Technical Brief

Scalable Process Filtration with Millipore Express® SHR 0.1 µm Filters

A variety of sizes and formats aimed to scale up your cell culture media process

INTRODUCTION

Flat disc and small pleated filter devices, such as Opticap® XL 150, 300 and 600 capsules provide convenient formats for low-volume sterile filtration of cell culture media and media additives. This technical brief evaluates the scalability of 47 mm discs and Opticap XL 150, 300 and 600 small-scale capsules (SSC) to larger area, autoclavable only, gamma sterilizable or presterilized Opticap XL3 pleated filter devices.

OBJECTIVE

Define and demonstrate the scalability of 47 mm discs to Opticap XL 150, 300, 600 and Opticap XL3 pleated filter devices.

METHODS AND MATERIALS

Membranes and Supports

Millipore Express SHR filters contain 0.1 µm polyethersulfone (PES) membrane which provide sterilizing-grade performance and mycoplasma removal. These filters are recommended for filtration of cell culture media and media additives, where the key performance needs are process efficiency and mycoplasma clearance.

Millipore Express SHR 0.1 µm filters contain a single layer of membrane sandwiched between two layers of non-woven support material which support the membrane and provide robustness during processing. Given that customer applications with Millipore Express SHR filters require compatibility with different device sterilization methods, the non-woven support materials vary. Non-woven membrane supports are comprised of either polypropylene, polyethylene or polyester. See Table 1 for materials of construction.

Table 1. **Materials of Construction for Millipore Express SHR 0.1µm Filters**

	Autoclave Only Opticap XL/XLT 3-30 in. capsules	**Gamma/Sterile Opticap XL/XLT 3-30 in. capsules**	**Gamma/Sterile Opticap XL 150, 300 & 600 small-scale capsules**
Core	Polysulfone	Polysulfone	Polysulfone
Outer Sleeve	Polypropylene	Gamma stable polypropylene	Gamma stable polypropylene
End Caps	Polypropylene	Gamma stable polypropylene	Gamma stable polypropylene
Membrane Support	Polypropylene	Polyester	Polyethylene
Membrane(s)	Polyethersulfone	Polyethersulfone	Polyethersulfone
O-rings	Silicone Rubber	Silicone Rubber	Silicone Rubber
Capsule Housing	Polypropylene	Gamma stable polypropylene	Gamma stable polypropylene
NaOH Compatibility	Fully compatible >1N	Limited compatibility	Fully compatible >1N

The average effective filtration area (EFA) measured in these trials is shown in Table 2. To determine the filter's EFA, the filters were stained with media solution during throughput testing and were subsequently cut open and the active (stained) area was physically measured.

Actual areas of the individual filters were within 3.3% of the averages listed in Table 2. The area of a 47 mm disc can vary depending upon the torque method used during holder assembly and the o-ring material type. For this study, a consistent torque setting at 25 in-lb and silicone o-rings provided a mean value of 13.0 cm^2 for 47 mm discs. All tested filters were from one membrane lot.

Note: Opticap XL3 capsules were tested as capsule sub-assemblies.

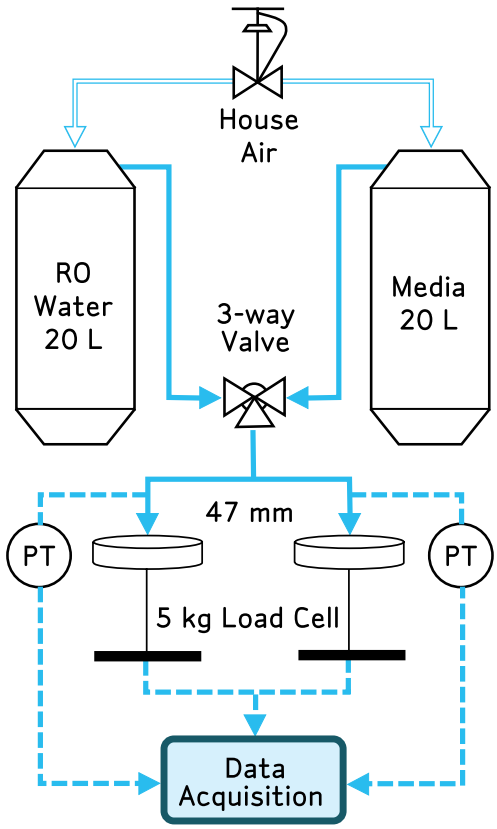
Table 2. Effective Filtration Area (EFA)

Device	Flat disc	Opticap XL capsule			Opticap XL3 capsule	
	47 mm	150	300	600	SHR-A (Autoclavable only)	SHR-G (Gamma compatible)
# filters tested	12	4	3	3	4	6
Area (cm^2)	13.0	247	493	1023	1397	1529

PROCESS STREAM

Soy-based media was prepared in 300–450 liter batches. In an open mixing vessel, 10 g/L Soy Peptone Type IV was mixed with 8.0 g/L sodium chloride, 2.2 g/L sodium phosphate dibasic, 0.2 g/L potassium phosphate monobasic and 0.2 g/L potassium chloride in 300–450 liters of reverse osmosis (RO) water. The media batch was then pumped into a 700 L disposable process container. A 20 or 225 liter pressure vessel was used to deliver the media.

Figure 1. Test System for 47 mm Disk Testing



TEST SYSTEMS

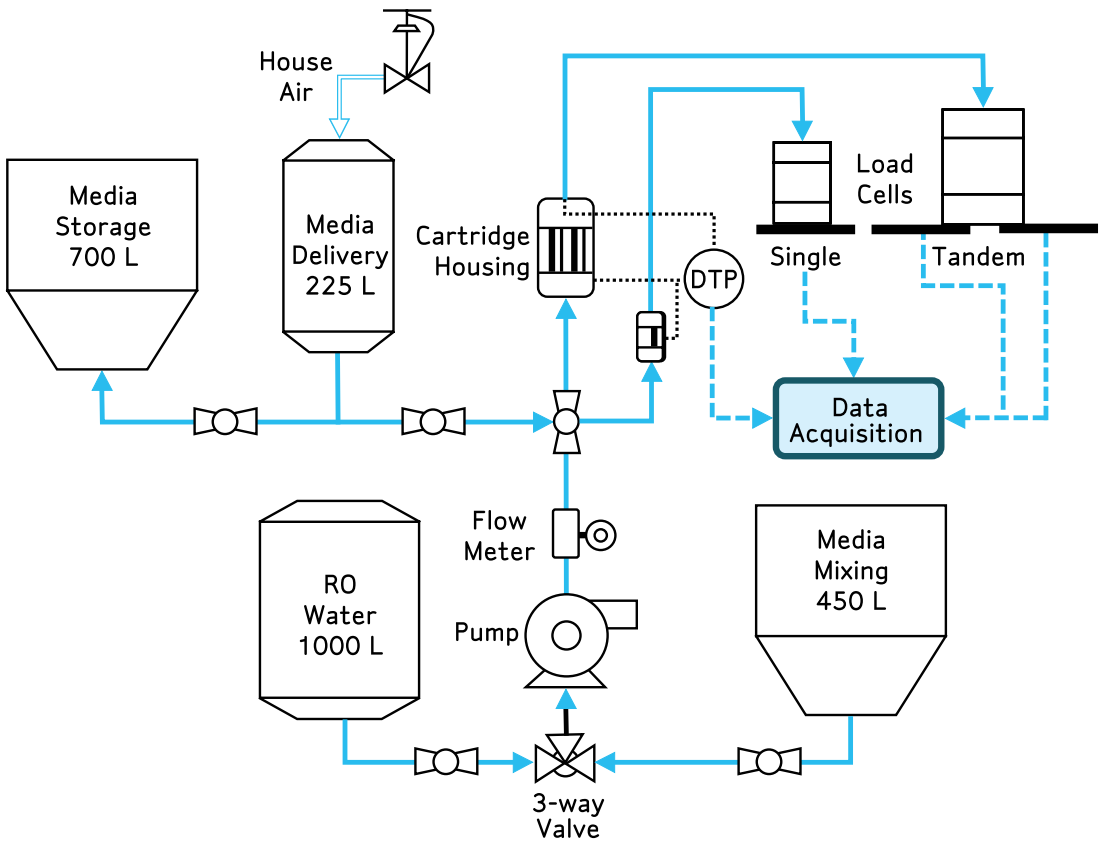
Two systems were used for permeability and capacity testing. For each test system, calibrated pressure transducers and calibrated load cells were used to measure pressure and filtrate weight over time. The data was automatically recorded using a data acquisition system (DAQ). Temperature was recorded manually. Figure 1 shows the test system for 47 mm disc testing. Larger process volumes for device testing required use of a centrifugal pump and 225 liter pressure vessel to deliver the water and media as shown in Figure 2. Differential pressure across the devices was measured. Tandem load cells were used to collect the filtrate weight of the Opticap XL3 filters.

TEST METHOD

To assess scalability, water permeability and throughput at a predetermined test time were measured at all membrane scales. Soy media was selected as a moderately fouling model stream for throughput testing. Testing the 47 mm disc and various device sizes demonstrated up to 118 fold scale-up to the Opticap XL3 filter devices.

Prior to testing, piping and devices were purged of air. Devices were wet with RO water for a minimum of two minutes at 5–10 psi differential pressure. Following a second purge, water permeability was then measured at 10 psi differential pressure for at least two minutes. A three-way valve was used to switch to the pressurized media tank for seamless transfer between water and soy media feed. The filters were challenged with media solution at 10 psi differential pressure for at least 30 minutes. Both systems were thoroughly flushed with RO water prior to subsequent runs.

Figure 2. **Test System for Device Testing**



RESULTS

Water Permeability

Water permeability at 23 °C is summarized in Figure 3. Mean water permeability of 47 mm discs was 606 Lmh/psi (dashed line). The mean permeability values of Opticap XL 150, 300 and 600 devices with Millipore Express SHR membrane was within 2% of 47 mm disc mean permeability. Mean permeability values of SHR-A (autoclavable only) and SHR-G (gamma compatible) Opticap XL3 capsules were within 6% of 47 mm disc mean permeability.

Throughput

Soy throughput at 30 minutes test time is summarized in Figure 4. Throughput refers to the filtrate volume per unit area of membrane.

Throughput values were normalized, using 47 mm disc data generated with each media batch, to account for batch to batch variability of the soy media among the test runs. Mean throughput of 47 mm discs was 1148 L/m^2 at 30 minutes (dashed line). The mean throughput of Opticap XL 150, 300 and 600 devices were within 9% of 47 mm disc mean throughput. Average throughput of the SHR-A (autoclavable only) Opticap XL3 capsule subassemblies and SHR-G (gamma compatible) Opticap XL3 capsule sub-assemblies were within 3% and 13% of 47mm disc mean throughput, respectively.

Figure 3. Water Permeability

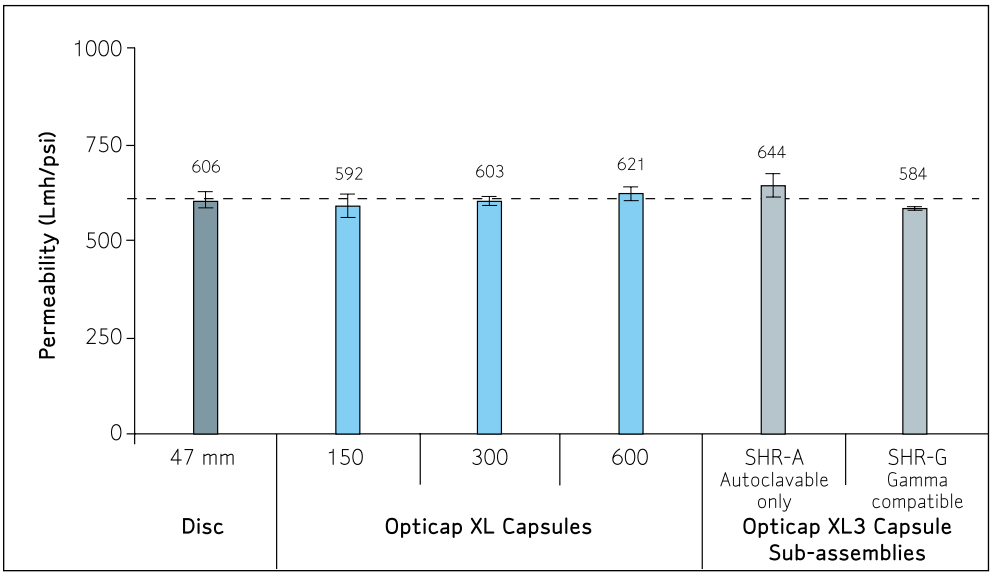
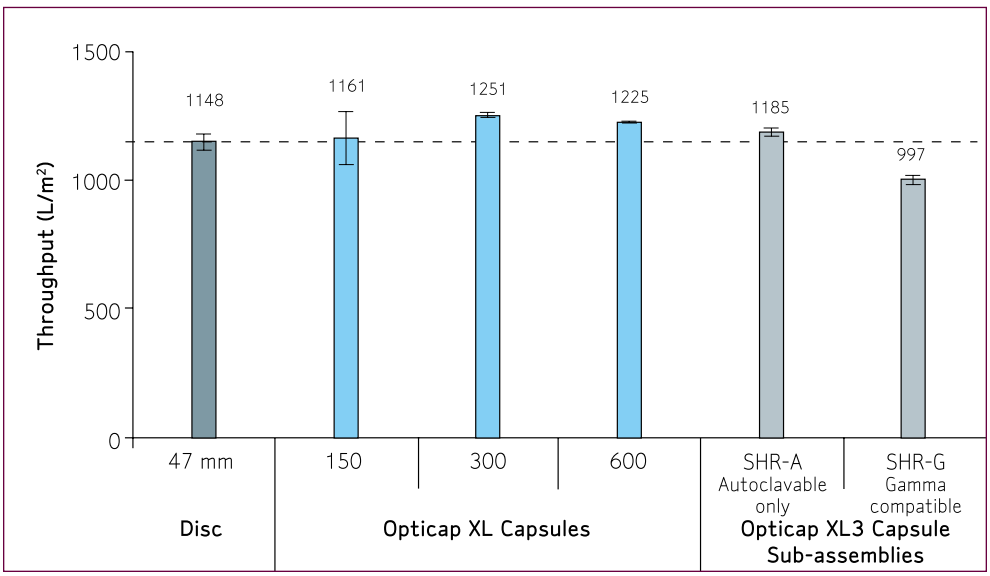


Figure 4. 30 Minute Normalized Throughput at 10 psi



THROUGHPUT CURVES

Throughput profiles of the test filters for the three runs are shown in Figures 5, 6 and 7. Each figure represents a run with a different media batch. In these figures, the dashed vertical line at 30 min refers to the throughputs used to generate the normalized results shown in Figure 4. The 30 minute test time point was used to calculate scaling factors since it captured the majority of the plugging profile and ensured an accurate prediction of the filters throughput performance. Flow decay at 30 min was measured at 70–85% for all tested filters.

Throughput measured on 47 mm discs, Opticap XL150, 300 & 600 devices and Opticap XL3 capsules show some small variability between the filters but all exhibit similar plugging behavior.

Figure 5. Run 1 Throughput Profiles

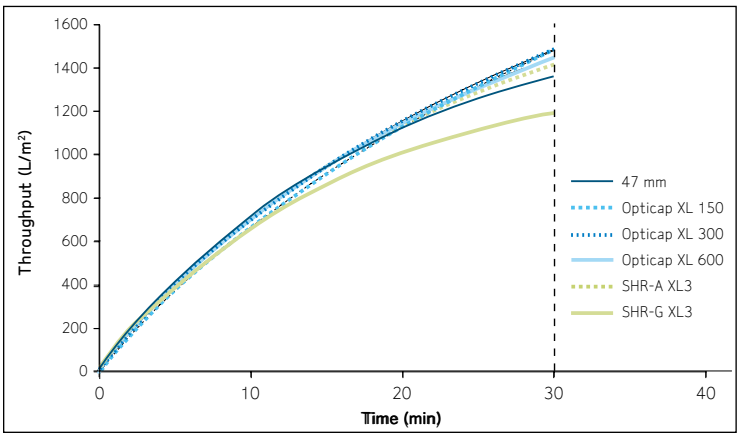


Figure 6. Run 2 Throughput Profiles

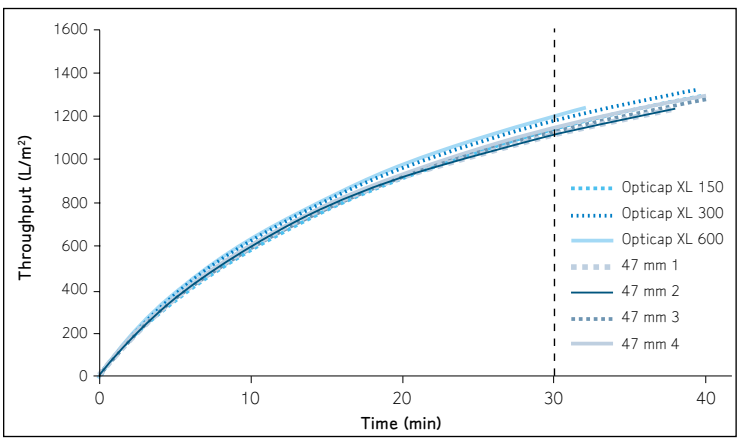
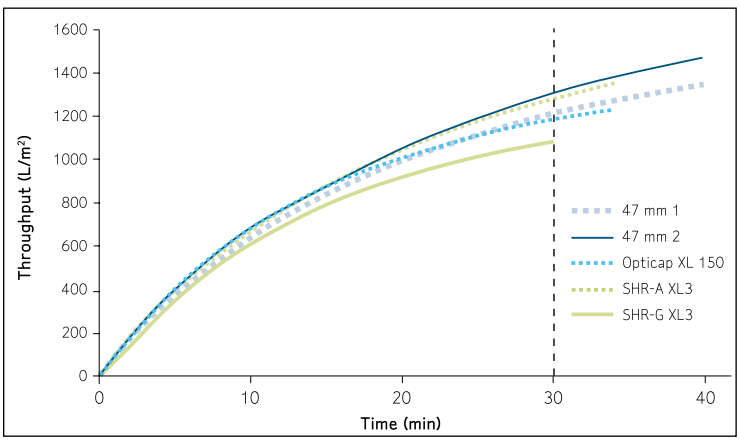


Figure 7. Run 3 Throughput Profiles



DISCUSSION

Table 3 presents the scalability of Opticap XL small-scale capsules and Opticap XL 3 capsules to 47 mm discs with Millipore Express SHR membranes. The following values are based on the permeability and normalized throughputs presented in Figures 3 and 4.

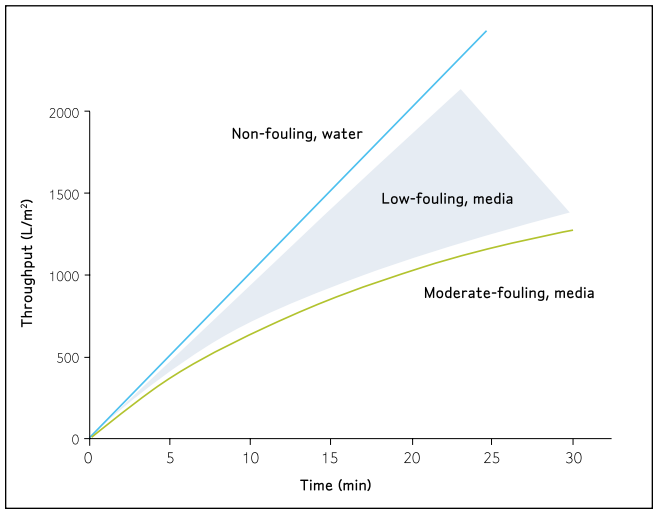
These values reflect throughput at 30 min test point where flow decay reached 70–85%. Performance of Opticap XL SSC devices to Opticap XL3 autoclave only capsules is demonstrated to be within 10% of 47 mm disc performance. The SHR-G gamma compatible capsule device performance demonstrates scalability within 13% of 47 mm disc performance.

In this technical brief, water and soy media were used as model streams to represent non-fouling and moderately fouling streams to bracket worst case for Millipore Express SHR filter scalability. Filtration of low-fouling streams, such as prefiltered media, which is sized primarily on flux is a more typical application for single layer Millipore Express SHR filters.

Figure 8 presents the low-fouling filtration curves for Millipore Express SHR membrane in a typical application versus the curves generated previously using non-fouling and moderately-fouling model streams.

For low-fouling media, scalability of Opticap XL devices for both permeability and throughput is predicted to be well within the 13% range seen with the moderately fouling media used in this study.

Figure 8. **Millipore Express SHR Throughput Range**



Permeability and Sizing for Flux Based Applications

Water permeability of all devices matched the permeability of 47 mm discs within 6%. This applies for non-fouling streams, such as buffers and some media.

Throughput and Sizing for Plugging Feed Steams

Throughput of all devices, except gamma compatible Opticap XL 3 (SHR-G) capsules, matched the throughput of 47 mm discs within 9%. Throughput of Opticap XL3 SHR-G capsules were within 13% of 47 mm disc throughput. This scalability result is applicable to moderately-fouling and low-fouling process streams.

Table 3. **Scalability to 47 mm Discs***

Device		Permeability (non-fouling)	Throughput (moderate fouling)
Millipore Express device Opticap XL small-scale capsule	150	0.98	1.01
	300	1.00	1.09
	600	1.02	1.07
Opticap XL3 capsule	SHR-A	1.06	1.03
	SHR-G	0.96	0.87

*Scalability value = Opticap XL 150, 300, 600 or Opticap XL3 capsule subassemblies/47 mm permeability or throughput

In general, these factors apply to the following filtration scalability studies:

- Variability in effective filtration area of individual device
- Variability in membrane properties
- Different structural properties of non-woven support types (polyester vs. polyethylene vs. polypropylene)
- Media batch variability
- Pressure differences due to various device housings, fittings and elevations
- Presence of upstream support
- Test error

Given the flow rates evaluated in this study, restrictions due to the device housings did not contribute greatly to pressure differences (<0.05%). As a result, such flow differences were not taken into account. Additionally, pressure differences due to fittings and elevations were deemed minor in the test systems and were not accounted for in the results.

Opticap XL 3 autoclave only and gamma compatible capsules contain different support materials. These support materials can have different flow resistances which can affect permeability and throughput. Furthermore, the 47 mm disc testing did not include testing with an upstream support which can alter flow resistance of the filter. While this case study does demonstrate scalability between 47 mm discs and devices, the degree of scalability may vary with the test stream.

Effective filtration area of individual devices was well controlled and within 3.3% of the averages. This variation will result in slight differences in throughputs.

As a general recommendation, test system and device factors which can lead to variability in scaling should be considered in process system sizing.

CONCLUSION

For Millipore Express SHR membranes, 47 mm disc performance can reliably predict (within 13%) the performance of Opticap XL 150, 300, 600 devices and Opticap XL3 autoclavable and gamma compatible capsule devices. Results with water permeability and soy throughput provided a range of non-fouling to moderately-fouling states to mimic and bracket filter performance in biopharmaceutical tissue culture media filtration applications.

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