QUALIFYING INSTRUMENTS

Exploring the facilitated qualification of liquid chromatography instruments using a new continuous digital flow meter

Figure 2. The Biotech Liquid Flow Meter for facilitated flow monitoring and instrument qualification

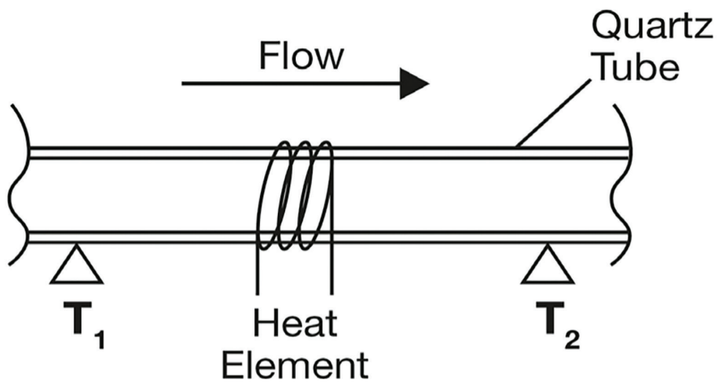
Qualification procedures for liquid chromatography instruments (HPLC & UHPLC) are designed to ensure that the analysis instruments work correctly and thus generate consistent and valid analytical results. An incorrect flow rate will inevitably affect substance retention times and chromatographic peak area integration, which in turn influence the accuracy of quantitative results, especially if the flow rate is unstable.

Instrument qualification tests have been defined [1] by the European Network of Control Laboratories (GEON), which is coordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM). Laboratories accredited according to ISO/IEC 17025 are required to implement these quality assurance procedures, although others aiming to provide high quality products and services, can certainly also benefit from similar efforts to ensure that trustworthy analysis results are continuously generated. Similar guidelines have been issued [2] by the United States Pharmacopeia (USP) as part of its general chapter <1058> which currently is under revision.

The periodic checks mentioned in the equipment qualification guidelines for instrument modules ("Level III") [1] issued by GEON, include experiments to verify that the flow rate is accurate [1,3], together with practical examples of how data could be gathered. The assessments involve ensuring that the absolute flow rate is within a suggested ±5% of the set value for HPLC instruments, and within ±3% for UHPLC systems. The typical acceptance limit for flow rate precision has been set to ≤0.5% relative standard deviation (RSD) for these tests. In essence, this corresponds to the operational qualification (OQ) in the USP nomenclature [2].

Traditionally, the liquid flow rate was measured by collecting the exit liquid while simultaneously recording the gathering time [3]. The collected liquid was then determined either volumetrically or gravimetrically, making these methods inherently manual and labour intensive. Previous digital liquid flow meters have mainly automated the volumetric measurement approach, and such devices have integration times ranging from tenths of seconds up to one minute at typical liquid chromatography flow rates (0.2 - 1 mL/min).

Figure 1. The measurement principle of a thermal flow sensor



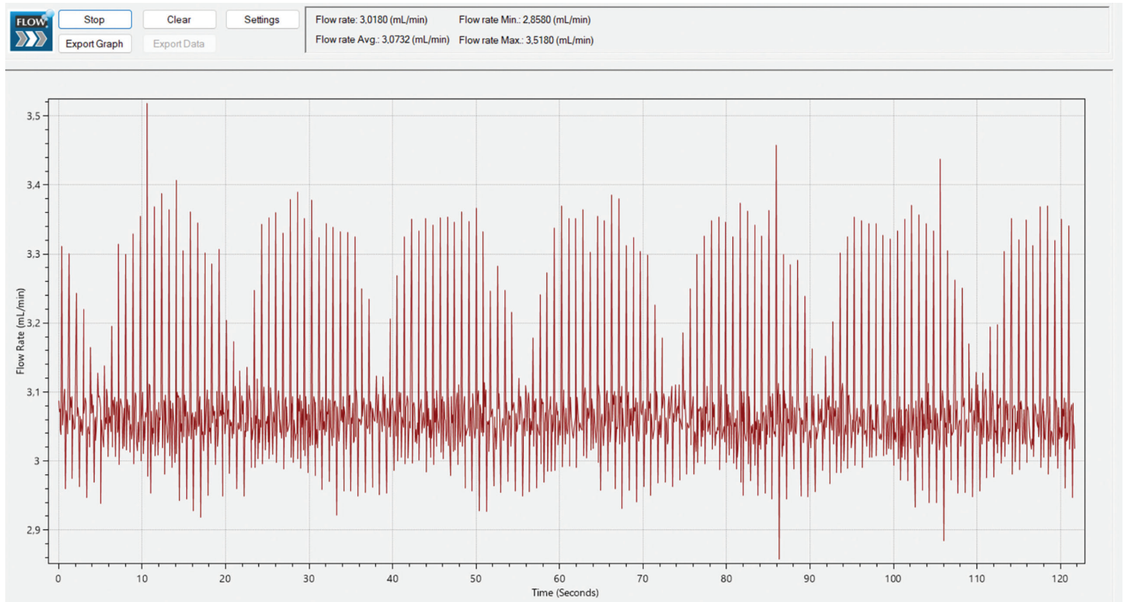


Figure 3. Example output from the Biotech Liquid Flow Meter during two minutes of high frequency data collection from a pump delivering a pulsating flow pattern

FLOW RATE DETERMINATION

A more recent technology for determination of flow rate is thermal conductivity [4]. This non-invasive principle involves two temperature sensors on a quartz glass tube, with a heating element positioned in-between, as depicted in Figure 1. With a built-in algorithm that converts heat difference to flow rate using internally stored calibration data, devices based on this principle can determine flow rate with a high frequency. The Biotech Liquid Flow Meter is constructed on this principle and produced into a handy physical size (see Figure 2). This flow meter can deliver readings every 78 milliseconds, thereby enabling high-resolution flow monitoring to detect variations and pulsating behaviour from pumps, as shown in Figure 3.

The specifications of this flow meter have been independently verified by a European accredited calibration laboratory using traceable standards. Their report concluded that the deviation from the reference value was below ±0.17% for all five tested flow rates within the range 0.15 to 5.0 mL/min. The uncertainty was determined to be 0.2% full scale deviations at the highest flow rate but lower within the rest of the tested range. These tests verify that the Biotech Liquid Flow Meter match the specifications from the manufacturer while also fulfilling the requirements for operational qualification of HPLC & UHPLC equipment and other fluidic systems where the quality of the results depend on a reliable flow rate.

A STANDARDISED PROTOCOL

When used within the Advanced Pump Validation Kit, i.e., with a standardised and automated protocol for data collection and calculation, the Biotech Liquid Flow Meter will provide a full data set plus a report for qualification of HPLC & UHPLC equipment within 10 minutes. This validation test report contains information about the average flow rate and its deviation from the nominal flow of the pump, plus relative standard deviation from five independent determinations, and a traceable reference to the stored raw data file.

Unique to the Biotech Liquid Flow Meter with the Advanced Pump Validation Kit is that it provides an independent assessment of flow pulsation. This can be used as an additional quality parameter for pumps to follow their wear and thus plan ahead for maintenance actions. The pulsation parameter is calculated as a relative max-min value within two minutes, which corresponds to how noise typically is defined and measured in analytical measurements including liquid chromatography. •

REFERENCES:

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[3] P. Uthaiwat, T. Leeudomwong, T. Sanponpute, "The comparison of flow rate calibration methods for high-performance liquid chromatography (HPLC) pump", Accreditation and Quality Assurance (2024) 29:205-214.

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