New Enabling Technologies for Continuous Final Formulation of MAbs

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INTRODUCTION

Cadence™ Single-Pass TFF (SPTFF) represents a novel method for achieving high concentration formulations [1-3]. Its simple operation is advantageous over conventional TFF and current high concentration strategies such as lyophilization, which is a multi-step process that can be very costly and time-consuming.

- SPTFF also enables alternate and effective delivery methods to further improve patient's quality of life
- SPTFF is particularly well-suited for the processing of fragile biomolecules
- SPTFF mode of operation provides a better management of highly viscous solutions as product is gradually concentrated along the entire length of the flow path with cross-sectional area changes

OBJECTIVE

- To provide a data-driven approach and assessment of the single-pass TFF technology attributes for the continuous final formulation of MAbs and address the subsequent product and process development requirements

BACKGROUND

SPTFF technology platform, including Cadence Inline Concentrators (ILC), is well-suited for numerous bioprocess applications and has been shown to remove constraints in existing facilities via:

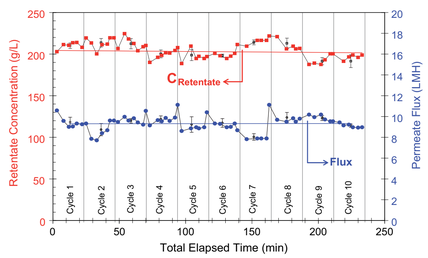
- In-process volume reduction applications (i.e., post-harvest, pre-capture, tank-to-tank transfer, etc.) [4-5]
- Process coupling runs with affinity, ion-exchange and membrane chromatography steps in batch and continuous mode showcasing enhanced productivity [6-7]
- Increased flexibility of manufacturing capabilities with significant cost savings [8-9]
- Achieving high concentration formulations with custom pre-assembled modules available in various flow path configurations [2, 9]

RESULTS AND DISCUSSION

1. High Concentration Formulations with Single-Pass TFF

- Cadence SPTFF modules provide stable and reproducible performance well-suited for high concentration applications:
  - As part of a continuous concentration strategy, 45 g/L of IgG feed solution was successfully concentrated to ≥ 200 g/L in single-pass during 10 cycles of processing with efficient cleaning and high yield product recovery steps in between (Figure 1)[2]

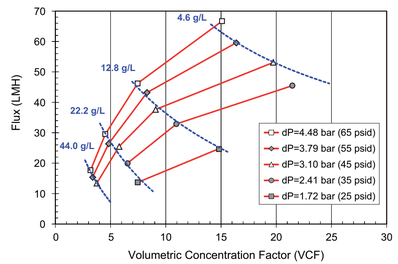
Figure 1
Evaluation of SPTFF Process Stability and Reproducibility at High Concentrations. 10 Cycles of Concentration, Cleaning and Recovery with 10 kDa Regenerated Cellulose, SPTFF Module (Total Area = 0.17 m²) [2]



RESULTS AND DISCUSSION *(Continued)*

- Ease of process optimization with SPTFF enables the generation of a design space achieved with a "single" SPTFF module only
- By assessing the process at wide range of operating conditions provide a stable and reproducible performance map, well-suited for high concentration applications (Figure 2)

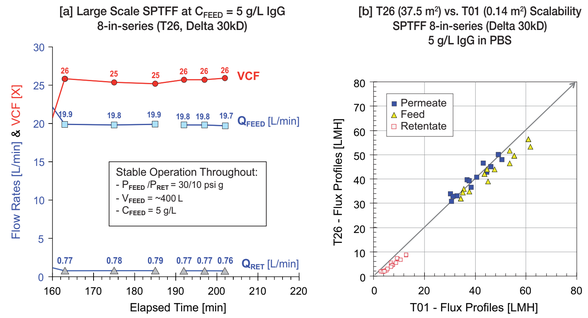
Figure 2
SPTFF Flux Excursions Performed with IgG Feed Concentrations of 4.6, 12.8, 22.2, and 44.0 g/L at Feed Pressures of 4.8, 4.1, 3.5, 2.8 and 2.1 barg (70, 60, 50, 40 and 30 psig) and a Retentate Pressure of 0.3 barg (5 psig) Resulting in Final Product Concentrations as High as 220 g/L



PD and Manufacturing Scale Formulation of MAbs with SPTFF

- Successful demonstration of 268X process scalability between 0.14 m² and 37.5 m² membrane area with 5 g/L IgG feedstock of ~400L batch size utilizing SPTFF 8-in-series 30 kDa regenerated cellulose modules (Figure 3)

Figure 3
*MAb Processing at 37.5 m² Scale (Linear Scale-Up from Process Development to GMP Manufacturing Scale) **[a]** Single-Pass TFF Run at 25X, and **[b]** 268X Scalability (0.14 m² vs. 37.5 m²) Demonstrated Under Similar Protein Loading. (Note: the $C_{wall,\ max}$ for the protein was ~140-150 g/L)*

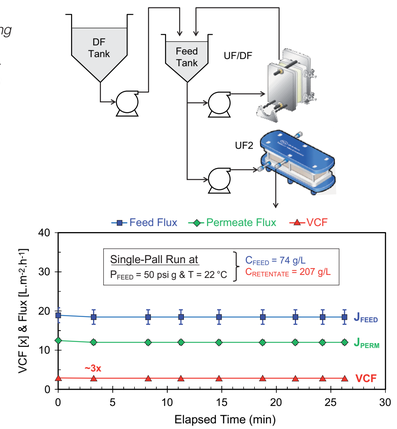


2. High Concentration Formulations with ILC

- ILC is an important addition to the process development tool-box, for platform process evaluation and is a crucial and proven enabler of integrated, streamlined and continuous bioprocessing initiatives [5-9]
- For instance, utilizing ILC for UF2 enables multiple advantages over a conventional UF system (Figure 4), such as:
  - Non-capital expense
  - Lower system hold-up volumes
  - High productivity and improved recovery (> 99%)
  - Reduced over-concentration targets

RESULTS AND DISCUSSION *(Continued)*

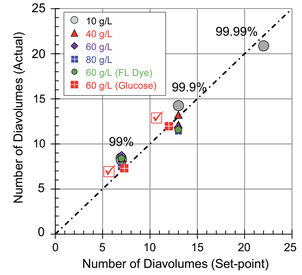
Figure 4
UF2 Single-Pass Processing of a 74 g/L MAb Feed at P_{FEED} =50 psig with a 4-in-series ILC Module (30 kDa Regenerated Cellulose) Following a Conventional UF/DF Step [9]



3. Continuous, Single-Pass and/or Inline Diafiltration (ILDF)

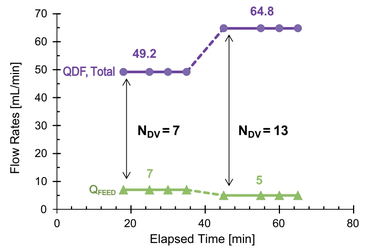
- ILC design principles and its versatile and robust performance led to the assessment of novel continuous diafiltration strategies, which resulted in a working prototype of a novel inline diafiltration (ILDF) module
- Feasibility runs with 10-80 g/L hIgG feeds resulted in successful removal efficiencies (≥ 99.9% or ≥ 3-log) between ILDF process targets and validated test data (Figure 5)

Figure 5
Performance Benchmark for the Continuous, Single-Pass, Inline Diafiltration Module with 30 kDa Regenerated Cellulose Membrane [Feed: 10-80 g/L hIgG in 0.025 M Na Acetate + 0.5 M NaCl (47 mS/cm) + 50 g/L Glucose and DF: 0.025 M Na Acetate + 0.05 M NaCl (6.7 mS/cm)]



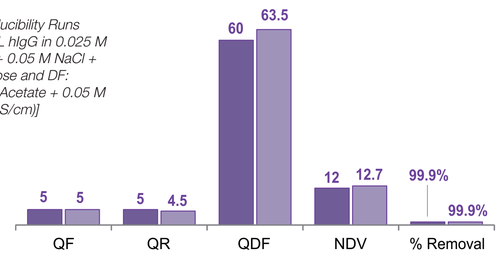
- Simplified design and process control was confirmed and showcased with process stability runs against instant process variants (Figure 6)
- Process robustness was also well-characterized via reproducibility runs (Figure 7) targeting high removal factors with the 60 g/L hIgG feed

Figure 6
ILDF Process Stability Against Step Changes in Flow Set-Points [Feed: 60 g/L hIgG in 0.025 M Na Acetate + 0.05 M NaCl + 50 g/L Glucose, and DF: 0.025 M Na Acetate + 0.05 M NaCl (6.7 mS/cm)]



RESULTS AND DISCUSSION *(Continued)*

Figure 7
ILDF Reproducibility Runs [Feed: 60 g/L hIgG in 0.025 M Na Acetate + 0.05 M NaCl + 50 g/L Glucose and DF: 0.025 M Na Acetate + 0.05 M NaCl (6.7 mS/cm)]



KEY FINDINGS AND CONCLUSIONS

- SPTFF technology platform:
  - Is revolutionary and presents versatile capabilities for the processing of biologics,
  - Is scalable, flexible and available in various formats and configurations in order to address molecule- and process-specific customization needs, specifically for high concentration formulations,
  - Can remove constraints in existing facilities, increase the flexibility of manufacturing capabilities by increasing productivity and facilitating further use of disposables,
  - Reduces process development and manufacturing cost of goods significantly via eliminating non-value added process steps and yield improvements,
  - Enables process coupling and integrated continuous bioprocessing
- ILDF design and ease-of process control:
  - Addresses an innovation gap for the biopharmaceutical industry,
  - Completes the product/technology offering for the realization of continuous final formulation,
  - Brings the BioPharm industry one-more step closer to the realization of an end-to-end integrated continuous bioprocessing platform via potential ILC/ILDF integration

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