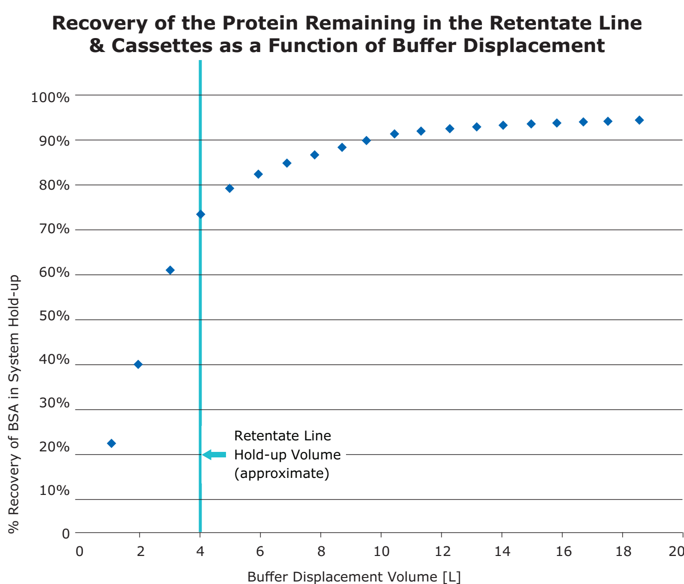

Figure 10.

Figure 11 is a calculation of the effect of reverse plug flow buffer displacement on pool yield and pool dilution factor.

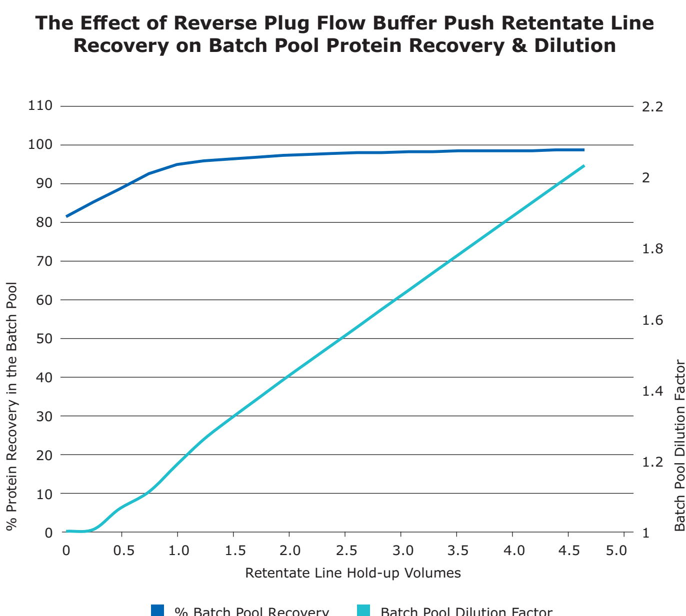

Figure 11.

Discussion

Methods 1 and 2 differ in their effectiveness and overall dilution of the recovered product pool. Method 1 achieved a more complete overall recovery (with an average of 99.3%) than Method 2 (with an average of 89.2%). The mass balance buffer recirculation at the end of each method was able to recover the remaining protein from the system, but is not typically used in a production environment. Despite the fact that Method 1 appeared most effective, it should be noted that the buffer volume used to achieve complete recovery may lead to a dilution of the final product pool.

Given that Method 2 used only air to displace the product in the hold-up volume, the final product pool remained undiluted.

Table 8 shows the impact of final pool volume on dilution during Method 1, with the following assumptions:

- Pool concentration pre-recovery = 10 g/L
- System hold-up volume after tank drain = 4 L
- Complete recovery of hold-up volume achieved in 7.6 L (based on an average of Runs 2 and 3)

Extrapolation of Method 1 to Larger Pool Volumes					
Final Pool Volume Pre-recovery	**16 L**	**20 L**	**50 L**	**100 L**	**150 L**
% of Final Pool Recovered from Tank Drain	75.0	80.0	92.0	96.0	97.3
% of Final Pool in Hold-up Volume	25.0	20.0	8.0	4.0	2.7
% Dilution of Final Pool at 100% Recovery	32.2	27.5	13.2	7.1	4.8
Total % Recovery at 20% Final Pool Dilution	80.0	84.0	100*	100*	100*

*Note: Complete recovery achieved with less than 20% dilution.

Table 8.

Method 2 is more easily applicable to larger pool volumes, since dilution is not a factor. The challenge that must be addressed with Method 2 is foaming of the product as the air is applied. While the air blowdown was performed at low pressure (< 5 psi), significant foaming was observed in both the sight glass on the product recovery port and in the recovery container. This study did not take into account the addition of a sterile filter on the product recovery port before the recovery vessel, as is sometimes used. It is possible that increased mixing would occur during Method 1 with a sterile filter in-line providing some resistance to flow. Therefore, it is important to ensure that the filter is appropriately sized for the final pool volume to minimize the resistance and overall buffer use. During Method 2, the sterile filter would help reduce foaming in the recovery vessel.

Method 1 was used to recover the protein for the high concentration batch experiments. The hold-up of the cassette devices and retentate line has been calculated to be ~4 L. The vessel drain step in this protocol recovered >81% of the protein in the system with no dilution. Figure 11 shows the trade-off between recovery of the protein remaining in the retentate line (including membranes) and dilution of the final recovery pool. 90% recovery is achieved for only a 6% dilution of the recovery pool. 93% recovery is achieved at the cost of 11% dilution of the pool. >95% recovery is achieved with less than a 20% dilution of the pool. The protein concentration of the first four liter aliquots of recovery, (equivalent to 1 retenate line volume), average nearly 170 g/L. The protein concentration of the fifth liter aliquot declined to ~50 g/L. It is expected the protein/buffer front would reside between the fourth and fifth liter aliquots for this system. The sharp decline in protein concentration shown in Figure 9 indicates some mixing has occurred between the fourth and fifth liter aliquots. Once again, this work was performed on a minimum-sized batch for the system and therefore represents a worst case for recovery. As the batch size increases, the amount of protein left in the retentate line becomes a lower proportion of the overall pool recovery, similar to the low concentration recovery shown in Table 8. Figure 11 can be used to optimize recovery and dilution.

Conclusion

For small pool volumes, Method 2 can be problematic, since a significant amount of product can be left unrecovered—about 9%, based on the test run data. In contrast, Method 1 can provide high recovery values for small pool volumes. However, one potential limitation is the dilution effects of the required buffer displacement volume. The amount of dilution realized during a Method 1 recovery procedure is determined by the plugflow characteristic in the system during the buffer displacement step. The plugflow characteristic is affected by system design and recovery process parameters such as displacement flowrate. The displacement curves developed for the Method 1 test runs suggest that the buffer displacement steps had good plugflow characteristics. The potential limitation of dilution can be managed by including an overconcentration step in the process operation prior to the recovery procedure. An overconcentration step is one way to ensure that target final product concentration is met. This may not be applicable in all situations depending on product concentration, viscosity and system design.

For large pool volumes, the potential limitations of both Method 1 (dilution) and Method 2 (unrecovered product) approach negligibly small loss in yield values. Therefore, either method may be appropriate for a large pool volume process. One special consideration for Method 2 is the potential of product foaming. The last step of recovery Method 1 (the retentate diptube section recovery) appears not to have been necessary. This section of line appears to have drained to the vessel by itself.

Foaming typically occurs at air-liquid interfaces and can lead to denaturation of the protein of interest. In order to help prevent this, product should never be transferred to an empty system. The addition of a sterile filter or peristaltic pump on the recovery port would also help minimize foaming by metering the flow of product during recovery. This study did not take into account the addition of a sterile filter on the product recovery port before the recovery vessel, as is sometimes used. It is possible that increased mixing would occur during Method 1 with a sterile filter in-line providing some resistance to flow. Therefore, it is important to ensure that the filter is appropriately sized for the final pool volume to minimize the resistance and overall buffer use. During Method 2, the sterile filter would help reduce foaming in the recovery vessel.

The high protein concentration work has shown some of the difficulties involved in recovering viscous high protein concentration protein products from a UF/DF system. It has also demonstrated that a reverse plug flow buffer displacement does not show excessive dilution of the protein product and the protein/buffer interface. It should be possible to optimize the recovery and dilution by careful evaluation of the step. The dilute case work indicates that Method 1 provides better yields than using an air push and avoids denaturation conditions such as foaming. Additional high concentration work could be done to compare recovery methods to confirm the conclusions suggested by the dilute case work.

The above recommendations apply for all recovery methods (gravity drain, air blowdown, plug flow buffer displacement and recirculation buffer flush). However, for Method 2, the system air inlet should be placed at the highest system point, usually at the highest point in the retentate line.

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2. Yadav, S., Shire, S., Kalonia, D., Summary of “Viscosity Analysis of High Concentration Bovine Serum Albumin Aqueous Solutions", Pharm Res. 2011 Aug; 28(8):1973-83. doi: 10.1007/s11095-011-0424-7. Epub 2011 Apr 14.

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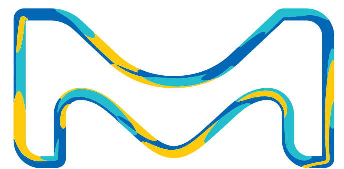

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