Brooks Instrument

A New Era of Liquid Chromatography: Improving HPLC Throughput with Automation and Real Time Diagnostics | Business White Paper

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Executive Summary

Are you achieving high throughput?
How many samples can your lab analyze per hour or per day?

Today's drug discovery labs are charged with moving thousands of samples through HPLC and MS screening processes. If your lab is operating 24x7 to keep up with the throughput demand, every second counts. To achieve high throughput, not only must the run time of a single analysis be shortened, but the total cycle time of the injection sequence and run time needs to be optimized. Solvent management automation and real time diagnostics allow you to increase sample throughput and maximize system uptime while meeting the need to produce reliable results and identify leads. This automation and diagnostics can be achieved by installing an in-line real time flow measurement device in the solvent management system.

By incorporating an in-line flow metering device in the solvent management system you will improve the accuracy of your system and at the same time be able to diagnose the health of the HPLC pump. This will help you manage the maintenance schedule for the system and, over time, will allow you to increase the time interval between maintenance cycles. You will also see in real time if there are flow pulsations or other issues with your fluid delivery. In next generation systems it is possible to use the output from the flow measurement device in a flow control feedback loop to completely eliminate pulsations and provide pump health diagnostics. Some flow metering devices will also provide additional benefits such as real time fluid density, concentration, or micro-bubble/two phase flow indication.

If your goal is reducing maintenance or increasing throughput, uptime or quality, the installation of an in line flow measurement device in your system will help you to achieve that goal.

What is HPLC?

Liquid chromatography involves the spatial separation of different sub phases (compounds or components) of a sample due to the different affinity of these sub phases with an adsorbent. A typical liquid chromatography system might comprise a separation column filled with the adsorbent (such as very fine powder, for example), a mechanism for discharging a liquid sample, a pump for forcing one or more liquid solvents and the liquid sample to and through the column, and a detector sensitive to different physical characteristics of the sub phases. Due to different respective affinity rates (absorption and desorption) of the different sample sub phases with the adsorbent, these sub phases will be penetrated through the column and adsorbent therein at different rates. This provides that the sub phases become isolated and axially spaced out as narrow bands, sequentially and separately passing the detector to be identified along with the possible determination of the percentage of each within the sample. Generally only a small quantity of liquid sample needs be used (a few mcls), and the volume of the column likewise can be small (perhaps only a few mls). It is preferred to pump the

solvent to high pressures to pass at an accurate and substantially steady flow rate through the sample and into the column.

Thus, a typical analytical high performance liquid chromatographic system (HPLC) might be comprised of a high pressure pump, a sample injector, a column and a detector in a serial flow connection to a waste vessel. The pump is suited to deliver liquid solvent and sample to the column at pressures typically in the 500-4000 psi range. The injector allows the introduction via a syringe or the like of the liquid sample into the solvent stream while maintaining the high pressures in the system. The column causes a major pressure drop and provides for the above noted axial separation of desired components or analytes from the complex sample form. The detector distinguishes the analytes separated from the sample, yielding information of the existence, concentration and identity of such analytes in the sample.

HPLC Relies on Accurate, Stable Flow

The HPLC pump must provide stable flow. Without it, other features are meaningless. HPLC relies on precise and accurate flow for valid analytical results. Without stable flow, response from Refractive Index and Electrochemical detectors is questionable. Quantitation from all other detectors also suffers, particularly for sensitive analysis.

GBC Scientific Equipment LC1120 HPLC Solvent Delivery System

There are many challenges associated with a typical HPLC pump as listed below:

- Flow / pressure pulsations
- Flow rate changes as a function of pressure
- Flow rate changes as a function of viscosity
- Viscosity changes as a function of temperature
- Valve contamination or clogging
- Piston/seal, cam and valve wear degrades accuracy and long term reproducibility
- Moving parts (piston/seal, cam and valve) require maintenance
- No positive verification of actual fluid delivery or flow rates)
- No closed loop control
- Minimal system or self diagnostic capability

There have been substantial improvements in pump technology. Many of today's pumps have a reduced number of check valves, small pressure / flow fluctuations, improved piston and seal designs for reduced maintenance and some improvement in diagnostic capability. Despite these improvements many of the issues listed above remain.

Integrated Flow Measurement Addresses the Challenges

Some advanced and next generation HPLC systems have incorporated in line real time flow measurement and control to generate precise LC gradients especially important at

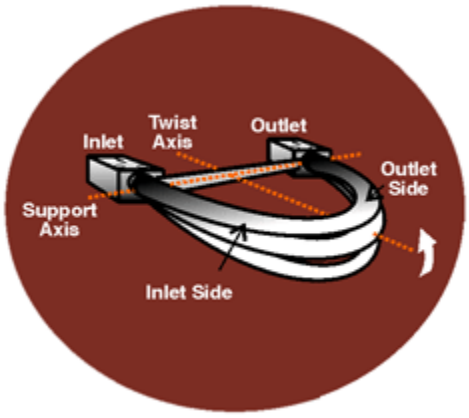
the nanoscale and capillary flow rates. These systems are realizing the following benefits:

- Continuously monitors actual flow rate with flow meters in each mobile phase path
- Provides active flow control with flow measurement feedback loop (control pump speed, integrated control valve or variable pressure source)
- Maintains flow rate regardless of system back pressure or fluid viscosity
- Achieves virtually instantaneous response to step changes in flow rate set point
- Provides improved separation speed and flow stability
- Provides improved diagnostic capability via active flow feedback for identification and prediction of leaks, blockages or pump wear

There are a variety of flow measurement technologies available that can be used in this application. Each has its own advantages and disadvantages as summarized below:

Flow Meter Technology	Accuracy (+/-)	Multi-variable	Integrated Control	Mass or Volumetric	Size	Turndown	Relative Pressure Loss	Lifecycle Cost (excluding accuracy)
TMF	1.0% R - 1.0% FS	N	Y	M	S	50:1	M	L
Orifice & DP Transmitter	1-5% FS	N	N	V	M	4:1	H	M
Electromagnetic	0.25 - 1% R	N	N	V	M	30:1	L	M
Vortex	0.65 - 1.35% R	N	N	V	M	25:1	M	L
Turbine	0.15 - 0.5% R	N	N	V	M	10:1	M	H
PD	0.15 - 0.5% R	N	N	V	M	10:1	M	H
Metering Pump	??	Y	Y	V	M	??	NA	H
Coriolis	0.10 - 0.3% R	Y	Y	M	M	100:1 +	L - M	L

The Coriolis mass flow technology is especially well suited for this application because of the very high accuracy independent of fluid properties, wide turndown, fast responding sensor, low life cycle costs and potential to have an integrated flow control valve.



Looking beyond today's flow measurement products to the next generation of sensors we can expect to see micro machined flow sensors providing several advantages including, size,

speed, accuracy, power and cost. A variety of MEMS products have been or are being developed including accelerometers, temperature sensors, pressure sensors, flow sensors and exclusion chromatographs

Conclusion

Integrated flow measurement provides several benefits:

- Automatically adjusts flow to compensate for changes in pressure or viscosity
- Ensures accurate flow measurement regardless of piston, seal or cam wear
- Helps to eliminate flow pulsations
- Indicates reduced flow due to clogging
- Signals when pump maintenance is required

Coriolis mass flow sensors provide additional benefits:

- Eliminates need to correct for fluid type / mix changes
- Provides bubble detection
- Provides density output which can be used for fluid type / mix / changeover verification

Installation of an in-line flow measurement device in your system will help you reduce maintenance, increase throughput, increase uptime and improve quality!

About the Author

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Prior to Brooks, he worked for Ametek and Unisys. Steve has a BS in Mechanical Engineering from Drexel University, an MBA in Marketing from Temple University and over 20 years of experience with process control instrumentation.