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Application Note

Higher Volume Processing Using Natrix® Q Device

Parallel Manifolding with Mobius® Single-use Assemblies

Introduction

The Natrix® Q chromatography membrane is a high capacity, high throughput strong anion exchange (AEX) membrane that improves process productivity and flexibility as compared to traditional chromatography resins. Available in several formats, these single-use chromatography membrane devices are ideal for both traditional batch and intensified or continuous purification applications. The Natrix® Q Process 600 device is the largest chromatography membrane device format, with a membrane volume (MV) of 460 mL and a process flowrate of 10 MV/min. Typical mass loadings are 10 kg mAb/LMV. To achieve higher loadings and throughputs for larger scale manufacturing, multiple devices can be manifolded in parallel (**Figure 1**).

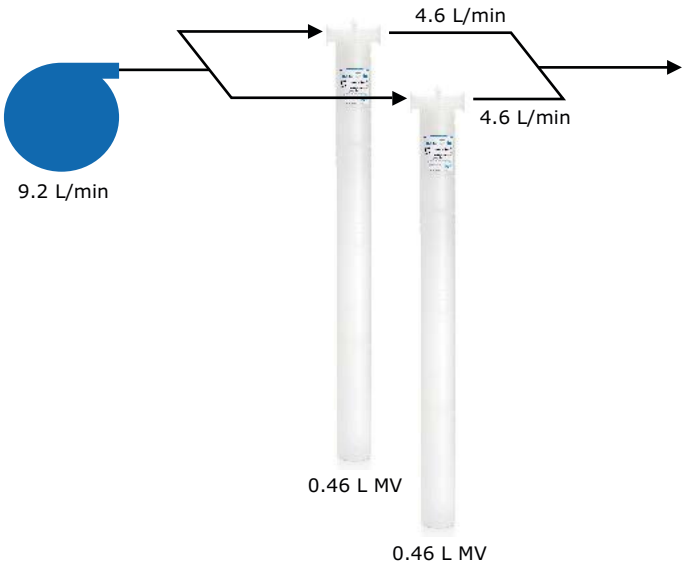


Figure 1.

Visualization of two Natrix® Q Process 600 devices with membrane volumes (MV) of 460 mL (0.46 L) manifolded in parallel.

When parallel manifolding, it is important to balance any minor variability in device permeability to enable more consistent flow and residence time in the individual devices. This can be achieved by incorporating flow restriction into the manifold, which respects the Natrix® Q Process 600 pressure rating (72 psi/5 bar).

This Application Note describes a series of tests to assess performance of a Mobius® tubing assembly containing two Natrix® Q Process 600 devices manifolded in parallel. An extreme difference in permeability between the two devices was simulated by applying a pinch clamp on the outlet of one device. The results help qualify an approach to maximize Natrix® Q performance (load and throughput) in commercial-scale manufacturing.

Manifold Design

A Mobius® tubing manifold consisting of two tubing sets was connected to the Natrix® Q Process 600 devices: one was connected to the inlets of the manifolded devices, the other to the outlets. The inlet tubing was ½ in. inner diameter (ID) throughout, whereas the outlet tubing included a 6 in. length by ¼ in. ID section to provide the flow restriction, **Figure 2**.

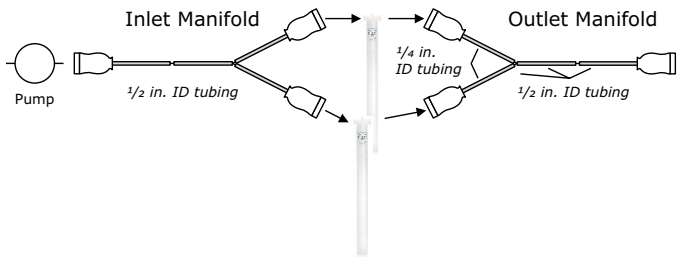


Figure 2.

Mobius® Tubing Manifold design for placing two devices in parallel with smaller ID tubing after each device.

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Study 1:
Tubing Manifold Restores Even Flow Distribution of Two Parallel Devices

Tests were performed with the Mobius® tubing manifold to determine suitability for use with two Natrix® Q Process 600 devices connected in parallel. In addition, the impact of backpressure on device permeability and flow rate was assessed. Tests included:

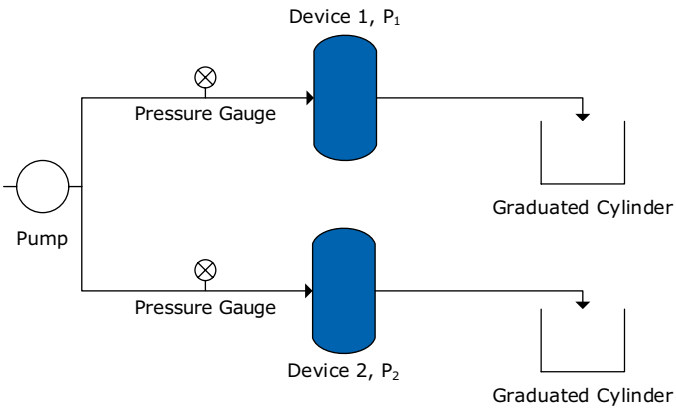
Test I. 'Baseline' run: assess flow modulation with two devices of similar permeabilities.

Test II. 'Worst Case' scenario: assess flow with two devices of different permeabilities, modeled by using a pinch clamp to add 2.0 psi backpressure after Device 2.

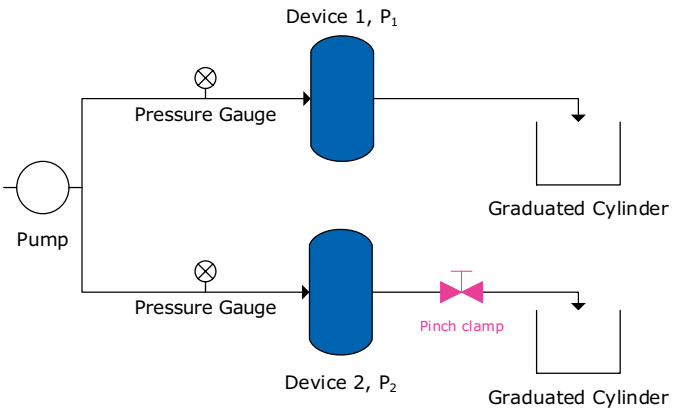
Test III. Tubing implementation: assess the narrow ¼ in. ID outlet tubing on the 'Worst Case' scenario.

Figure 3 shows a schematic of the tests, with P_x representing the device's permeability. It was important to measure individual device flow rates for all three tests. For Test I and Test II, ½ in. ID tubing was used at the outlet of each device. For Test III, only the ¼ in. ID section of the Mobius® tubing manifold was connected to each device outlet.

A) Test I – Baseline



B) Test II – Worst Case



C) Test III – Worst Case with Narrow Outlet Tubing

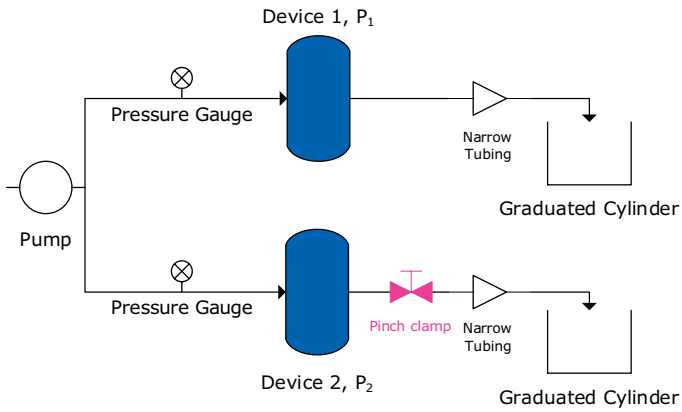


Figure 3.

Process Flow Diagram (PFD) for the three tests performed with a simulated pressure drop on Device 2.

For each test, an 80 mM sodium chloride solution was passed through the manifolded Natrix® Q Process 600 devices at 10 MV/min, or 9.2 L/min for three minutes and flow data was captured by a graduated cylinder and a balance. Inline pressure gauges at the inlets of the Mobius® tubing manifold monitored pressure throughout each test.

System pressure through each parallel stream were also noted at 10 MV/min. The Mobius® tubing manifold added 3.9 psi to the system pressure, well below the device pressure rating of 72 psi.

Flow rates of each device for the three test conditions are shown in **Figure 4**. Results show similar flow rates for the devices in the 'Baseline' run with similar permeabilities. However, under the 'worst case' conditions, the relative flow rate difference caused by individual device permeabilities was 46%.

By implementing the narrow tubing on the outlets of the manifolded devices, relative differences in flow rates were reduced to 16%.

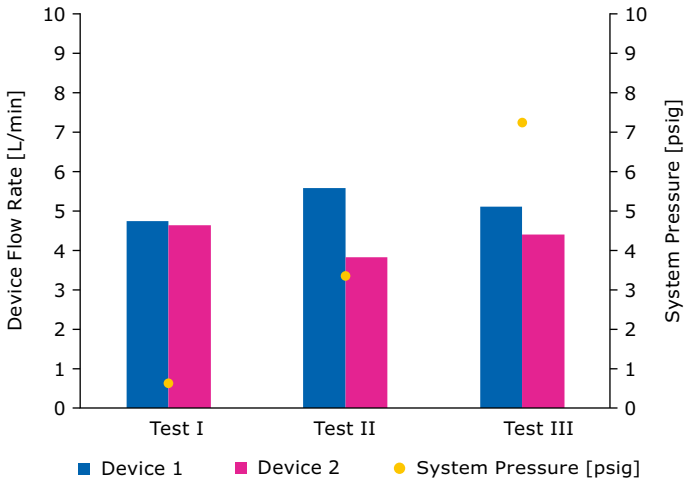


Figure 4.

Flow distribution between the three test scenarios showing the flow imbalance.

Results confirmed that an equal and inline resistance in the single-use tubing manifold mitigated potential permeability differences between devices manifolded in parallel.

	Device 1 % flow	Device 2 % flow	Relative difference in % flow	System pressure [psi]
Test I – Baseline	50.5	49.5	2.0	0.6
Test II – Worst Case-pinch clamp	59.4	40.6	46.3	3.4
Test III – Worst Case with ¼ in. tubing	53.7	46.3	16.0	7.3

Study 2: Binding Capacity Study confirms equivalent performance between parallel and individual devices

To ensure the purification capability of the Natrix® devices were not affected by parallel manifolding, a binding capacity study was performed with two Natrix® Q Process 600 devices manifolded in parallel with the Mobius® tubing manifold. A CoPrime® Biochromatography System, provided the pump capacity up to 20 L/min. The specifications of Natrix® Q membrane chromatography devices list a minimum Bovine Serum Albumin (BSA) binding of 200 g/L_{MV}; this was the benchmark for tests of the Mobius® tubing manifold.



CoPrime® Biochromatography System

Performance of two parallel manifolded Natrix® Q Process 600 devices was compared to that of a single Natrix® Q Process 600 device. The tests included:

Test I. 'Baseline' run: Single Natrix® Q Process 600 device with ½ in. tubing.

Test II. Mobius® tubing manifold implementation: assess the narrow ¼ in. ID outlet tubing with two parallel devices and a similar setup as the previous study (pinch clamp after Device 2 to add 2.0 psi backpressure to model different permeabilities).

Total flow rate was maintained at 10 MV/min, during the Equilibration and Loading step prior to Elution, which corresponded to 9.2 L/min for the parallel, and 4.6 L/min for the single devices.

Binding capacity for Test I and Test II were determined by a 10% cutoff of the BSA breakthrough curve by A280. The maximum A280 reading through the CoPrime® Biochromatography System was previously measured.

For mass bound calculations, 1 M sodium chloride solution was used to elute protein from each of the parallel devices in Test II. Valves were placed after each device, and they were opened and closed to allow for individual device flow. The flow rate was also reduced to 4.6 L/min to maintain 10 MV/min. During normal operation and implementation, the manifolded devices would elute simultaneously at a 9.2 L/min flow rate. **Figure 5** shows a schematic of the tests.

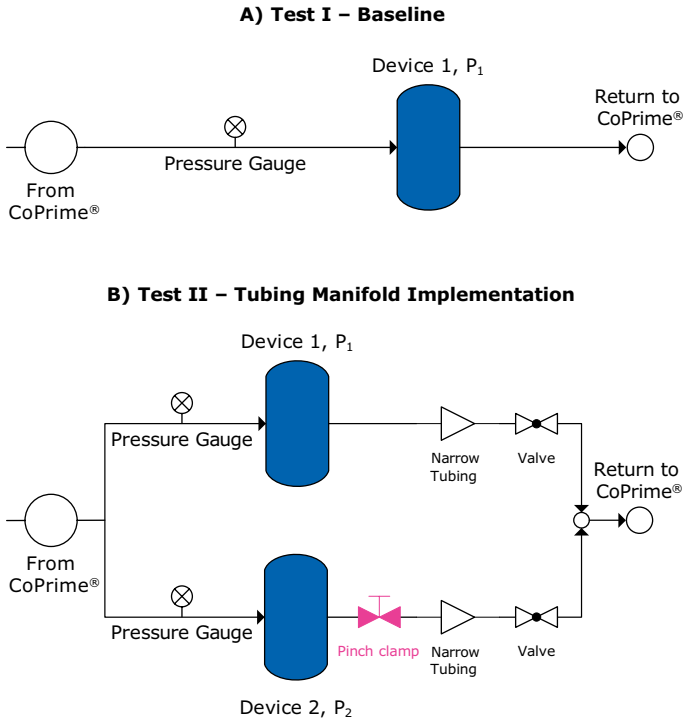


Figure 5.

PFD for the two tests performed for the binding capacity study.

Breakthrough Curve and Binding Capacity are Comparable

Breakthrough curves from tests with single and manifolded devices were near identical, shown in **Figure 6**, confirming that the Mobius® tubing manifold minimized differences in device permeabilities and restored even flow distribution across two devices. Without these manifolds to balance volumetric flow, it is likely that Device 1 would have experienced protein breakthrough earlier than Device 2, which would reduce overall mass loading of the manifold. The overall breakthrough curve of the manifolded setup would shift to the left.

BSA binding capacities were 226 g_{BSA}/L_{MV} for Test I and 232 g_{BSA}/L_{MV} for Test II, which are in line with the expected 200 g/L_{MV} benchmark values for Natrix® Q AEX membrane chromatography devices.

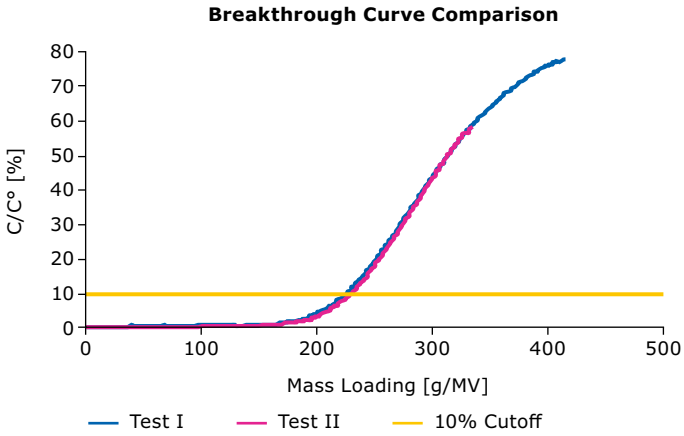


Figure 6.

A280 breakthrough curve between the parallel device and single device setup.

Total Mass Bound and Elution Profile are Comparable

The Mobius® tubing manifold implementation in Test II provided equal flow distribution and enabled expected binding capacity performance with Natrix® Q Process 600 devices manifolded in parallel. Following protein loading, the Natrix® Q Process 600 devices were eluted individually, and eluate samples were collected for analysis. **Figure 7** shows the mass of BSA protein eluted from each device.

The BSA bound on the parallel devices were within 10%, suggesting that the manifold equalized performance despite a difference in device permeability. A slightly higher amount of BSA was loaded onto the individual device as reflected in the breakthrough curve.

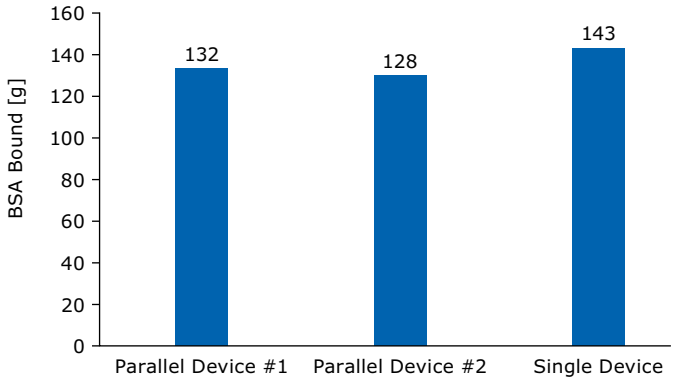


Figure 7.

Mass BSA bound and collected from each Natrix® Q Process 600 device.

Elution peak profiles for each of the single and two manifolded devices were generated by A280 (**Figure 8**). BSA began eluting after 4 MV consistently across all devices, indicating reproducibility of the Natrix® Q Process 600 devices.

The slightly higher loading on the individual device is reflected in the extended elution profile on the right hand side.

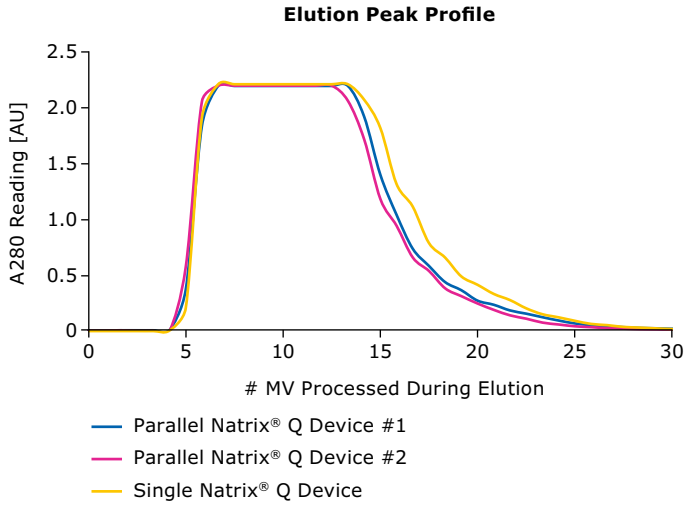


Figure 8.

Elution peak profile of the three Natrix® Q Process 600 devices tested.

Study 3:
Comparable Performance with More Than Two Devices in Parallel

This concept of manifolding devices in parallel could, in principle, be expanded to any number of devices. The basic premise for successful implementation remains the same: an equal and in-line resistance by a narrow outlet tubing will help equalize flow. To test this approach, Mobius® tubing manifolds were designed to accommodate four Natrix® Q Process 600 devices manifolded in parallel; the manifold included ¼ in. ID × 6 in. length narrow tubing in the outlet. A similar test approach was used:

Test I. 'Baseline' run: assess flow modulation with four devices of similar permeabilities.

Test II. 'Worst Case' run: Assess flow with four devices of different permeabilities, modeled by using a pinch clamp to add 2.0 psi backpressure after Device 1 and 3.

Test III. The 'Worst Case' run including the narrow ¼ in. ID outlet tubing.

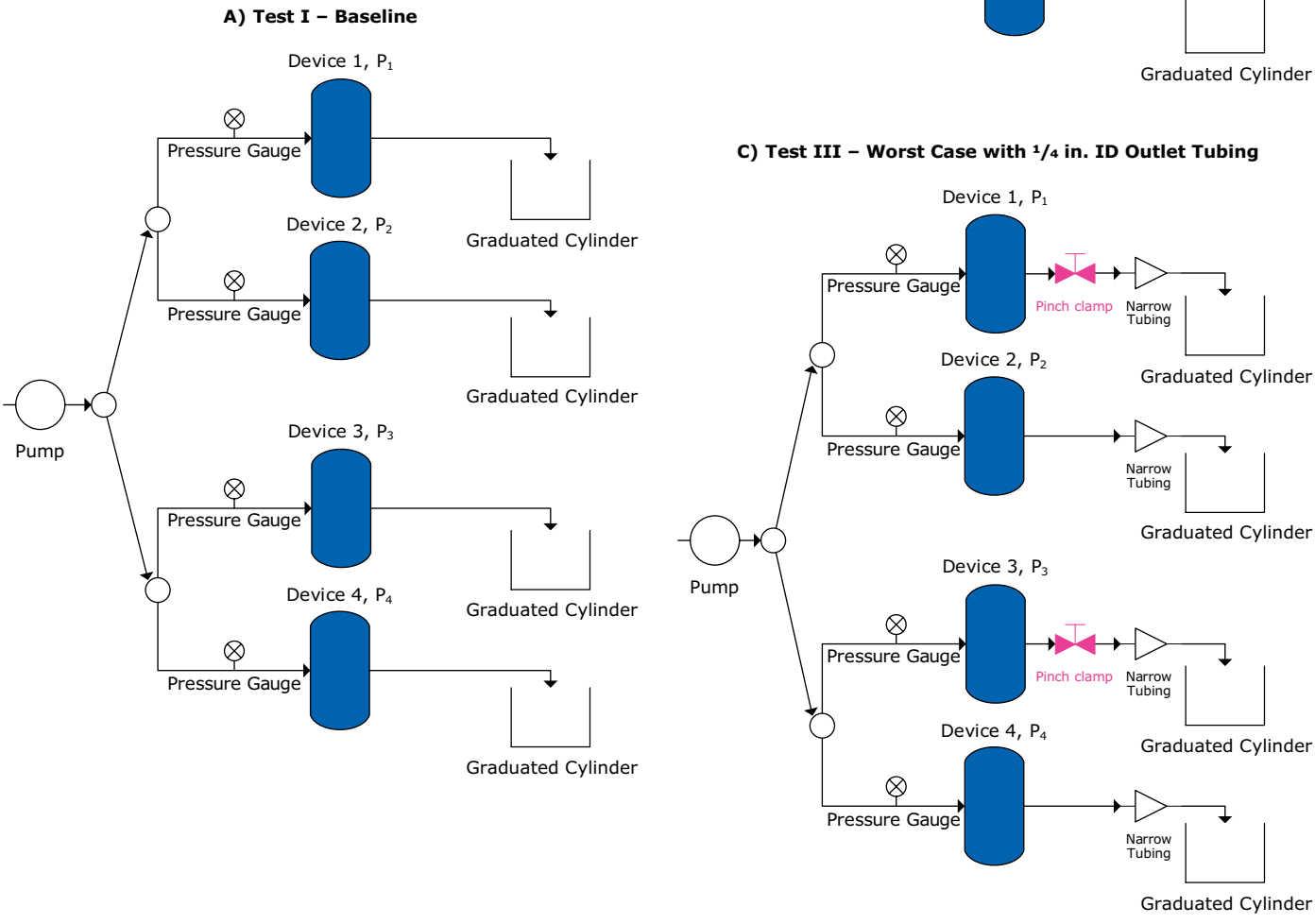


Figure 9.

PFD for the three tests performed with a simulated pressure drop on Devices 1 & 3.

An 80 mM sodium chloride solution was passed through the manifolded Natrix® Q Process 600 devices at a total flow rate of 18.4 L/min for three minutes. Individual device flow rates were measured using a graduated cylinder and weight balance.

As shown in **Figure 10**, results from the baseline tests suggest equal flow distribution is possible with 4 parallel devices. However, as shown in Test II, if one or more of the four manifolded devices has lower permeability than others, flow imbalance occurs, which may impact purification performance. By adding an inline resistance in the form of a narrow tubing in the outlet of the Mobius® tubing manifold, more consistent flow is observed across the manifolded devices.

For manifolding more than 4 devices in parallel; pump capacity may limit implementation.

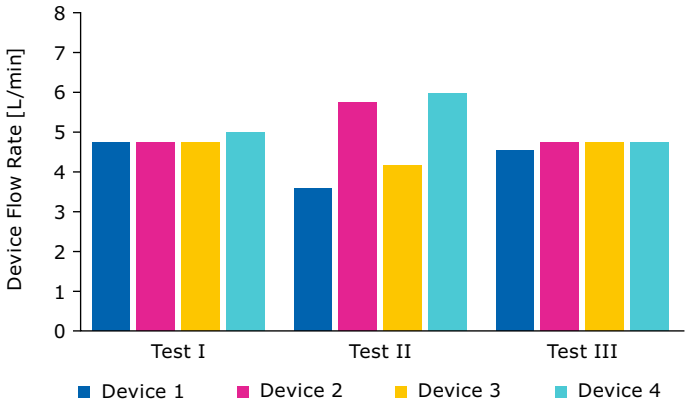


Figure 10.

Flow distribution between the three scenarios tested showing the flow imbalance (%).

	Device 1 % flow	Device 2 % flow	Device 3 % flow	Device 4 % flow
Test I – Baseline	25	25	25	26
Test II – Worst Case-pinch clamp	19	30	21	31
Test III – Worst Case with 1/4 in. tubing	24	25	25	25

Conclusion

The Natrix® Q Process 600 device is a chromatography membrane device that can typically achieve mass loadings of 10 kg mAb/L_{MV}. Processing batches with more mass than a single device can accommodate requires parallel manifolding of multiple devices. Mobius® tubing manifolds can be employed to add inline resistance downstream of each Natrix® Q Process 600 device to guard against possible device permeability differences. These tubing manifolds equalize flow between manifolded devices and result in more predictable performance.

Results from these studies demonstrate the capabilities of single-use tubing systems to mitigate the impact of device permeability differences and enable comparable flow and consistent binding capacity without adding significant pressure. Results were confirmed in setups with two and four Natrix® Q Process 600 devices. In theory, the Mobius® tubing manifold could be applied to any number of devices in parallel, but it should be noted that pump capacity must be scaled and could be a limitation.

The Mobius® tubing manifolds are made-to-order assemblies that support the plug-and-play Natrix® Q chromatography membrane devices. These membrane chromatography devices and enabling single-use tubing assemblies offer benefits to biopharmaceutical manufacturers seeking easy-to-implement flowthrough purification steps with high mass throughputs at any scale.

Standard assembly drawings that include two or four devices are listed below. For additional information, please contact your sales specialist: **SigmaAldrich.com/support**

Assembly Drawing Number

	Inlet Manifold	Outlet Manifold
Two Devices	MIL0000L2259991	MIL0000L2259992
Four Devices	MIL0000L2310177	MIL0000L2310178

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