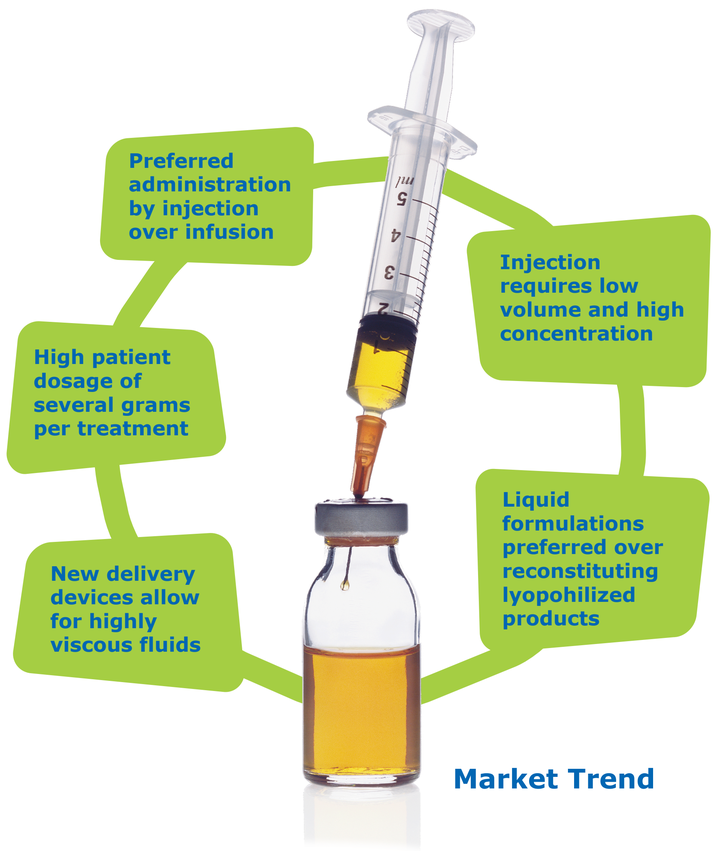
High Viscosity Tangential Flow Filtration (TFF) Applications

Dana Kinzlmaier, Elizabeth Goodrich, *Applications Engineering, EMD Millipore Corporation*



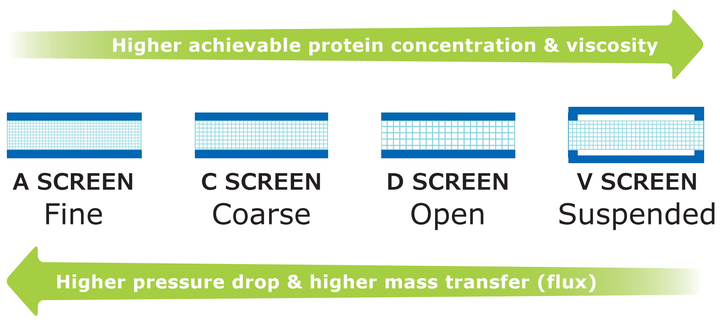
Introduction

Current trends in the bioprocessing industry are driving mAb and plasma producers to formulate at higher protein concentrations. As a result, formulating using tangential flow filtration (TFF) may be limited in reaching these concentrations due to high pressures caused by highly viscous feed streams. Filtration devices used during processing have to be optimized in order to handle both high viscosity and pressures while maintaining high flux and excellent product recovery. In this study, a family of filtration devices was evaluated to characterize the impact of membrane material and channel geometry on process performance and cleanability when working with high concentration feed streams. The results show the performance of each filtration device over multiple re-uses and presents a solution that can overcome process limitations due to high viscosity formulations.

Design Background

Flat sheet membrane cassettes are a very efficient module design for downstream concentration and diafiltration operations due to their high packing density, linear scalability and high mass transfer coefficients. Screens inserted into the cassette feed channels contribute to the high mass transfer since they increase fluid turbulence and decrease protein polarization, meaning that higher fluxes are achieved with lower crossflow requirements.

As the concentration and viscosity of protein solution increases during ultrafiltration, feed channel pressure drop increases as well, eventually reaching a high limit above which the process cannot continue. Tighter screens and channels exhibit higher pressure drops and therefore reach this process limitation at lower protein concentrations. However, very open screens and channels have much lower mass transfer, meaning that fluxes are low and more membrane area is required to complete a process.



To address this tradeoff, a new cassette was developed that uses an open " D" screen as well as special internal channel design optimization to reduce pressure drop while also maintaining a high mass transfer coefficient. As a result, it can achieve the high protein concentration of more open channels while maintaining the high flux and low membrane area of tighter channels.

The figure above illustrates screen types that are currently used in Pellicon® cassettes. It shows that as the screen and channel become more open, mass transfer and pressure drop decrease, while the maximum achievable protein concentration and viscosity increase.

The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

Cassettes used for Testing

- 0.11 m^2 Pellicon® cassettes
- 30 kD Ultracel® membrane with C, D and V screen
- 30 kD Biomax® membrane with A and D screen

The performance of each cassette was evaluated for
- Product Recovery
- Final protein concentration/viscosity
- Process consistency over multiple uses
- Feed channel pressure drop
- Mass transfer coefficient
- Membrane cleanability

Methods

Process Run

- Bovine gamma globulin used as a feed solution
- Concentrate from 10 g/L to maximum achievable concentration
- Initial process operating conditions:
  - Set feed flow rate to 6 L min^{-1} m^{-2}
  - Set transmembrane pressure (TMP) based on flux versus TMP optimization
- Process control strategy as viscosity increases:
  - Maintain TMP by adjusting retentate valve until retentate pressure reaches 10 psi minimum
  - Then maintain feed flow rate until P_{Feed} reaches 60 psig max
  - Then ramp down the feed pump to maintain PFeed at 60 psig until the feed flow rate reaches 1 L min^{-1} m^{-2}

Cleaning Procedure

This table summarizes the cleaning procedure used for each membrane material and channel type.

Step	Solution	Temp [°C]	Volume [L/m²]	Mode	Time [min]
1	Buffer	Ambient	10	SPFO, drain	n/a
2	0.5N NaOH 1N NaOH 0.1N NaOH	Ambient	10	SPFO	n/a
3	0.5N NaOH 1N NaOH 0.1N NaOH	Ambient	5	TRFO	60 60 30
4	Water	Ambient	20	SPFO, measure NWP	n/a
5	0.1 N NaOH	Ambient	10	TRFO, store	15

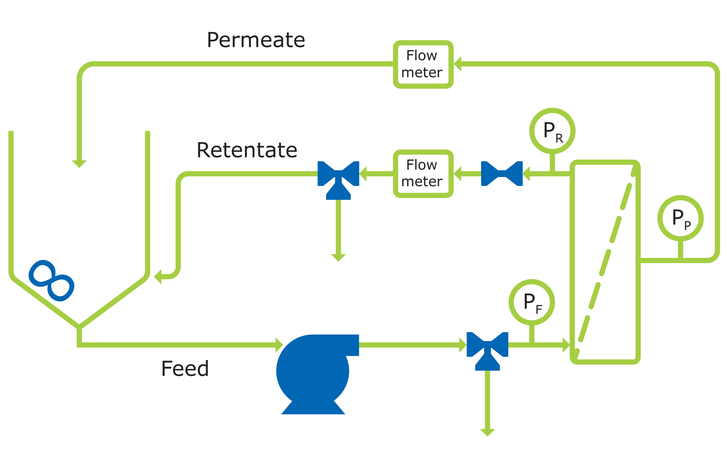
Biomax® Membrane Cleaning Runs 1-7 **Ultracel® Membrane Cleaning Runs 1-10**
Biomax® Membrane Cleaning Runs 8-10 **Ultracel® Membrane Cleaning Runs 11-15**

Each cassette was challenged with bovine gamma globulin solution and cleaned multiple times to demonstrate process consistency and cleanability of 30 kD Biomax® and Ultracel® Membranes.

Total Number of Process Runs and Cleaning Cycles for Pellicon® Cassettes with 30 kD Ultracel® and Biomax® Membranes

Membrane	Screen Type	Number of Process Cycles
Ultracel®	C	10
	D	15
	V	3
Biomax®	A	10
	D	10

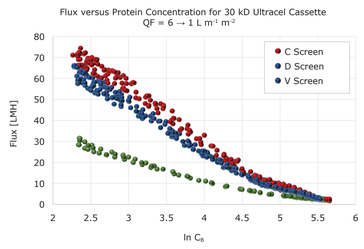
System Schematic



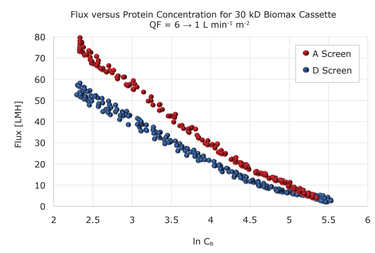
Results

Process Performance – Flux and Pressure Drop

Testing results for Pellicon® cassettes with 30 kD Biomax® and Ultracel® membranes demonstrate consistency over multiple process runs. The flux for cassettes with Ultracel® membrane with C and D screen is very similar and only minimal drop in flux was observed between Pellicon® cassettes with A and D screen Biomax® membranes. The cassette with V screen has much lower flux, as expected.

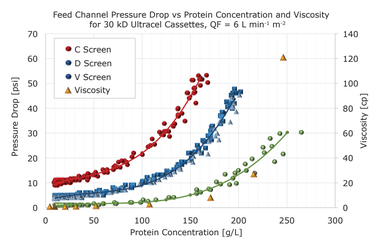


Flux versus Protein Concentration for 30 kD Ultracel® Cassettes with C, D and V Screen

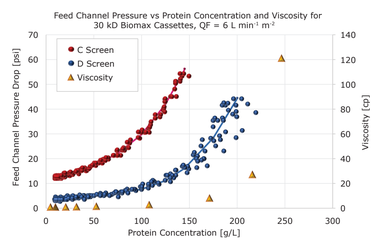


Flux versus Protein Concentration for 30 kD Biomax® Cassettes with A and D Screen

Feed channel pressure drop depends on the cassette screen type and tracks with increasing viscosity and concentration of the protein solution as illustrated in the graphs below. Significantly lower pressure profile was observed for more open D screen cassettes with both Ultracel® and Biomax® membranes, enabling them to reach higher final viscosities and protein concentrations.



Feed Channel Pressure Drop versus Protein Concentration and Viscosity for Cassettes with 30 kD Ultracel® Membranes with C, D and V Screen



Feed Channel Pressure Drop versus Protein Concentration and Viscosity for Cassettes with 30 kD Biomax® Membranes with A and D Screen

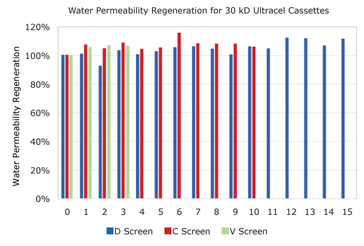
Process Performance – Mass Transfer, Yield, Concentration

Excellent yield was observed for all devices over multiple uses. The more open D screen cassettes achieved higher viscosity and final concentration with no significant loss in mass transfer.

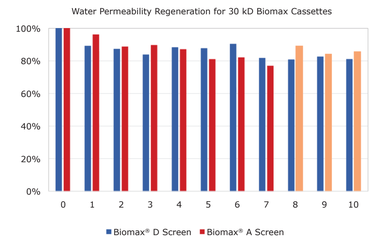
Membrane Type	Screen Type	Mass Transfer Coefficient [LMH]	Final Protein Conc [g/L]	Final Viscosity [cP]	Yield [%]
30 kD Ultracel®	C	24	226	40	102
	D	22	242	75	99
	V	10	277	200	99
30 kD Biomax®	A	25	200	25	99
	D	19	240	75	98

Membrane Cleanability and Reuse

Pellicon® cassettes with Biomax® and Ultracel® membranes and the newly designed D screen for high viscosity applications maintain the same cleanability and reusability as the rest of the Pellicon® family. Water permeability was consistently restored to pre-process values after cleaning with room temperature sodium hydroxide. For the Pellicon® cassette with Biomax membrane and A screen, the concentration of sodium hydroxide was increased to 1N for cleaning cycles 8-10, because at the end of cleaning cycle 7 the permeability recovery dropped below the 80% minimum acceptable target that was set for this study. Permeability was consistently restored afterwards.



Water Permeability Recovery after Cleaning; Cassettes with 30 kD Ultracel® Membranes with C, D and V Screen



Water Permeability Recovery after Cleaning; Cassettes with 30 kD Biomax® Membranes with A and D Screen

Conclusion

This work illustrates process consistency and cleanability of Pellicon® cassettes with both 30 kD Ultracel® and Biomax® membranes over multiple uses. Novel D screen cassettes, designed for high viscosity applications are capable of concentrating protein solutions to significantly higher viscosities compared to traditional A and C screen cassettes.

About two fold higher viscosity could be achieved with Pellicon® cassettes with Ultracel® membrane D screen compared to Ultracel® C screen with a minimal drop in mass transfer coefficient (<10%). Three fold higher final viscosity was achieved with only 25% lower mass transfer coefficient when comparing the performance of Pellicon® cassette with 30 kD Biomax® membrane D screen to A screen cassette.

Water permeability was easily restored using room temperature sodium hydroxide. Flux, pressure drop and protein yield were consistent across up to 15 process runs for the entire cassette family.