Simplifying Progress

Case Study: UF | DF Development Challenges – Gap in Scale-Down Technologies for Tangential Flow Filtration

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1. Introduction

The biopharmaceutical industry is currently facing a number of challenges. In recent years, companies have experienced a decline in peak sales of their newly launched products while at the same time the cost of developing a new biological drug continues to increase. The industry's pipeline of products is becoming increasingly diverse and requires production platforms that are more adaptable and flexible than ever before. Take ultra- and diafiltration operations, for example. Increasingly, biopharmaceutical companies seek to increase the concentration of their final product, e.g. for subcutaneous injections. It is imperative that they understand the stability of their final product and how this can be influenced with different buffer solutions.

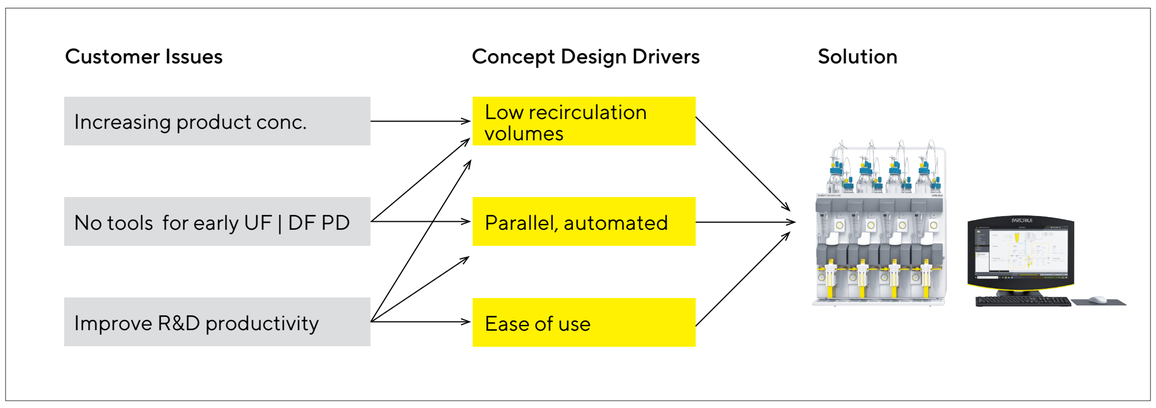

Figure 1: Requirements for a small-scale, multi-parallel high throughput device

2. Gap in Scale-Down Technologies for Tangential Flow Filtration*

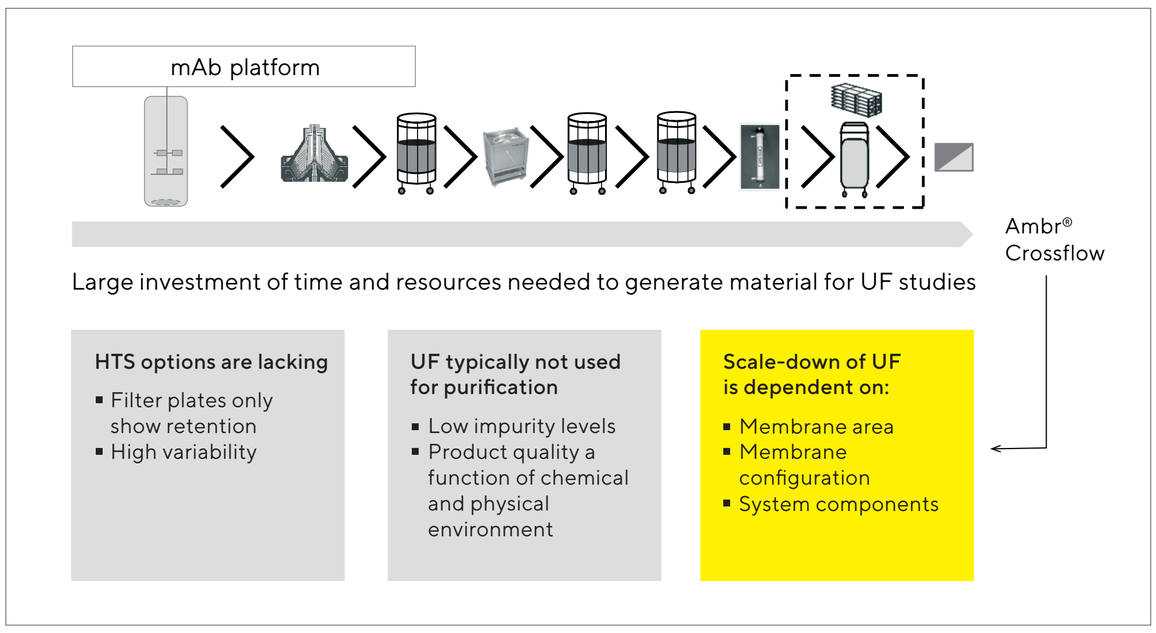

Figure 2: UF | DF development challenges

3. Ambr® Crossflow

Ambr® Crossflow provides access to molecule behavior at early development stages related to viscosity, buffer composition, shear stress and performance in membrane processes. It enables many important additional decision criteria for the final candidate selection and speeds up this process significantly.

A small-scale, high through put automated system allows the investigation of a larger number of molecule | buffer combinations and process control conditions. As a result, productivity and efficiency in the early R&D stage are significantly improved while the cost per experiment is reduced.

Figure 3: Ambr® Crossflow – The high throughput solution for parallel screening

4. Flux Characterization Study*

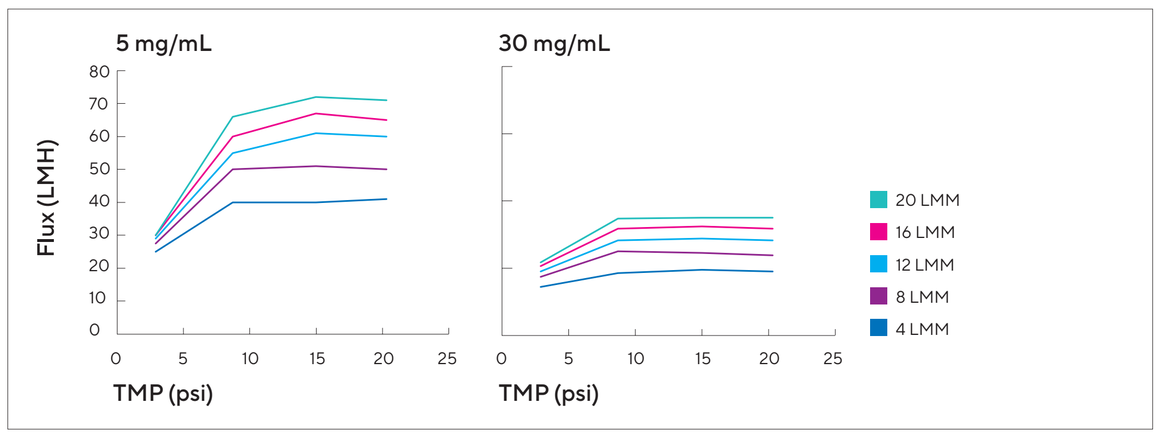

Figure 4: Ambr® Crossflow characterization: TMP and flux scouting. Absolute flux is lower than large scale, crossflow trends hold

A flux characterization study was performed with mAbs at three different feed concentrations, four different TMPs and five crossflow rates. A total of 45 pre-programmed conditions were evaluated in an experimental setup. Due to the low hold-up volume of the system, only 0.21 g of product was required for the entire study. Performing an equivalent study on a standard benchtop tangential flow filtration system would have increased the time to perform the study by 10-fold and required 5-fold more material.

5. The Effect of Buffer Choice on Diafiltration Flux Rates and Protein Stability

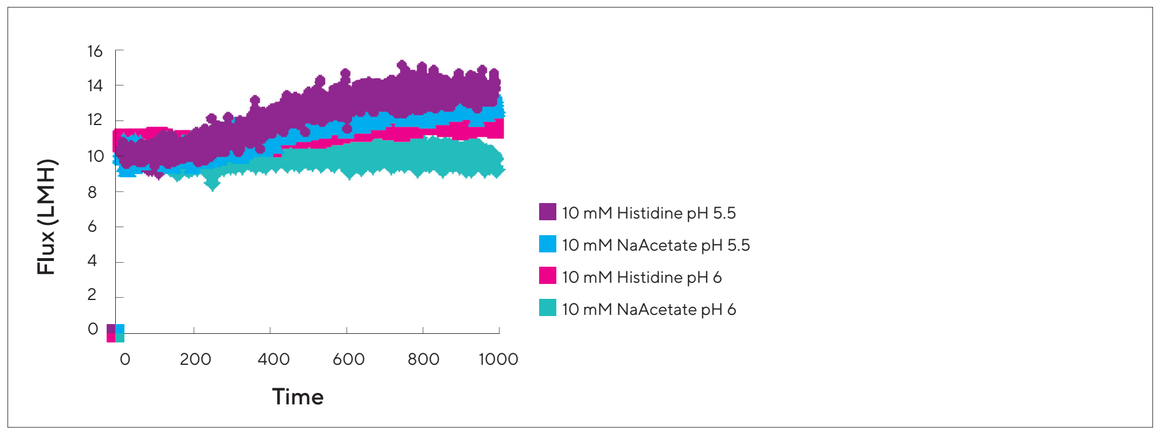

Figure 5: Impact of buffer choice on flux* Diafiltration flux profile from Ambr® Crossflow at 40 mg/mL

In a second experiment the Ambr® Crossflow was used to study the effect of buffer choice on diafiltration flux rates and protein stability. The four buffers were 10 mM sodium acetate pH 6, histidine pH 6, 10 mM sodium acetate pH 5.5 and histidine pH 5.5. The results show that the two buffers at pH 5.5 resulted in higher flux rates. Turbidity measurements performed at 350 nm showed that the histidine buffers led to a more stable product than the acetate buffers. While higher flux rates might be expected at larger scales, the relative ranking of the buffers for optimum diafiltration flux and stability will be scalable.

6. Characterization: Operational Performance Is Reproducible and Consistent*

Relative errors were calculated using variations between the targeted and actual values of the parameters.

	Recovery, %	UF load volume relative error, %	UF product volume relative error, %	UF product concentration relative error, %
Average of 15 runs	98.77	3.1	2.4	-1.1

- Acceptable product recovery (> 95%), UF product concentration (within ±5% target) and HMW impurity level (data not shown)
- Discrepancy in loaded feed and product pool volumes data
- Lower permeate flux was observed compared to the platform process, causing a longer process

7. Conclusion

In conclusion, the Ambr® Crossflow is an automated high throughput device that will help downstream process engineering assess the manufacturability of their candidates at the earliest stages of product development. The material requirements are very low and the system is easy to use. The parallel execution of automated tangential flow filtration experiments will help improve the productivity of biopharmaceutical development and support the launch of new drugs for unmet clinical needs.

- Provides unique combination of membrane technology and HTS automation
- Robust operation – the system is consistent and reliable
- Performance can be correlated to lab scale
  - Loading and final concentration targets achieved
  - Recovery and product quality are comparable

*Case study data generated by: Jennifer Pollard Biologics Proc Dev & Clin Mfg, MSD, Kenilworth, NJ USA