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Application Note

Scalability of the Viresolve® Pro Solution using the Micro 40 Scaling Tool

Overview

The Viresolve® Pro Solution offers a range of devices designed to meet your virus filtration needs from process development through production-scale operations. The Viresolve® Pro Solution was designed to scale linearly across these device formats with regard to permeability, throughput capacity, and retention. Developed for process development and viral clearance evaluations, the Viresolve® Pro Micro 40 small-scale tool closely represents the larger device formats in terms of fabrication and materials of construction. Effective filtration areas (EFA) of the different device formats are listed in **Table 1**. This report summarizes scalability performance across the Viresolve® Pro Solution from process development to production-scale devices.

Device Format	Primary Use	Effective Filtration Area (m^2)
Micro 40	Process development and viral clearance evaluations	0.00034
Modus 1.1	Pilot-scale	0.017
Modus 1.2	Pilot-scale	0.07
Modus 1.3	Pilot-scale	0.22
Magnus 2.1	Production-scale	0.51
Magnus 2.2	Production-scale	1.53

Table 1. Effective filtration areas of Viresolve® Pro devices.

Scaling Strategy

The small-scale Viresolve® Pro Micro 40 Device is integrity tested during production using the same binary gas test used on larger Modus and Magnus devices. Since the same rigorous integrity testing standards are applied across all formats, virus retention performance can be expected to be consistent among the device formats. To scale up from a Viresolve® Pro Micro 40 Device to a larger device format, the flow rate and capacity of the Micro 40 device is normalized to filtration area. To account for variability, it is recommended to include a safety factor when calculating final filtration area requirements. The safety factor can be rationally determined by considering anticipated process variability.[1]

Materials and Methods

A representative set of Viresolve® Pro Devices was built for this study using the same lot of membrane across different device formats (**Table 2**). Before use, the integrity of all devices was confirmed with binary gas testing.[2] Devices of all formats were tested in parallel for permeability, throughput capacity, and virus retention (**Figure 1**).

In each of the two filtration runs, devices were wet with water for 10 minutes at 30 psi. Permeability was measured for 10 minutes at 30 psi using a solution of phosphate buffered saline (PBS) buffer. Devices were then challenged with a 0.6 g/L IgG solution in PBS buffer spiked with $3x10^7$ plaque forming units (PFU)/mL of PhiX-174 until the flux decayed by 75% (V75) relative to the initial buffer flux. The IgG-based feed solution for this study was specifically formulated to achieve a high degree of fouling at low concentration so that the test would reach the desired filtration end point (V75) at throughput volumes less than 150 L/m^2. Throughout the tests, inlet pressure and filtrate mass and temperature were recorded as a function of time. Filtrate pool samples were collected at V75 and assayed for PhiX-174 titer. The virus log reduction value (LRV) was calculated according to the equation below.

$$LRV = \log\left(\frac{Titer_{feed}}{Titer_{filtrate}}\right)$$

Device Format	Replicates
Micro 40	10
Modus 1.1	2
Modus 1.3	2
Magnus 2.1	2

Table 2. Viresolve® Pro Solution scalability trial: devices and number of replicates.

Devices run in parallel	5	1	1	1

Figure 1. Schematic of scalability tests with number of devices in each run. Two separate filtration runs were performed.

Results & Discussion

Since process development and clearance evaluations are conducted using Micro 40 devices as compared to the Modus and Magnus devices used at pilot and production scale, it is critical that permeability, throughput capacity, and virus retention are predictable and consistent for all device formats in the Viresolve® Pro Solution. The results of studies to evaluate performance are summarized below.

Scalability: Permeability

To assess scalability of the Micro 40 device to the larger Viresolve® Pro Device formats for non-plugging streams, the PBS buffer permeability of each format was quantified at 30 psi inlet pressure (**Figure 2**). The scaling factor is calculated as the ratio of the larger-scale device permeability to that of Micro 40 devices. The error bars represent the range of the duplicate values for the Modus and Magnus devices and one standard deviation for the ten Micro 40 devices used in the scalability trial. The buffer permeability of Viresolve® Pro Modus and Magnus Devices were within 9% and 2% of the permeability of Micro 40 Devices, respectively. Based on these results, Viresolve® Pro Device users can expect similar processing times for flux-based, non-plugging applications, regardless of scale.

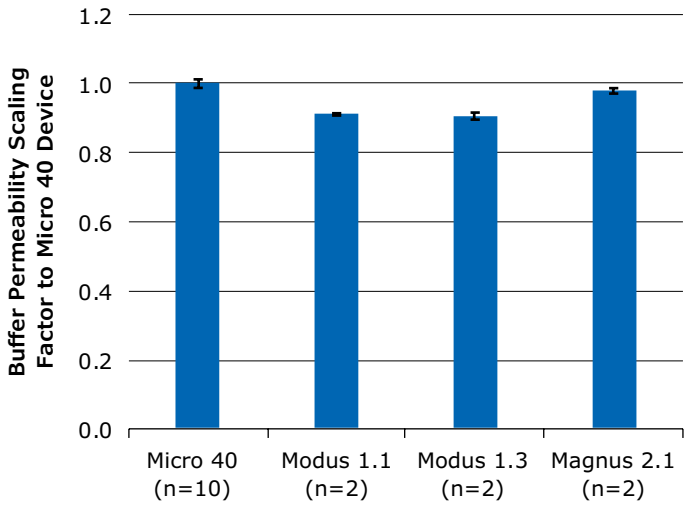

Figure 2. Scaling factors for buffer permeability.

Scalability: Throughput Capacity

The scalability of the Viresolve® Pro Solution for applications with plugging streams was evaluated using an IgG stream that was tailored to be more fouling than the typical Viresolve® Pro application. A common filtration end point for plugging streams is 75% flux decay (V75). **Figure 3** shows the average capacity scaling factor at V75 for each device format. All Viresolve® Pro devices had capacities at V75 that were within 12% of the Micro 40 devices, demonstrating linearly scalable throughput at the filtration end point. Furthermore, similar fouling behavior was observed across the different device scales (**Figure 4**) which indicates that the same underlying phenomena govern the filter performance at each scale. Therefore, throughput capacity should scale linearly between device formats irrespective of filtration endpoint. This is reinforced in **Figure 5**, which shows volumetric throughput as a function of time. For a given processing time, the throughput is consistent across the different device formats.

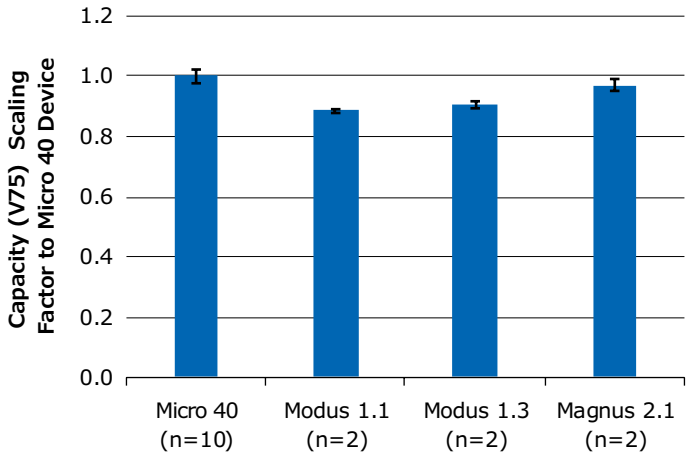

Figure 3. Scaling factors for capacity at 75% flux decay.

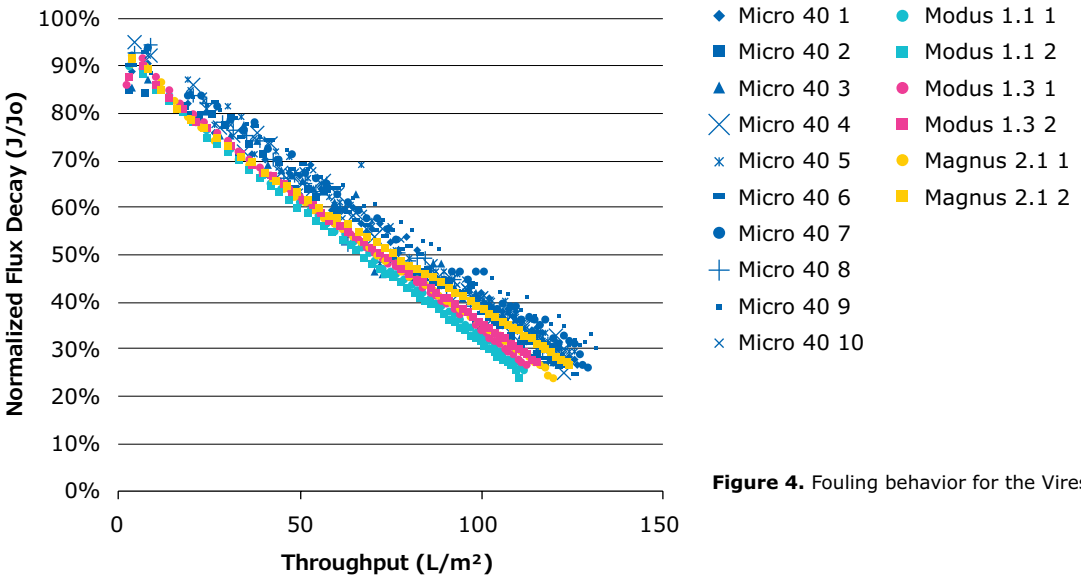

Figure 4. Fouling behavior for the Viresolve® Pro Devices.

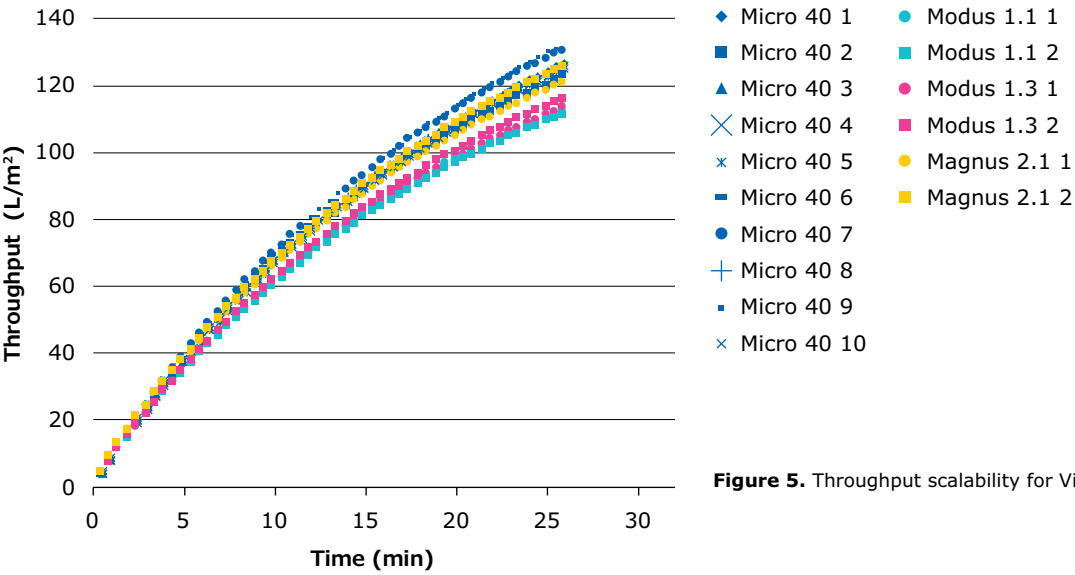

Figure 5. Throughput scalability for Viresolve® Pro Devices.

Scalability: Retention Performance

Equivalent virus retention performance should be expected across Viresolve® Pro Devices at all scales to ensure the retention performance measured in small-scale clearance studies accurately predicts the clearance capability of large scale operations. Retention equivalency across all formats was assessed using PhiX-174, a bacteriophage model of 26–32 nm diameter[3], often used to predict retention of small parvoviruses such as minute virus of mice (MVM) or porcine parvovirus (PPV). Using a PhiX-174 spiked IgG solution, the LRV of the final filtrate pool at V75 was quantified (**Figure 6**). PhiX-174 retention at V75 was greater than 6 logs for all devices, and LRVs were within a range of 0.7 logs, which is considered to be within the uncertainty of the titration assay. Therefore, Viresolve® Pro Device users can expect equivalent retention performance across all device sizes.

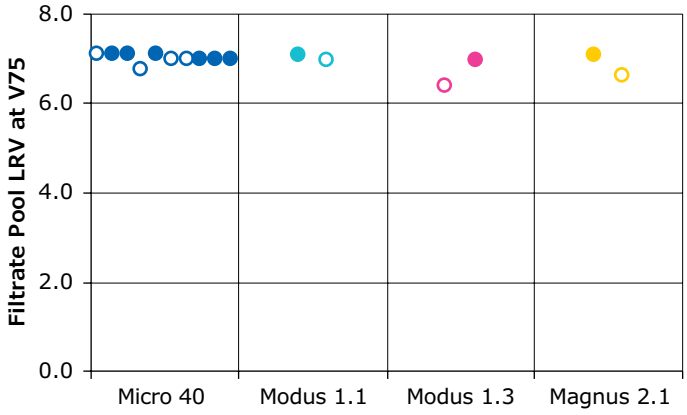

Figure 6. Pool LRV data at 75% flow decay. Filled in circles indicate samples at the assay limit.

Conclusions

These outcomes confirm the linear scalability of the Viresolve® Pro Solution across a range of filtration areas (3.4 cm^2 to 1.53 m^2) in terms of permeability, throughput capacity, and virus retention. As a result, the Viresolve® Pro Micro 40 Device can be used for process development and optimization with a smooth and straightforward scale-up path to large-scale implementation with Viresolve® Pro Modus and Magnus Devices.

References

1. H. Lutz. “Rationally defined safety factors for filter sizing”. Journal of Membrane Science, 341 (2009): 268-278.
2. S. Giglia and M. Krishnan. "High sensitivity binary gas integrity test for membrane filters." Journal of Membrane Science 323 (1) (2008): 60-66.
3. S. Giglia et. al. "Measurement of pore size distribution and prediction of membrane filter virus retention using liquid–liquid porometry." Journal of Membrane Science 476 (2015): 399-409.

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