The aim of this work was to develop a miniature liquid chromatography system mainly aimed at online reaction monitoring.

The system has the following design criteria:

- **Cost/Performance Ratio:** The modular design using syringe based solvent pumps and LED based detection allows for an optimized performance for a task while keeping the costs down.
- **Small:** A small footprint would allow the system to be placed directly next to the reactor e.g. inside the fume hood.
- **Modular:** Rather than being an all-round instrument the modular nature of the system allows a custom configuration for the task ahead. Configurations will allow for isocratic and gradient separations, dilution/derivation of samples and automated sampling (see Figure 1).
- **Performance:** While aiming at the use of micro- and capillary columns (0.15-1 mm ID and up to 100 mm long) the system has to be able to pass system suitability tests required by the US Pharmacopeia.

The current system is powered by stepper motor driven syringe pumps, Labsmith miniature valves, a detector using UV-LEDs and a photodiode and an Arduino based control structure. User control is through a Windows-based software. Potentially, the whole system can be run off batteries and controlled via a smart device for remote applications.

### The system

The system is a modular design - for example the four pumps are identical (same stepper motor, same housing, same syringes, same connection).

### The valves

The valves used are Labsmith Micromatic Products (Labsmith, Livemore, CA). The system uses up to 3-5 port valves (AV020) with a swept volume of 100 µL, a 6-port injection valve (AV020) with a 600-µL external loop and an optional 8-port selection valve (AV801). The 8-port selection valve allows the automated injection of the sample, two standards, a resolution solution, a blank and a wash solution, while the other two ports go to the injection valve and to waste. All valves are motorized and are controlled from the user software.

### The detector

The detector consists of an Agilent 12 nL z-cell in a 3D-printed housing. A UV-LED (255 nm) and a photodiode sensor. We found that the sensitivity of the detector is a function of current applied to the LED and that a cooled cell allowed us to increase the current/sensitivity. The cooled housing is made of machined aluminum with an integrated fan (Figure 2).

LED design is changing constantly, 235 nm is the lowest wavelength available but other wavelengths are under development. There is also a project to move from single wavelength detection to multi wavelengths detection.

### The control architecture

System control is performed on three levels: the user interface is located on a Windows-based computer/laptop. It allows the user to set up methods, execute analysis and save the data. Communication between the computer and the system is done via USB or Bluetooth. High level system control is performed by an Arduino Mega board. This board (master) handles communication with the computer and sends control parameters to the individual system components. Finally, the components are controlled by Arduino Nano boards (slaves). These boards carry the majority of calculations.

### Pump accuracy and precision

The solvency of the pump was measured gravimetrically. Using a 250 µL syringe flow rates between 1 and 50 µmin showed a precision of ± 1.0% RSD and an accuracy of ± 0.5% RSD (Table 1).

### Linearity, LOD and LOQ

Linearity of the test mix was tested with concentration reaching from 0.4 to 200 µg/ml. LOD (S/N >3) started for some compounds at about 1 µg/ml while LOQ (S/N =10) was reached at 10 µg/ml. Linearity was achieved over the concentration range tested (Figure 5).

### Conclusions

From the outset the system was designed to be a cost-effective way to monitor a specific reaction. An important design criteria was the small footprint of the instrument making it possible to place it next to the reactor. While trying to emulate many of functionalities of a conventional HPLC system the targeted application of reaction monitoring does not require the same level of performance as for example bioassay analysis. Reaction monitoring typically involves the analysis of a few compounds only, the starting materials, the product and a few side products.

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