Millipore®
Preparation, Separation,
Filtration & Monitoring Products

CoPrime® Biochromatography Process-Scale System

A fully automated, configurable system for biopharmaceutical manufacturing and cGMP process-scale applications

Using This Guide

This performance guide is a reference document that provides highlights of key performance aspects of the CoPrime® Biochromatography Process-Scale System. This guide includes information from a number of applications and case studies that were designed and/or selected to provide a diverse overview of the system's performance under a range of expected processing conditions.

The results included in this guide summarize outcomes and observations obtained in studies conducted using particular model feed streams and experimental conditions. It is important to note that results are intended as general examples and should not be construed as product claims or specifications.

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Introduction

The CoPrime® Biochromatography Process-Scale System is designed to achieve optimum separation and purification of monoclonal antibodies, vaccines, plasma and therapeutic proteins. The system is ideally suited for pilot and production manufacturing.

The CoPrime® system was designed based on 30 years of process knowledge, system design, and engineering expertise to provide biopharmaceutical manufacturers with a configurable and intuitive process-scale purification system. The system has an extended flow rate range and greater gradient accuracy across an extended flow rate window. The innovative design allows for seamless implementation into any process, resulting in an integrated and homogeneous downstream process, improving operational efficiency.

A fully-configured CoPrime® Biochromatography System is able to run up to 20 L/min at 4 bar. A fully configured system is equipped with:

- Human Machine Interface (HMI) equipped with Common Control Platform® (CCP®) V6 software to control the complete system, run recipes, and generate batch reports
- Primary line with five inlets with an air sensor on the product inlet, a Quattroflow™ 1200S membrane pump, a pressure switch, and a mass flowmeter
- Secondary line with two inlets, a Quattroflow™ membrane pump 1200S, a pressure switch, and a second mass flowmeter
- Bubble trap equipped with a vent valve connected to drain via an air break
- Pre-column filter housing with a pressure sensor
- Pre-column instrumentation composed of pH and conductivity sensors
- HETP inlet which is a 3-way NovAseptic® valve to inject an HETP sample as close to the column as possible
- Pre-column air sensor and a pressure sensor to protect the column
- Chromatography 4-way NovAseptic® valve to process through the column in forward or reverse or to bypass it without disconnecting the column
- Post-column instrumentation composed of pH, conductivity and UV dual-wavelength sensors
- Five outlets and a drain line
- Two CIP manifolds to connect all inlets together and all outlets to the drain
- Feedback switches on NovAseptic® valves

Summary of Studies

Gradient Test

In some cases, chromatography processes require gradients in solution conditions to achieve their process objectives. These gradients may be continuous (linear) or discrete (step) in time. In either case, the accuracy of the gradients is critical to the success of the chromatography process. The CoPrime® Biochromatography Process-Scale System employs dual pumps to deliver accurate and reproducible gradients. The necessary efficient mixing is achieved in the bubble trap.

Step gradient per percentage

Objective

The objective was to verify that the system could perform a step gradient per percentage and to check the mixing accuracy of the system.

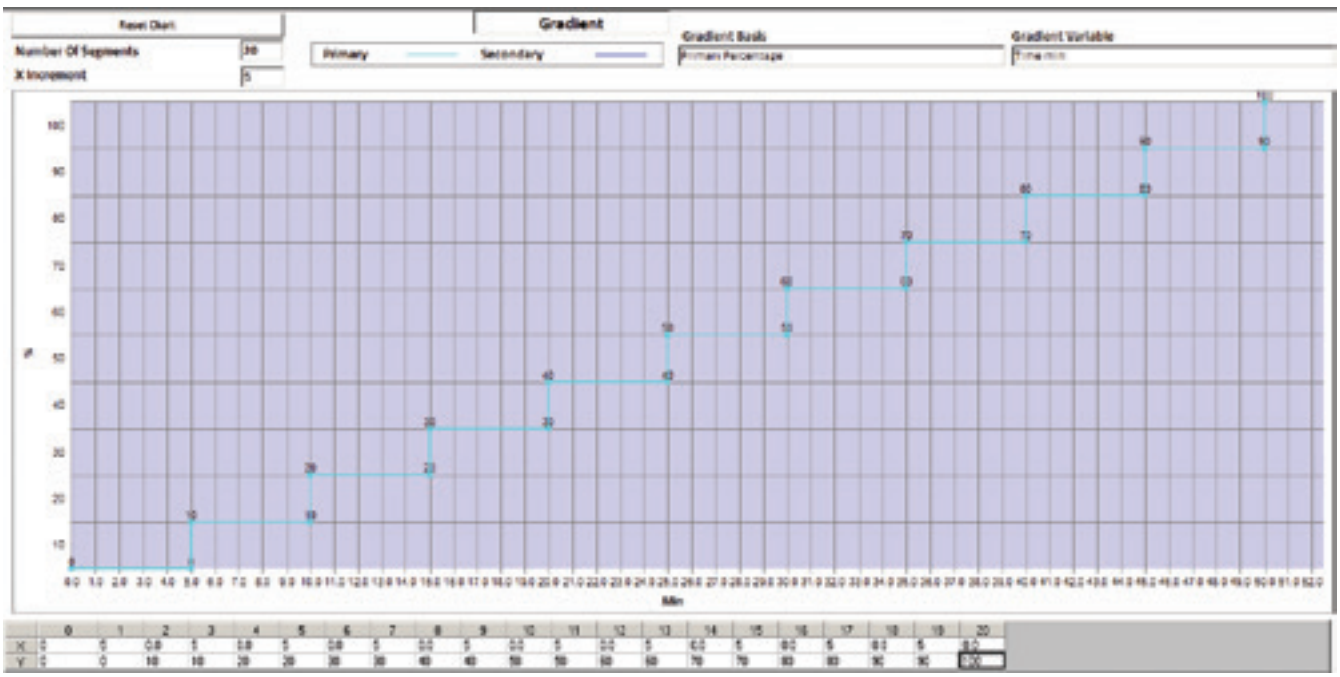
Materials and Methods

A tank with a solution of 0.5% acetone in water was connected to the primary inlet and a tank filled with water was connected to the secondary inlet. A manual valve was installed to simulate a column backpressure.

A recipe was run which maintained constant flow control. Eleven mixing steps were executed by percentage at every 10% from 0 to 100%. All run data, including total flow and absorbance, was extracted during the run.

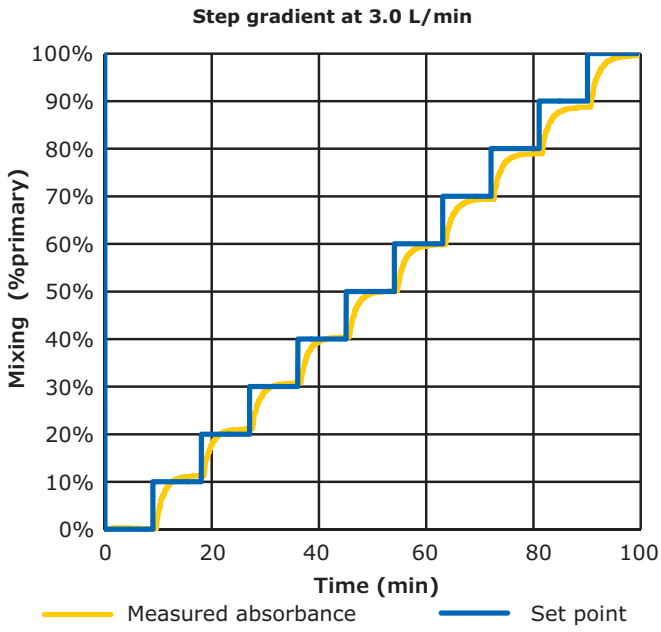
The absorbance obtained at each mixing set point was compared to the theoretical expected absorbance. The objective was to prove mixing accuracy within 2% of the set flow rate within the range of 10-90%.

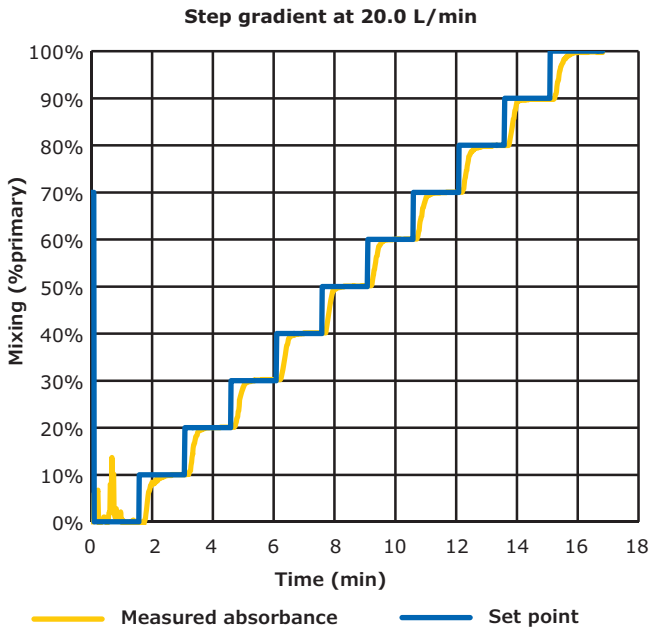
Step gradient by percentage in the CCP® Software Recipe Editor



Results and Conclusions

The system achieved the established goal of mixing accuracy within 2% of the desired range of 10-90% at three different flow rates: 3, 4 and 20 L/min.





Maximum errors during step gradient tests

Flow rate (L/min)	Maximum errors on mixing (%)	Maximum error on flow rate (%)
3	1.3% at 10% mixing -1.3% at 90% mixing	0.0 %
4	1.4% at 20% mixing 1.2% at 30% mixing	0.0 %
20	0.2% at 20% and 50% mixing -0.2% at 90% mixing	-0.1 %

Linear gradient per percentage

Objective

The objective was to verify that the system could perform a linear gradient per percentage.

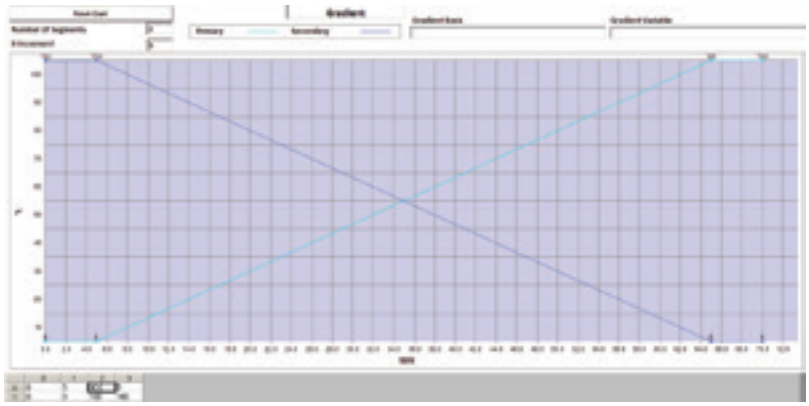
Materials and Methods

A tank with a solution of 0.5% acetone in water was connected to the primary inlet and a tank filled with water to the secondary inlet. A manual valve was installed to simulate a column backpressure.

A recipe was run which maintained a constant flow control and executed a linear gradient by percentage ranging from 0 to 100%.

The real absorbance was compared to a calculated theoretical absorbance. Using this comparison, the errors related to flow rate and mixing were calculated in the range of 10-90%.

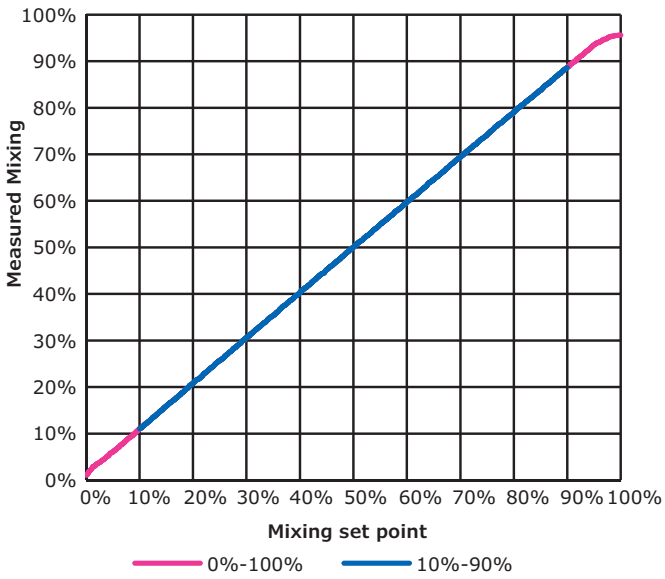
Linear gradient by percentage in the CCP® Software Recipe Editor



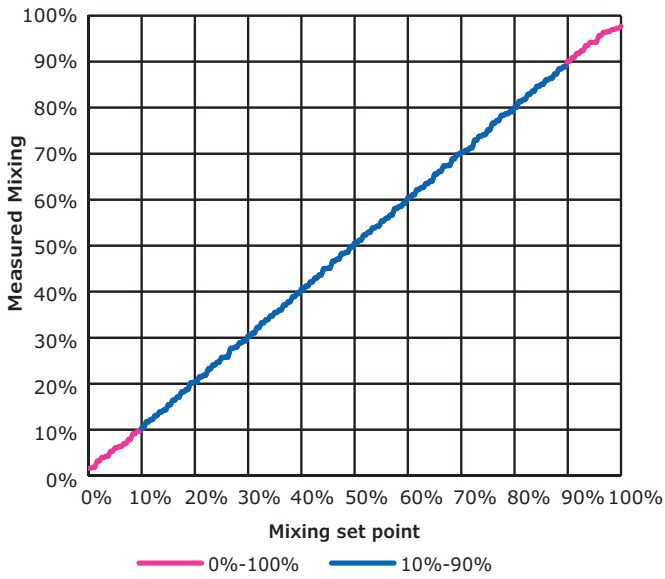
Results and Conclusions

The system achieved the established goal of mixing accuracy within 2% of the desired range of 10-90% at three different flow rates: 3, 4 and 20 L/min.

Mixing measured during linear gradient per percentage at 3 L/min



Mixing measured during linear gradient per percentage at 20 L/min



Maximum errors during linear gradient per percentage tests

Flow rate (L/min)	Maximum error on mixing (%)	Maximum error on flow rate (%)
3	-1.4%	1.0%
4	-1.3%	0.8%
20	1.0%	0.4%

Linear gradient per conductivity

Objective

The objective was to verify that the system can perform a linear gradient based on conductivity.

Materials and Methods

A solution of 1M NaCl in water was connected to the primary inlet and water to the secondary inlet. A manual valve was installed instead of a column to generate backpressure.

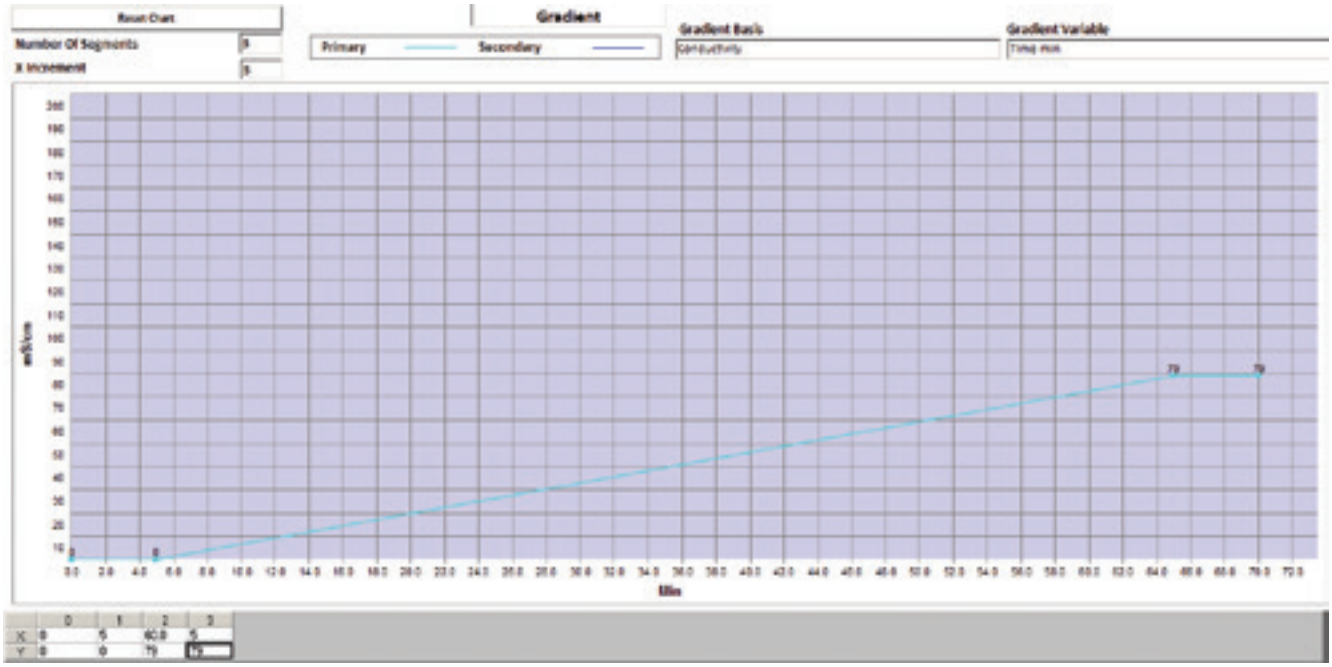
A lookup table was built by running a recipe which set a constant volumetric flow control and executed five mixing steps by percentage (0, 25, 50, 75, and 100%). At each step, the system associated the mixing percentage set point to the conductivity measured to obtain the linear gradient via conductivity.

Using the lookup table, the errors associated with the total flow and conductivity were calculated and the CCP® Software Report Generator was used to compare the conductivity curve during the linear gradient to the theoretical expected conductivity curve.

Mixing lookup table

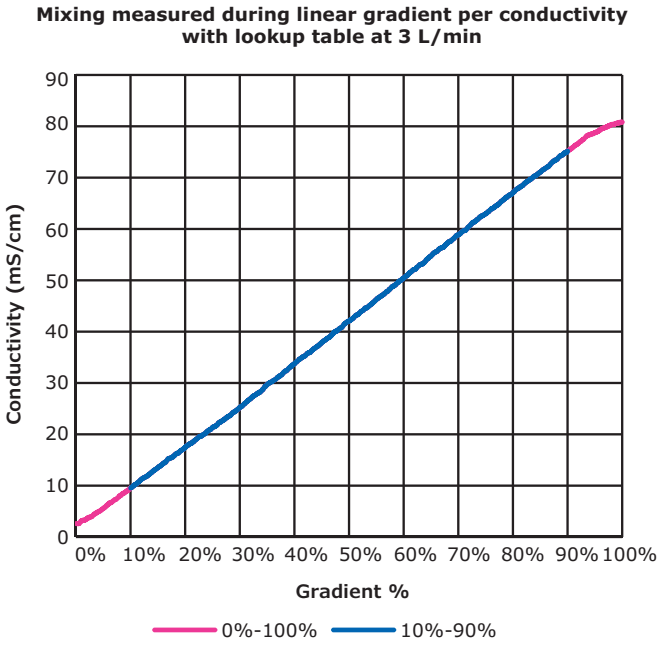
Segment	Conductivity	%Primary
0	0.2 mS/cm	0.0 %Pri
1	23.8 mS/cm	25.0 %Pri
2	43.1 mS/cm	50.0 %Pri
3	61.4 mS/cm	75.0 %Pri
4	79.1 mS/cm	100.0 %Pri

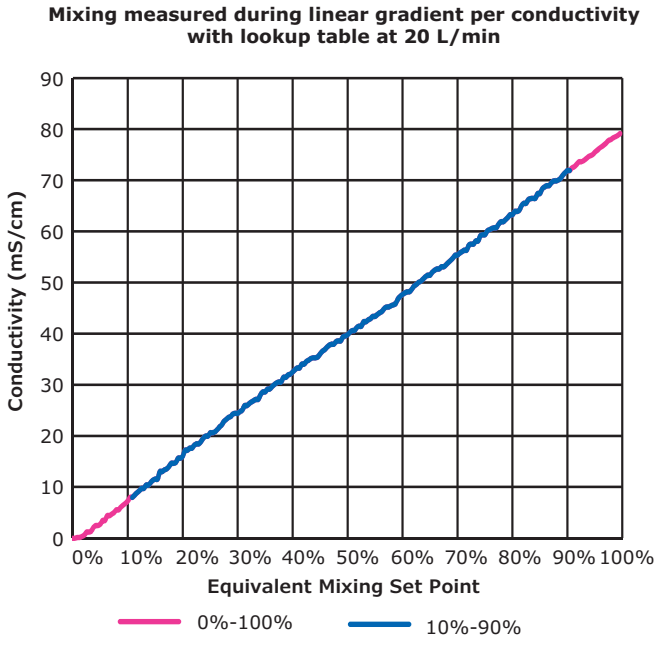
Linear gradient by conductivity in the CCP® Software Recipe Editor



Results and Conclusions

The system achieved the established goal of mixing accuracy within 2% of the desired range of 10-90% at three different flow rates: 3, 4 and 20 L/min.





Maximum errors during linear gradient per conductivity with lookup table tests

Flow rate (L/min)	Maximum error on mixing (%)	Maximum error on flow rate (%)
3	-1.4%	0.0%
4	-1.4%	1.0%
20	-1.4%	-0.4%

Column Qualification

Objective

The objective was to qualify the chromatography column.

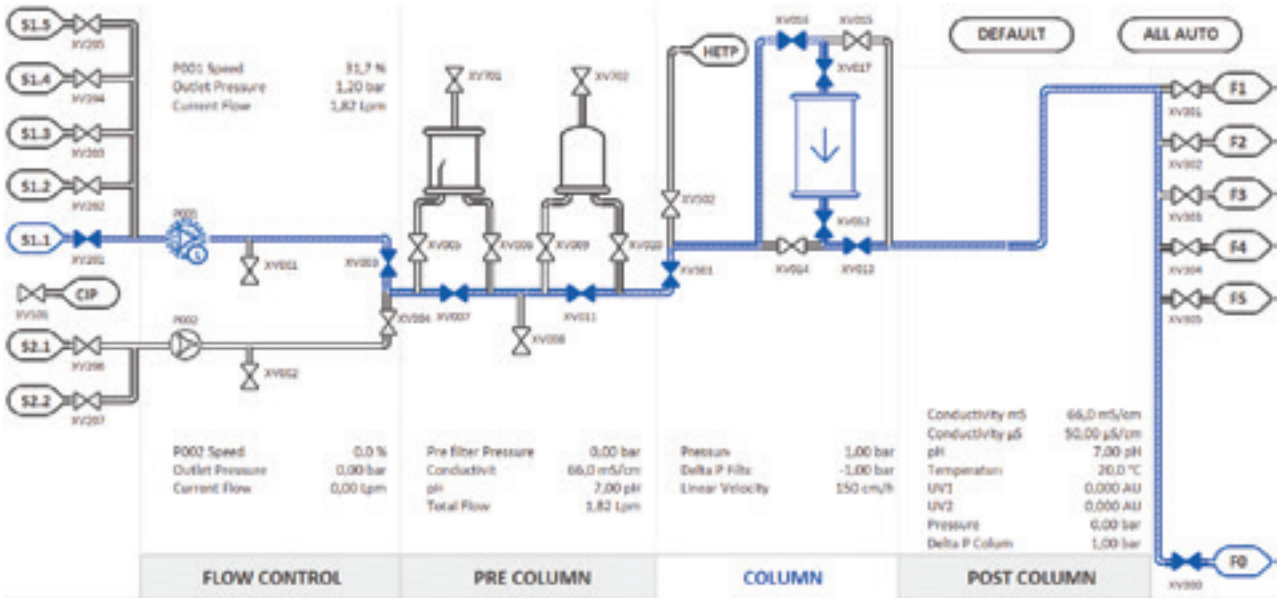
Materials and Methods

A small volume of acetone 2% w/w was injected through a QuikScale® column with a 30 cm diameter and 22 cm bed height containing Fractogel® EMD SO_3- (M) resin. The peak measured by the UV sensor at the column outlet was analyzed to determine the column's asymmetry and the Height Equivalent to the Theoretical Plate (HETP).

The UV base line was set with equilibration buffer (NaCl 150mM) at 150 cm/h, according to the following flow path shown in the figure below.

A recipe controlled the linear velocity at 150 cm/h across the column, switched from buffer to sample inlet, started the HETP test and switched back to buffer inlet after a defined volume of sample had been injected into the column. The CCP® Software Report Generator was used to calculate the HETP and asymmetry with the CCP® recipe information.

Flow path for HETP test

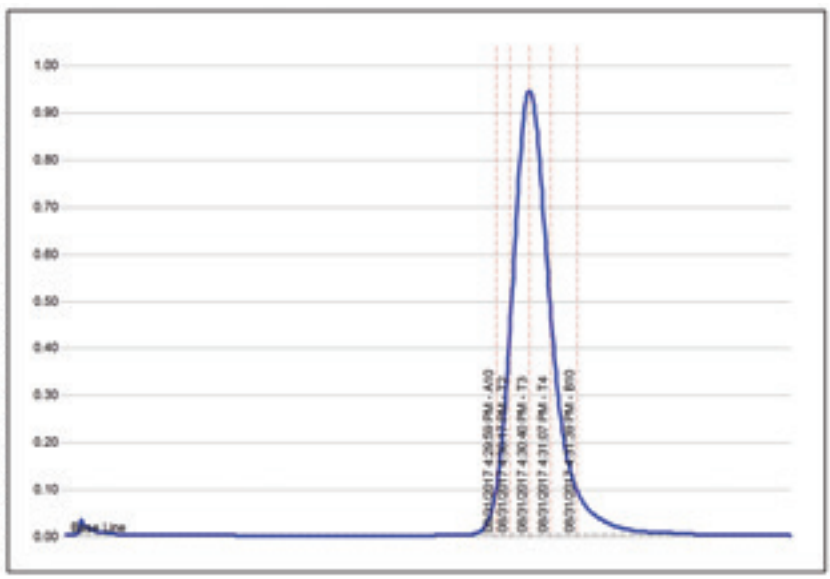


Results and Conclusions

When injecting the pulse from an inlet on the primary line with the bubble trap and filter bypassed, an HETP of 0.0302 cm and an asymmetry of 1.439 was observed. These are typical values for Fractogel® EMD SO_3- (M) resin.

CCP® report of HETP test

HETP Start	
08/31/2017 4:21:07 PM	
HETP End	
08/31/2017 4:36:04 PM	
Baseline Time	
4:21:07 PM	
Peak Max	0.943
Half Height	0.472
Baseline Offset	0.004
10% Height	0.094
Note: T1=0	
T2	550
T3	573
T4	600
A10	532
B10	632
HETP cm	0.0302
Asymmetry	1.439
Bed Height	22
Column Volume	15.5
Plate Number (N)	728.48
N per Meter	3311.26
Analysis Type	Pulse



System Pressure Performance

Objective

The objective was to verify the pressure generated by the system across the complete range of flow rates.

Materials and Methods

Water was recirculated at different flow rates: 1.6, 3, 4, 8, 9.5, 12, 16 and 20 L/min. The pressure generated by the system was measured with the CIP column spool piece and several different flow paths.

Both pumps were tested alone and together with the four different flow paths:

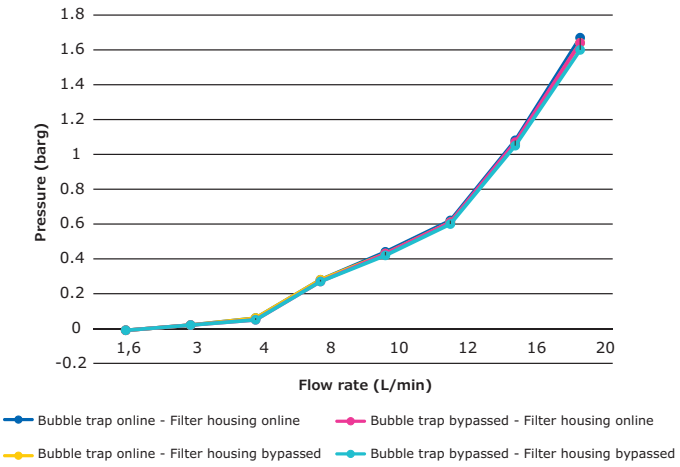
1. Bubble trap and filter housing bypassed
2. Bubble trap online and filter housing bypassed
3. Bubble trap bypassed and filter housing online
4. Bubble trap and filter housing online

Results and Conclusions

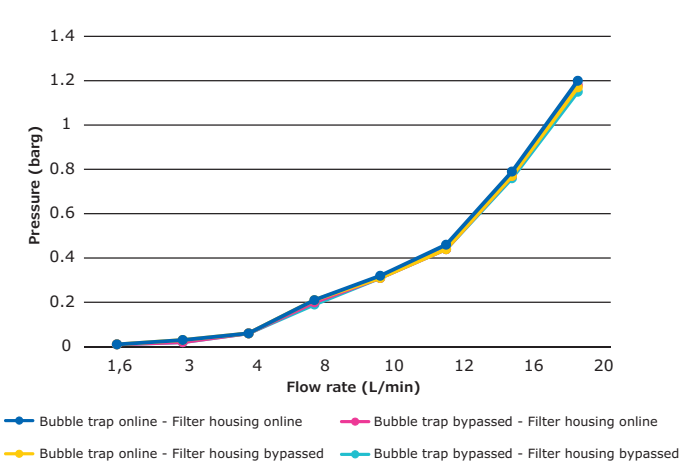
The highest pressure drops were obtained when only one pump was running.

Pressures were very similar regardless of the flow path or the pump running. A significant decrease in the pressure drop was observed when both pumps were running with a 50% mixing ratio. The bubble trap and the empty housing did not generate a significant pressure drop.

Maximum pressure measured at pump outlet with a single pump running



Maximum pressure measured at pump outlet with a 50% mixing ratio



Holdup Volumes

Objective

The objective was to measure the volume of each section of the system.

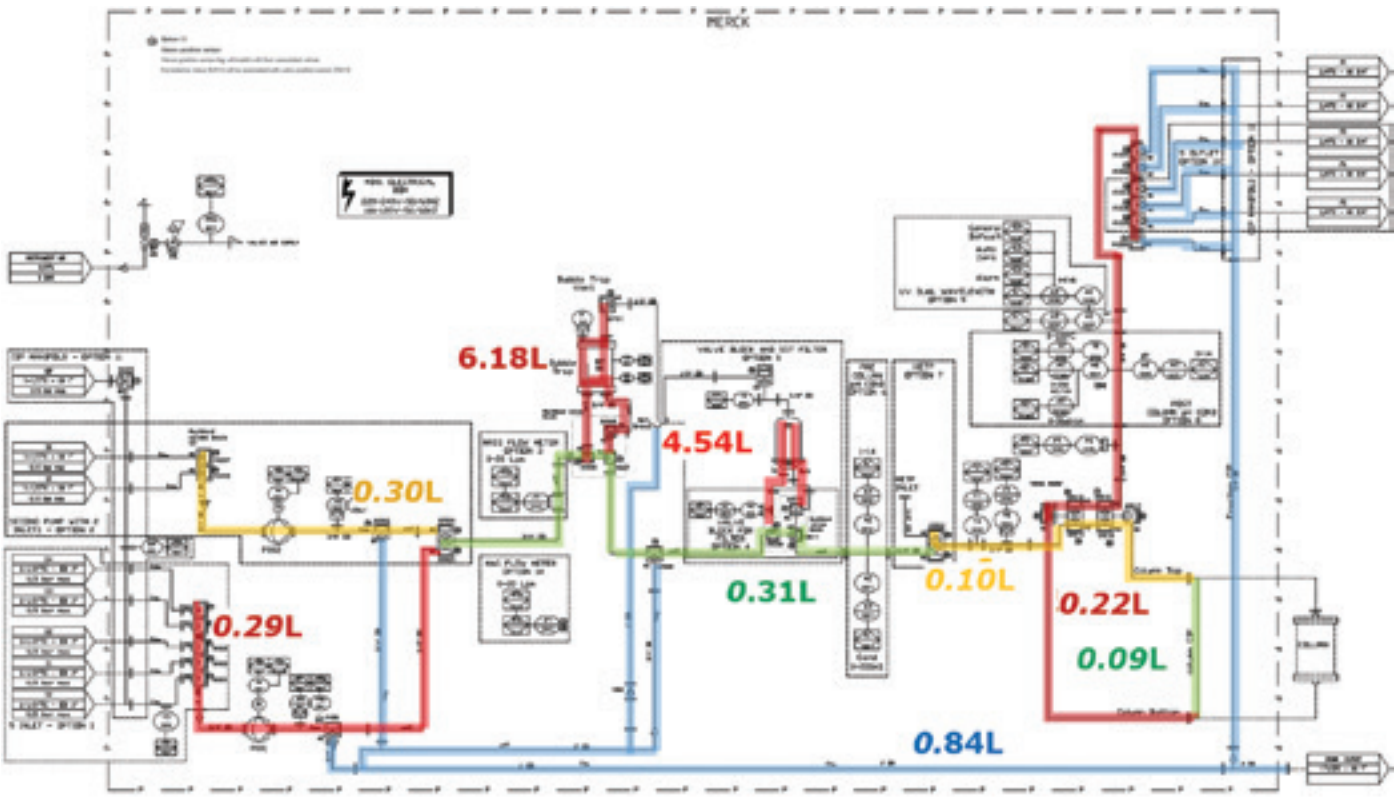
Materials and Methods

The volumes of different sections of the system were measured to calculate the holdup volume of the system. The system was filled with water, including the bubble trap, the filter housing without a filter installed, the CIP column, the inlet, and the fraction spools. Then, the following sections were opened and flushed with compressed air and the recovered water was weighed to determine the volume of each section.

Results and Conclusions

Nine parts of the system were measured and the volume of each flow path was estimated.

P & ID with sections for holdup volume measurements



Item	Description	Volume (liter)
1	Drain line with inlet and fraction spools	0.84
2	Pump 01 line	0.29
3	Pump 02 line	0.30
4	Column CIP spool	0.09
5	Fraction line	0.22
6	Pre-column line	0.10
7	Bubble trap and filter by-pass line	0.31
8	Bubble trap full	6.18
9	Filter housing without filter	4.54

Drainability

Objective

The objective was to evaluate the drainability of the system.

Materials and Methods

The system was filled completely with water, including the bubble trap and filter housing. All the valves were opened to collect the water by gravity drain, with pumps running for 1 minute at 30% capacity to help drain the pump lines. The system was then blown down with compressed air while the water was collected at the drain. Then, several lines including the CIP spools were dismantled and the volume remaining in those pipes was measured.

Results and Conclusions

13 123.3 g was initially introduced and 12 893.9 g (99.4%) of the water was recovered by gravity drain and air blow down. This result validates correct drainability of the piping.

Cleanability

Objective

The objective was to demonstrate the system's ability to be cleaned.

Materials and Methods

To evaluate the cleanability of the system, the Total Organic Content (TOC) of flushing water and swabs around the system were analyzed. The target was to achieve TOC below 10ppm. A CCP® software recipe was used to divide this test into three phases:

1. First cleaning to establish a test baseline with water sampling and swabs after gravity drain
2. Serum recirculation at 10 L/min and 3 bar backpressure with swabs after gravity drain
3. Second cleaning to evaluate the system cleanability with water sampling and swabs after gravity drain

Each cleaning was divided into:

- Drainage by gravity of the system
- Water flush of the system at 15 L/min for at least 5 times the volume of each section and until post-column conductivity got lower than 20 µS/cm
- NaOH 0.5 M cleaning for at least 1 hour at 5 L/min
- Drainage by gravity of the system
- Water final flush of the system at 15 L/min for at least 5 times the volume of each section, until post-column conductivity gets lower than 20 µS/cm

Water was collected from the drain outlet at the end of each final flush and from the RiOs™ and Milli-Q® systems used for the test. Swabs were taken from several areas:

- On the seat of the inlet valve
- On the membrane of the bubble trap manometer
- Inside the filter housing
- Inside the column CIP spool
- Into the drain line

Results and Conclusions

The TOC of the water samples taken after the initial CIP were between 0.04 and 0.05 ppm. The serum concentration was approximately 7g/L (≈7000ppm). The TOC levels of the water samples taken after the post-serum CIP were between 1.08 and 1.20 ppm, which is a significant decrease of the TOC level after the serum run.

The TOC of the swabs taken after the initial CIP were between 0.16 and 0.25 ppm, and the levels after serum runs were between 1.5 and 156 ppm. The levels after the final CIP were between 0.45 and 0.72 ppm. This result shows the system can be considered clean, as the swab analyses are in the same range as the Milli-Q® water.

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