Case Study: Increasing Virus Filter Throughput by Process Optimization Studies

Birte Kleindienst; Peter Kosiol
Sartorius Stedim Biotech GmbH, August-Spindler-Str. 11, D-37079 Goettingen, Germany

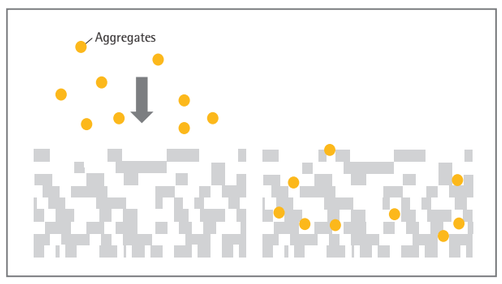
1. Introduction

Monoclonal antibodies and recombinant proteins are typically derived from cell lines for which current regulatory guidelines such as ICHQ5A request at least two orthogonal steps for the inactivation and | or removal of viruses. One of the method being virus retentive filters with nominal pores sizes of 20 nm effective for both small non-enveloped and large enveloped viruses. However, virus filtration performance is often a function of feed stream properties such as buffer composition, pH, conductivity, process pressure, impurity, aggregate levels, protein concentration and protein characteristics. The poster summarizes different optimization studies that can be conducted with virus filters in order to increase virus filter throughput like the use of an adsorptive pre-filter, increase of adsorptive pre-filtration area, feedstream dilution or change of pH and conductivity.

2. Fouling Behavior of Virus Filters

Different feedstream properties can lead to different fouling behaviors being observed during virus filtration operations.

The main reason for flow decay in virus filtration is fouling caused by fouling species that are present in the feed stream such as process impurities and protein aggregates. Aggregates may have a similar size to the pores of the virus filter and become retained by the virus filter membrane.



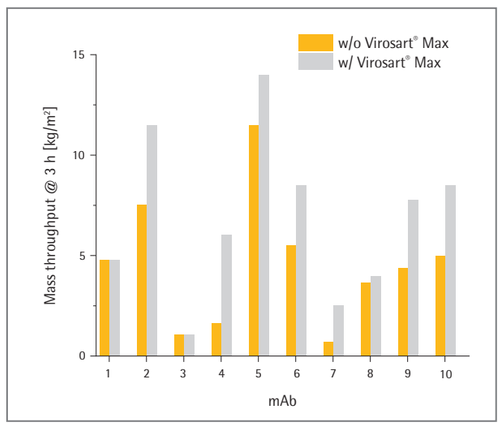
3. Adsorptive Pre-Filtration

Characteristics of Virosart® Max
Virosart® Max is a pre-filter which is designed to significantly increase the performance of downstream virus filters.

Working principle
- Combination of adsorptive capacity and size exclusion leads to removal of virus filter foulants
- Aggregates and | or small hydrophobic molecules are typical virus filter foulants

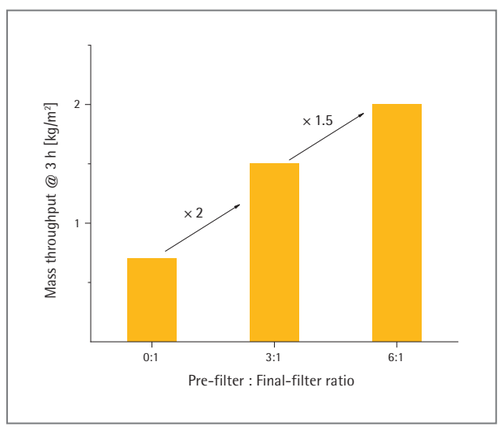
Filter Configuration
- Material: Optimized polyamide
- Pore size: 0.1 µm (nominal)
- Format: Triple-layer pleated elements
- Size: Available from 5 cm^2 to 30“ elements

Impact of Adsorptive Pre-Filter
The overall product throughput of Virosart® HF lab modules was tested with and without Virosart® Max for 10 mAb solutions representative. All filtration runs were run at 2.0 bar | 30 psi constant pressure. Overall product throughput can be improved by 10 % up to 50 % specifically for feed streams containing a high amount of foulants such as aggregates.



Optimization: Pre-filter to Final-filter Ratio
Further improvement of process economics can be achieved by optimizing the ratio of adsorptive pre-filter to final-filter area. By increasing adsorptive pre-filter area, more foulants that tend to block the virus filter, e.g. aggregates can be removed.

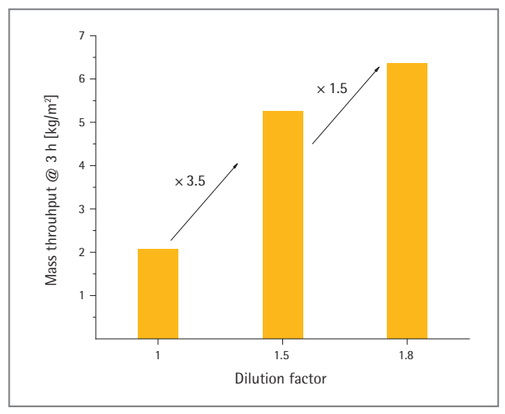
In this study, different pre-filter to final-filter ratios were tested in order to achieve optimal virus filter throughput with a mAb model feed stream. The capacity can be doubled by using a pre-filter to final filter ratio of 3:1 with an overall capacity of 1.5 kg/m^2 after 3 hours of filtration when compared to the case without adsorptive pre-filter. The highest product throughput of 2.0 kg/m^2 can be reached by using a 6:1 pre-filter to final-filter ratio.



4. Dilution of Process Feed Stream

There are feed streams that can be challenging for virus filters to process even with the use of an adsorptive pre-filter. Dilution of the process feed-stream can help here as it can influence molecule folding as well as protein-protein interaction. It can therefore have a positive impact on product throughput performance of the virus filter.

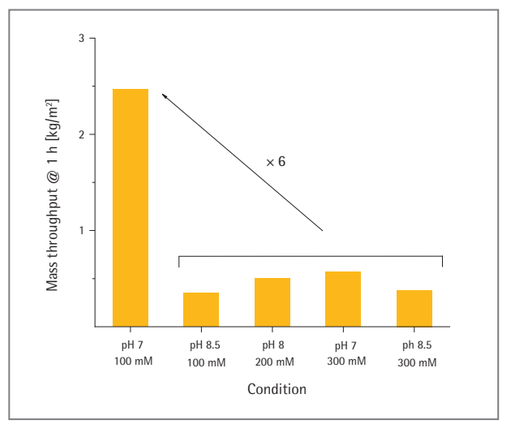
A mAb feed stream was diluted in two steps, each time by factor 1.5. Diluting the feed stream can increase product throughput significantly over Virosart® HF from 2 kg/m^2 up to approx. 6.5 kg/m^2 after 3 hours of filtration.



5. pH and Conductivity

Adapting the pH and conductivity of the feed stream can influence molecule folding as well as protein-protein interaction and can therefore have an impact on product throughput performance during virus filtration.

The effect of pH-shift and conductivity shift of a challenging-to-filter mAb feed stream was tested on the throughput of Virosart® HF. The optimal feed stream conditions for the mAb appears to be at pH 7 and 100 mM showing 6 times the product throughput in comparison to the other conditions tested.



6. Summary

The decision tree blow is giving guidance during the optimization of the virus filtration step.