Breaking Barriers: Mitigation Strategy for viscosity induced High-Concentration TFF Challenge

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Introduction

Recent advances in biologics development are primarily focussed on development of high titre producing cell lines to substantiate the requirement of high dosage mAbs which may be as high as 600-700 mg drug per dose. This also brings in the requirement of subcutaneous injectables to alleviate the hassles of IV infusion. Therefore, to achieve both these objectives, substantial work has also been initiated for development of high concentration formulation along with high titre cell lines.

One of the biggest challenges for the development of high concentration formulation is increase in viscosity which impact the injection force and patient comfort. As part of purification process flow, the concentration of the protein molecules is achieved by TFF unit operation which is also the unit operation where this challenge is encountered the most. This poster focuses on the strategy to mitigate this challenges and achieve a concentration of >200 mg/mL for mAbs as well as other mammalian recombinant proteins.

Barriers during TFF

Viscosity Increase	Pressure Limitations	Scalability challenge
• Indicators – Δ P increase	• Higher pressure can lead to process disruption	• Non linear changes in flow dynamics during scale up

Key contributors

- Protein-protein interaction
- Module resistance
- Suboptimal TMP or Cross flow rate

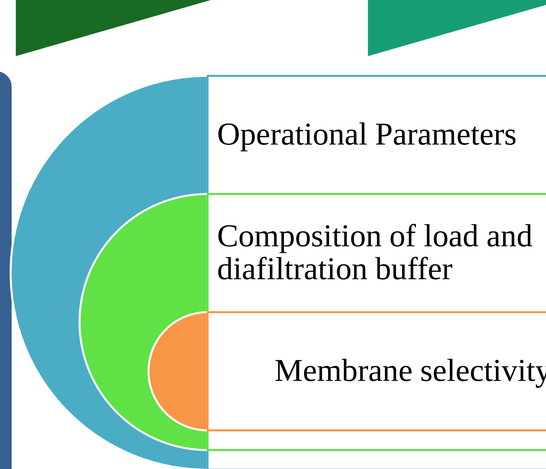
Levers optimized and Indicators

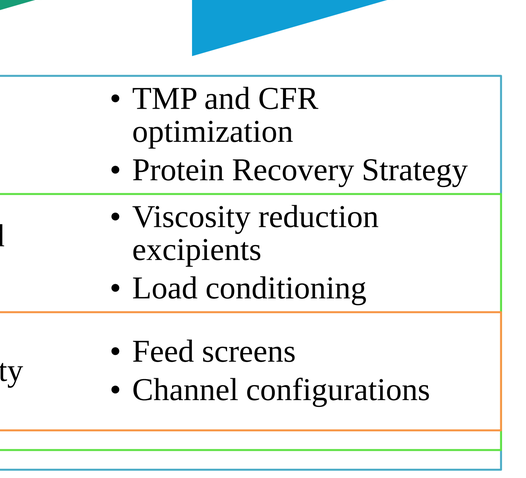
Operational Parameters	• TMP and CFR optimization • Protein Recovery Strategy
Composition of load and diafiltration buffer	• Viscosity reduction excipients • Load conditioning
Membrane selectivity	• Feed screens • Channel configurations

Key Indicators

- Trend for Differential Pressure (ΔP) (Indicator for viscosity increase)
- Retentate Concentration at ΔPmax
- Recovery %

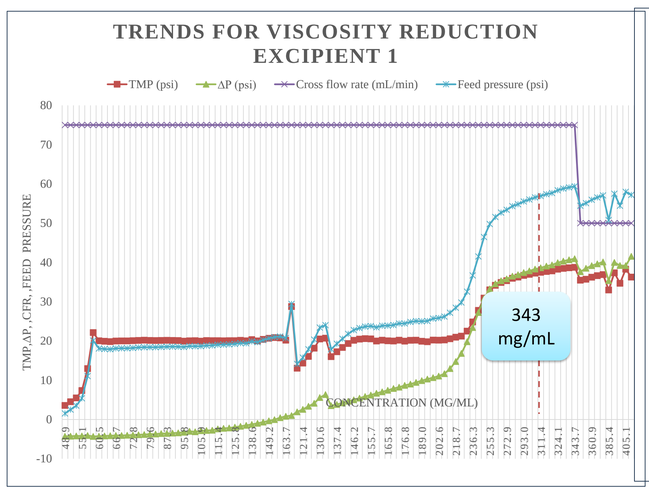
Module Resistance

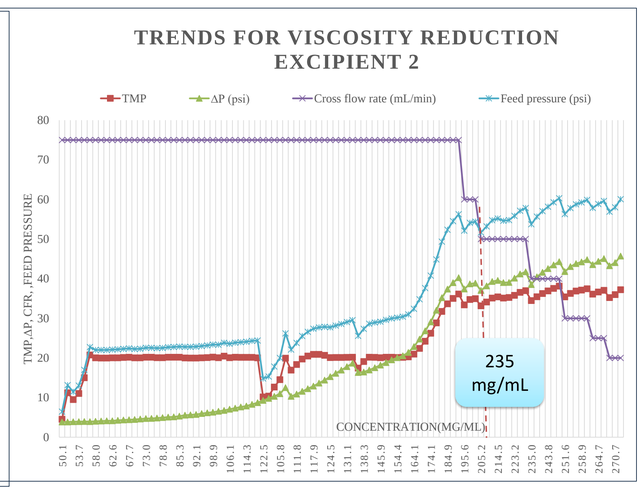




Lower module resistance is observed for TangenX EP screen for which the feed channel configuration supports higher flow rate of >500 LMH. This promotes sweeping phenomenon and prevents protein accumulation

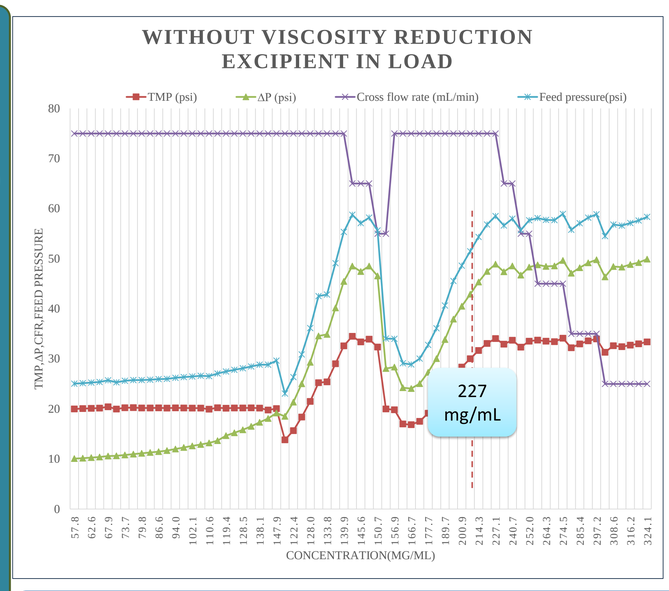
Viscosity reduction excipients

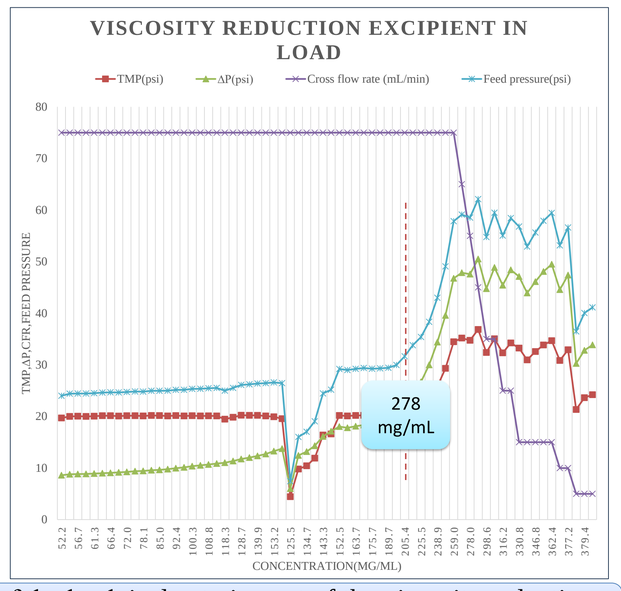




Impact of viscosity reduction excipients were studied with two excipients. It was observed that excipient 1 provided comparatively better control on differential pressure compared to excipient 2

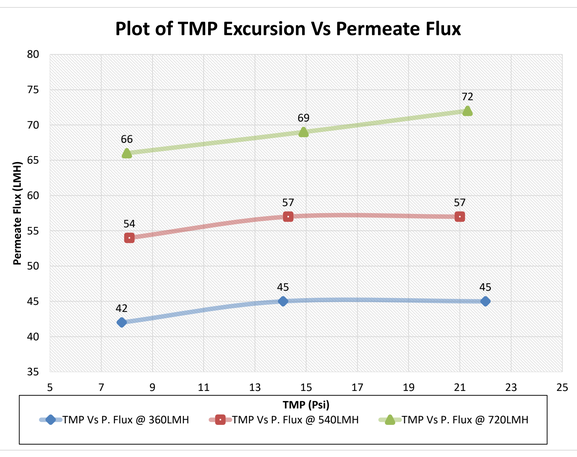
Load conditioning

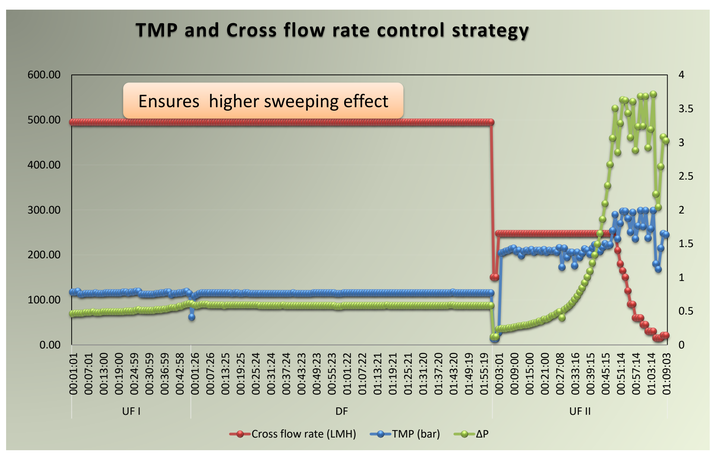




The delay observed for increase in ΔP after conditioning of the load, is due to impact of the viscosity reduction excipient on reducing the P-P interactions and thus deferring the gel formation.

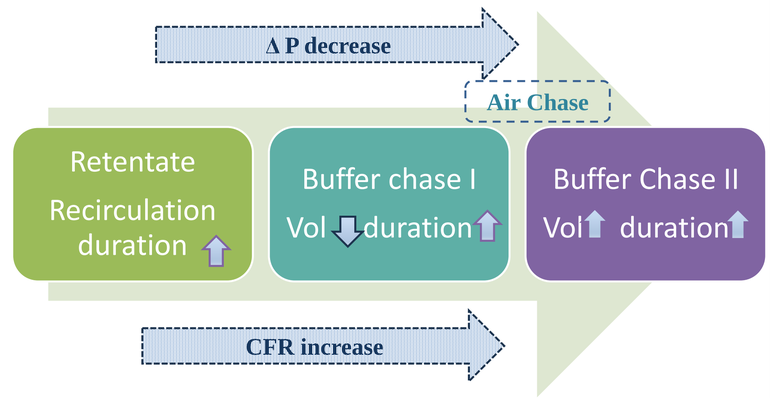
TMP, Cross flow rate

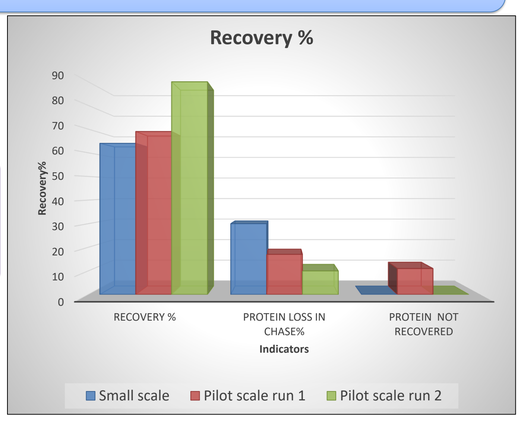




A dual strategy of maintaining a higher CFR for the initial UF and DF ensures sweeping action on the membrane surface. Higher TMP and reduced CFR during UFII prevents clogging followed by protein displacement in solution

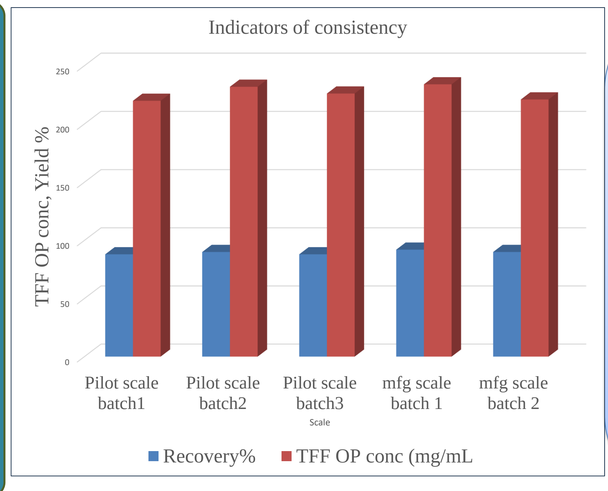
Recovery strategy





Low recovery observed during development and pilot scale. Post optimization during scale up of recovery strategy, protein was efficiently displaced from the surface and an increment of 21% recovery was achieved in Pilot scale run2.

Conclusion



During high-concentration TFF unit operations, pressure drop escalation and gel layer formation on the membrane surface are significant challenges to achieving concentrations >200 mg/mL at the drug substance stage. The strategies discussed in this work effectively mitigate these issues by reducing protein-protein interactions and minimizing gel layer formation on the membrane surface. This results in better displacement and higher recovery during the TFF process. By applying these approaches, consistent concentration >200 mg/mL was successfully achieved at the pilot scale and subsequently scaled up to 2000L at GMP.

*Raghunath, Bala & Wang, Bin & Pattnaik, Priyabatra & Janssens, Jeroen. (2012). Best Practices for Optimization and Scale-Up of Microfiltration TFF Processes. Bioprocessing Journal. 11. 30-40. 10.12665/J111.Raghunath.