Development of a Temperature Control System for a Benchtop ÄKTA pure™ 150

Authors: Anna Scribner, Kristen Hung, Christine Pham

tanvex CDMO

ABSTRACT

The temperature of chromatographic operations at manufacturing scale which utilize a chilled mobile phase can be difficult to replicate in a scale down model. At the scale of a benchtop ÄKTA Pure™ 150, small volumes and heat transfer effects may result in material that has come up to ambient temperature prior to entering the chromatography column, even if the buffer or load material is chilled. To counteract this, a countercurrent shell-and-tube heat exchanger was engineered around the column inlet line to chill the mobile phase just prior to entering the chromatography column. The temperature system was measured and characterized for a 1.0 cm x 10.0 cm column of DEAE Sepharose Fast Flow resin. A temperature profile which more closely mimics that of the manufacturing scale was successfully obtained in this study, confirming the applicability of the shell-and-tube heat exchanger for the scale down model.

BACKGROUND

In the development of an anion exchange chromatography operation, utilizing a chilled column was found to significantly increase operation yield. The lowered temperature was determined to be most important during the load phase. Both the scale-down model and the commercial-scale operation were developed to use both a jacketed column and a chilled load vessel; however, due to the differences of scale, the temperature profile in the scale down model and that of the commercial operation differ significantly from each other. Given the effect of temperature on yield for this process step and the importance of using a scale down model that replicates the manufacturing operation, a new temperature control system was developed for the scale down model to achieve a comparable temperature profile.

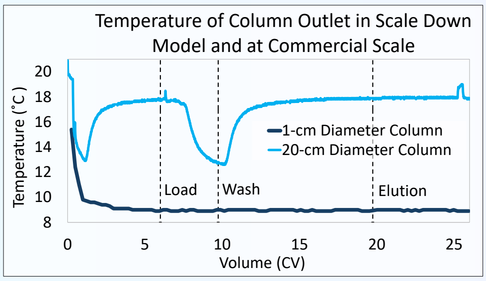

Figure 1. The temperatures at the outlet of the column through the Equilibration, Load, Wash, and Elution phases differ between the Scale Down Model and the Manufacturing Scale Operation.

Table 1. System and Operation Specifications in the Scale Down Model Compared to the Manufacturing Scale.

	Scale–Down Model	Manufacturing Operation
ÄKTA System	ÄKTA pure™ 150	ÄKTA ready™
Column Body	CHROMAFLEX® Jacketed Column	AsahiKASEI Low Pressure DAC Column
Column Dimensions	1.0 cm x 10.0 cm	20.0 cm x 10.0 cm
Surface Area : Volume Ratio	1 : 0.25 cm^{-1}	1 : 5 cm^{-1}
System Flow Rate	1.96 mL/min	785 mL/min
Temperature Control System	Water is circulated to the column jacket from a LAUDA Chiller set to 10.0˚C throughout cycle. Load material is chilled at 10.0˚C.	

METHODS

At the system flow rate of 1.96 ml/min (150 cm/hr), chilling the buffer or load material prior to entering the ÄKTA system is not effective; by the column inlet valve, the fluid temperature has increased to match the ambient temperature. This issue was resolved by chilling the column inlet line in a counter current shell-and-tube heat exchanger in which chilled water is peristaltically pumped through the tubing shell opposite to system flow.

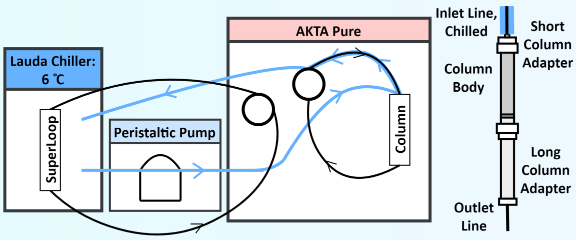

Figure 2. This diagram of the ÄKTA Pure™ 150 system illustrates the flow path and use of the heat exchanger along the inlet line.

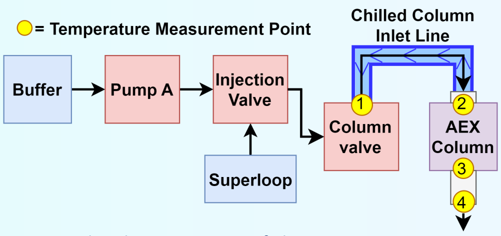

Figure 3. In the characterization of the system, temperatures were measured manually at various points throughout the ÄKTA and column hardware:

1. Column Valve (column inlet line port)
2. Top adapter outlet
3. Bottom adapter inlet
4. Bottom adapter outlet

When operating the assembled system, the only point which may be measured is point 4; final temperature profiles were measured from this point. Due to the heat gain across the bottom adapter, point 3 is considered the measurement point which is most comparable to the commercial operation temperature measurement. The temperature increase between points 3 and 4 was measured outside of the assembled system; this data was used to estimate the temperature at point 3 when the system is assembled.

RESULTS

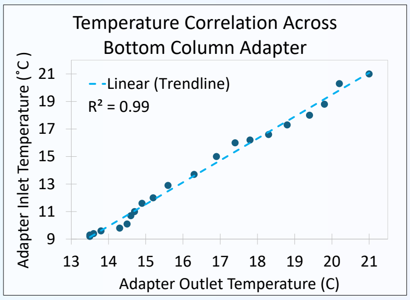

Figure 4. The temperature increase across the lower column adapter was measured at the flow rate of 1.96 mL/min. The resulting linear trendline equation was used to estimate the temperature at point 3 in the system based upon measurements taken at point 4.

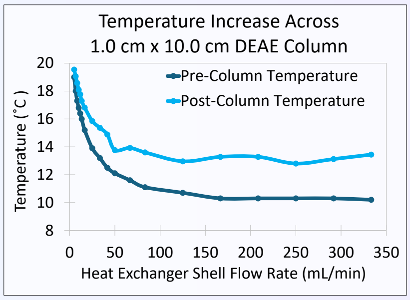

Figure 5. Temperature measurements were taken after the temperature had reached a steady state for a specific shell flow rate. This illustrates the typical temperature increase across the resin column, depending upon the mobile phase temperature prior to entering the column.

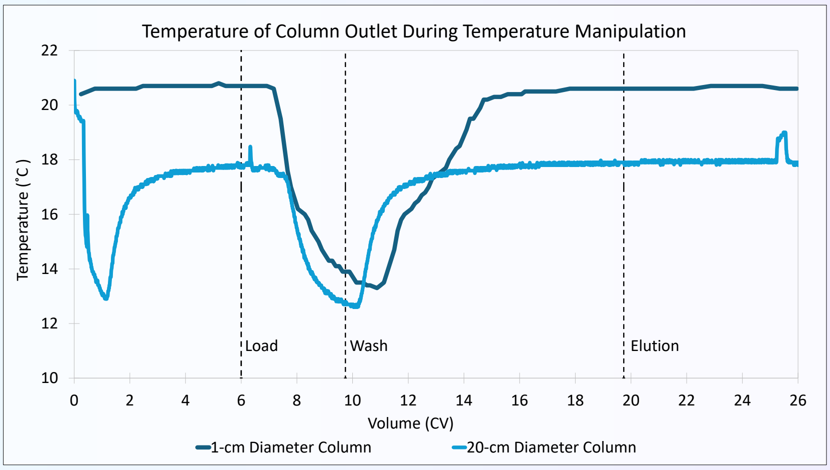

Figure 6. The column inlet line was chilled solely throughout the load phase. The temperature profile was measured from the column bottom adapter outlet, and the temperature at the adapter inlet was estimated as described in **Figure 4**. The resulting temperature profile in this figure shows more similarity to the commercial operation temperature profile than the initial scale down model.

CONCLUSIONS

At the flow rate used in the scale down model, temperature was not controllable through conventional means. The inlet line heat exchanger proved more effective in controlling the temperature of material flowing onto the resin column. By utilizing this system, the temperature profile through the equilibration, load, wash, and elution phases better approximated the temperatures seen at commercial scale.

anna.scribner@tanvex.com

10394 Pacific Center Ct.
San Diego, CA 92121

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