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Versatile Ultrafiltration Solutions: Applying Single-Pass TFF (SPTFF) for High-Concentration Biologics

The Strategic Importance of High-Concentration Biologics

The evolution of biopharmaceutical development is increasingly focused on high-concentration formulations, a strategic shift driven by significant clinical and patient-centric advantages. As the industry moves toward more convenient and effective therapies, the ability to concentrate biologic drug substances without compromising quality has become a critical capability. This trend is not merely an incremental improvement but a fundamental change in how next-generation therapies are designed and delivered.

The market drivers behind the shift to high-concentration biologics are clear and compelling, reflecting a deep understanding of patient needs and clinical efficiency:

- **Improvement of Patient Experience:** High-concentration formulations enable shorter injections, reducing the need for prolonged intravenous infusion.
- **Reduction of Handling Complexity and Risk:** Liquid drug products eliminate on-site dilution or reconstitution, lowering handling complexity and preparation risk.
- **Compatibility with Advanced Delivery Systems:** Concentrated biologics support wearable injectors and other delivery systems designed for viscous formulations.
- **Development of Potent, High-Dose Therapies:** Concentrated formulations allow effective dosing in reduced volumes while maintaining stability and efficacy.

While the clinical and commercial benefits are significant, the development of high-concentration biologics introduces inherent manufacturing challenges that require well-controlled and reliable process solutions.

The Biophysical Hurdle: Processing Challenges at High Concentrations

A deep understanding of the physical challenges in concentrating proteins is strategically vital for successful process development. As protein concentrations increase, the formulation's biophysical properties change dramatically, creating significant obstacles for traditional downstream processing techniques. These changes fundamentally alter the fluid dynamics and molecular interactions within the solution, pushing conventional equipment beyond its operational limits.

The key biophysical challenges that limit mass transfer and complicate the use of conventional recirculation-based Ultrafiltration/Diafiltration (UF/DF) systems include:

- **Increased Viscosity**: As protein molecules become more crowded, the solution's viscosity increases rapidly. This reduces the filtration flux (the rate of fluid passing through the membrane) and elevates shear stress on the protein molecules.
- **Donnan Effects**: At high concentrations, charged protein molecules create an unequal distribution of ions across the filtration membrane. This phenomenon alters the local ionic environment and buffer composition.
- **Volume Exclusion**: The high density of protein molecules reduces the amount of free volume available at the membrane interface. This crowding effect hinders the passage of solvent and smaller solutes, further contributing to a decline in mass transfer efficiency.

These factors collectively make it difficult for conventional methods to reach high concentration targets efficiently and reliably. This necessitates an evaluation of process technologies specifically designed to overcome these biophysical hurdles.

A Practical Solution: Comparing Conventional TFF with Single-Pass TFF (SPTFF)

For concentrating biologics, manufacturers have two primary process options: Conventional Tangential Flow Filtration (TFF) and Single-Pass TFF (SPTFF). While both technologies share the goal of concentrating a product stream, their operational methodologies and performance outcomes differ significantly, especially when processing high-viscosity, high-concentration formulations.

- **Conventional TFF**: This technology operates on a recirculation-based principle. The process fluid is passed multiple times over the filtration membrane from a feed tank, with the retentate being returned to the tank. The target concentration is achieved gradually through repeated circulation, requiring ongoing monitoring and control to maintain stable operating conditions.
- **Single-Pass TFF (SPTFF)**: This approach processes the solution through a series of filtration modules in a single continuous flow path without recirculation. When properly designed and operated, it enables efficient and gentle processing to final target concentration.

An evaluation of the critical differences between these two technologies highlights the distinct advantages of SPTFF for well-controlled bioprocessing environments.

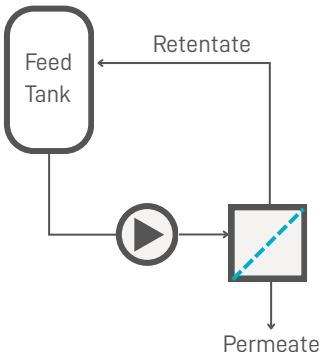
Process Options for Concentration

Conventional TFF

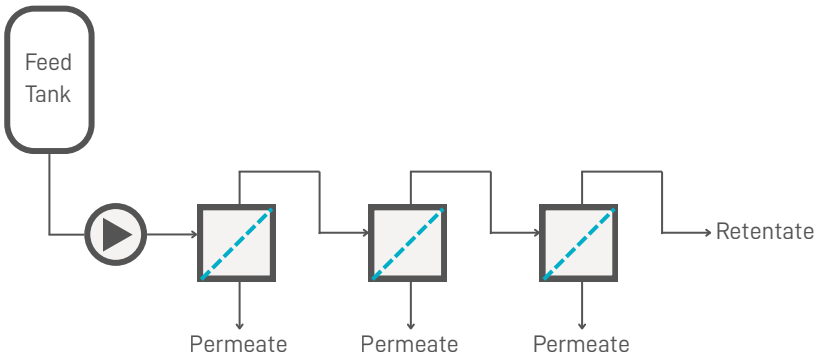
Recirculates the solution multiple times, gradually reaching the target concentration while requiring continuous protein monitoring.

Single-Pass TFF (SPTFF)

Processes the solution once, enabling fast and gentle concentration of high-concentration formulations.



(Recirculation mode)



(Staged membrane modules)

Conventional TFF vs. SPTFF

Aspect	Conventional TFF	SPTFF
Flux at high viscosity	Flux drops significantly as viscosity increases	Avoids late-stage flux collapse
Shear exposure	Higher cumulative shear	**Lower and more controlled shear exposure**
Concentration control	End-stage concentration becomes slow and difficult to control	**Concentration increases in a controlled, staged manner**
Hold-up volume	Larger system volume, more residual hold-up	Low hold-up volume, improved recovery

Case Study: Mycenax's Evaluation of SPTFF for High-Concentration mAb Processing

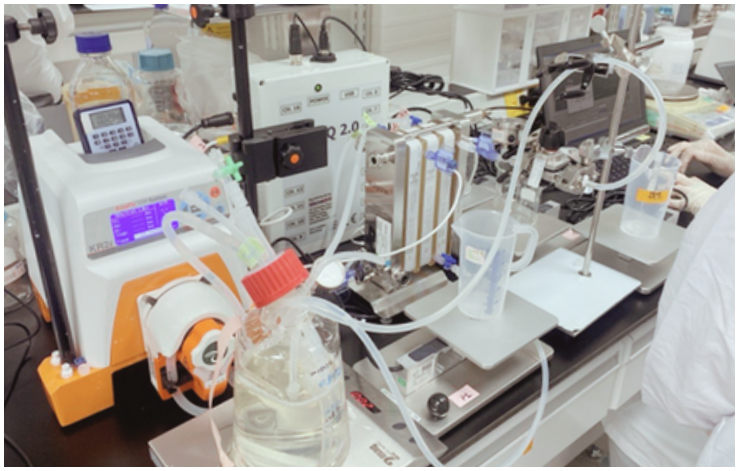
From a CDMO perspective, adopting advanced technologies like Single-Pass TFF is critical for successfully managing the elevated viscosity and reducing the shear exposure associated with high-concentration biologics. To this end, Mycenax conducted a practical evaluation of SPTFF technology to assess its performance in processing a high-concentration monoclonal antibody (mAb), demonstrating a commitment to integrating cutting-edge solutions for client projects.

Methodology and Objectives

For the evaluation, Mycenax utilized Merck's Pellicon® SPTFF modules in a laboratory-scale setup designed to simulate a real-world manufacturing scenario. The study was structured around clear performance goals to determine the technology's suitability for demanding concentration applications.

The core objectives of the study were to examine:

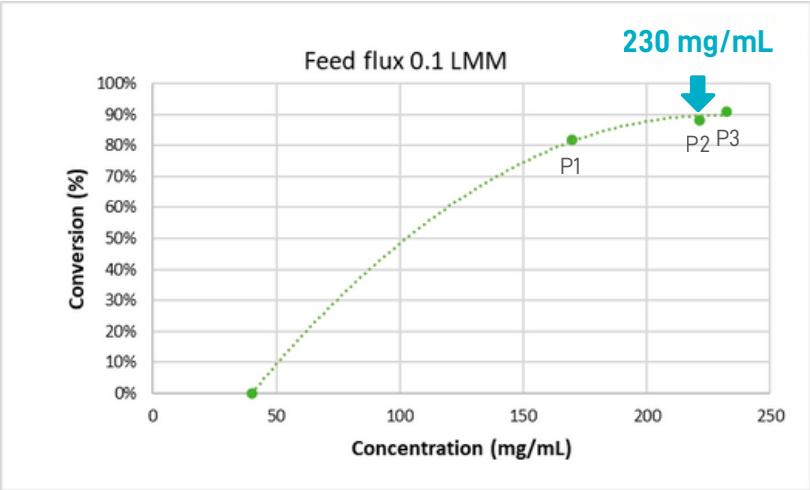
- The feasibility of achieving very high protein levels in a single pass.
- The process behavior under conditions of elevated viscosity.
- The ability to maintain product quality throughout the concentration step.



Results and Interpretation

The study yielded excellent performance results, confirming the capability of SPTFF to meet aggressive concentration targets. Analysis of the process data demonstrated that by optimizing the feed flux and strategically modulating retentate pressures (conditions P1-P3), the system successfully elevated the conversion rate to the levels required for substantial volume reduction. This precise parameter control enabled the process to sustain a conversion rate of approximately 90%, directly enabling the success of the concentration step.

Specifically, the final concentration achieved in the study was 230 mg/mL. This was accomplished without compromising monoclonal antibody integrity, as confirmed by SE-HPLC, which demonstrated that key product quality attributes were maintained before and after processing.



mAb quality	SE-HPLC Analysis		
	HMW	Main	LMW
Before concentration	1.0%	99.1%	ND
After concentration	1.0%	99.0%	ND

•Three retentate pressure conditions (P1, P2 and P3) were evaluated.

The data demonstrates that the percentage of high molecular weight species (aggregates) showed no change and the main peak remained essentially unchanged, indicating that the SPTFF process did not induce product aggregation. A key operational finding was that three different retentate pressure conditions (P1, P2, and P3) were evaluated, and the higher-pressure conditions (P2 and P3) enabled achievement of protein concentrations exceeding 200 mg/mL while maintaining critical product quality attributes.
These successful results support the applicability of the SPTFF platform to high-concentration processing, together with Mycenax's expertise in process optimization and technology implementation.

Conclusion: Partnering for Efficient High-Concentration Biologic Development

The development of high-concentration biologics presents significant biophysical and manufacturing challenges that require advanced, fit-for-purpose technologies. This article has demonstrated that Single-Pass TFF (SPTFF) effectively addresses the primary hurdles associated with potential concerns related to increased viscosity, shear exposure, and process control, enabling the reliable and efficient production of highly concentrated protein formulations. The case study results confirm that SPTFF can achieve aggressive concentration targets—in this case, 230 mg/mL—while maintaining product quality.

As a trusted CDMO partner, Mycenax combines extensive development experience with strong collaborations with technology leaders like Merck. This strategic approach allows us to support clients developing high-concentration biologics with efficient, risk-aware solutions tailored to their unique product needs. By leveraging proven, state-of-the-art platforms like SPTFF, we help our clients navigate the complexities of modern bioprocessing and accelerate their path to the clinic and market.