Dynamic vs constant liquid flow calibrations down to 20 nL/min

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Abstract

Calibration of flow devices is important in several areas of pharmaceutical, flow chemistry, HPLC and microfluidic applications, where dosage of process liquids or accurate measurement of the flow rate are important. The process-oriented liquid itself might influence the performance of the flow device. Therefore, the calibration of the flow meter or microfluidic device with the process-oriented liquid is important and performing dynamic flow profile changes to simulate any dosing process gives important insight in the behaviour of these flow devices and their accuracies under non-constant flow conditions. Therefore, METAS has developed facilities with METAS piston provers to address the issue of measuring with process-oriented liquids non-constant flow profiles for flow rates down to 20 nL/min. The stated measurement uncertainties for the constant flow rate and for the dynamic flow profile changes are 1 % and 2 % at 20 nL/min. The piston provers, the new developed capillary beaker for the gravimetric reference method, validation measurements as well as response time characterization with incompressible and compressible liquids are discussed in this paper.

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1. Introduction

Calibration of flow devices is important in several areas of pharmaceutical, flow chemistry, HPLC and microfluidic applications, where dosage of process liquids or accurate measurement of the flow rate are important. The process-oriented liquid itself might influence the performance of the flow device [1]. Therefore, the calibration of the flow meter or microfluidic device with the process-oriented liquid is important and performing dynamic flow profile changes to simulate any dosing process gives important insight in the behaviour of these flow devices and their accuracies under non-constant flow conditions.

Therefore, METAS has developed facilities with METAS piston provers to address the issue of measuring with process-oriented liquids non-constant flow profiles for flow rates down to 20 nL/min [1-3]. The piston provers allow changing the flow rate within seconds and the generated flow rate change is traceable due to the calibrated position measurement and the inner diameter of the piston. In addition, pressure sensors upstream and downstream of the flow device indicate the increase and decrease in flow rates due to the changes in pressure.

The gravimetric method of the Microflow facility has also been upgraded with a capillary beaker, where the outlet needle is placed inside a vertically mounted capillary to minimize instabilities in weighing data during flow rate changes [4]. The capillary is filled with water and the contact between the outlet needle and the beaker is a constant water contact zone in the capillary. Due to capillary forces the meniscus between the capillary and the outlet needle remains almost stable even when a strong change in the flow rate occurs. The water enters then the beaker through the capillary and the water level in the beaker is raised without changing the level in the water contact zone.

2. METAS piston provers

The METAS piston provers consist of a high precision linear stage with a fixed linear measuring system, mounting parts to fix commercially available syringes or homemade prover cylinders in front of the table and mounting parts to fix and move the piston in the prover cylinder in order to generate the flow rate (see Figure 1) [2]. The position of the linear stage is determined by counting the pulses sent by the linear measuring system or the motor encoder signal by means of an FPGA, which is a Field Programmable Gate Array with hard coded program code running on a defined constant cycle time of the order of 25 ns (40 MHz). For each additional pulse in any direction, a time stamp of the FPGA is recorded and a pair with the position and the timestamp is formed. This pair of values is then read from the main software and the real time position can be recorded. The real time speed is then determined by a linear fit of several pairs of position data with the corresponding time stamps as the slope corresponds to the speed. Multiplying the speed with the calibrated cross section of the piston gives the traceable volume flow rate. The speed range for the METAS piston prover of the Microflow facility resp. of the Milliflow facility is from 0.1 mm/s to 0.1 µm/s resp. from 4.0 mm/s to 4.0 µm/s.

Further, calibrations of the speed of the piston and the dimensions of the prover body will guarantee traceability to length and time, which make the piston prover a primary standard for volume flow.

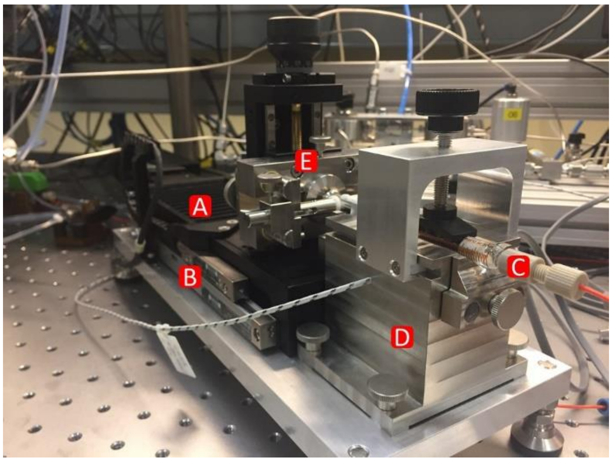

Figure 1: METAS piston prover of the Microflow facility with a speed range from 0.1 mm/s to 0.1 µm/s. (A) high precision linear stage, (B) linear measuring system, (C) syringe, (D) mounting syringe body, (E) mounting and positioning for syringe plunger. The same design and components are used for the METAS piston prover of the Milliflow facility, but with a different speed range from 4 mm/s to 4 µm/s.

3. Constant water contact for filling the beaker

The generated dynamic flow profile changes are already traceable as the piston provers are primary standards for volume flow. However, it might be interesting in some applications to collect the water after the DUT (device under test) by means of the gravimetric method. The important point is then that the water contact between the outlet needle and the beaker on the balance remains almost constant even when a strong change in the flow rate occurs.

The Milliflow facility deals with flow rates between 400 mL/min and 0.2 mL/min and the beaker contains a vertically mounted glass filter, where the outlet needle is in general positioned 200 µm to 50 µm above the glass filter depending on the diameter of the outlet needle (1 mm to 0.3 mm) (see Figure 2) [2]. At low flow rates, the water enters the measurement beaker by forming a water bridge due to capillary forces avoiding droplet formation at the outlet needle for a continuous collection of the water. The water flows down to the bottom of the beaker, where the water level is increasing. Thus, the water contact between the outlet needle and the glass filter remains the same independent on the water level inside the beaker.

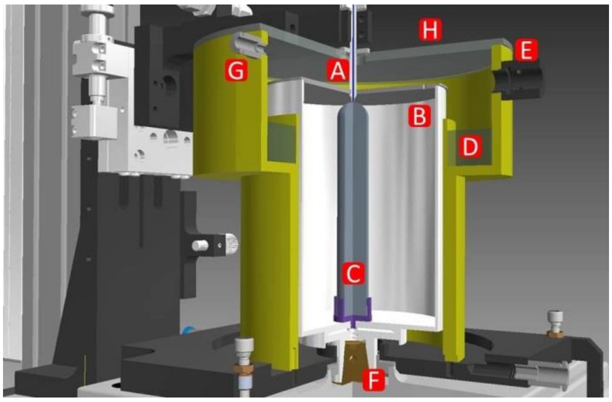

Figure 2: Weighing zone on the balance of the Milliflow facility. (A) outlet needle, (B) beaker with cover, (C) glass filter, (D) water in evaporation trap, (E) mount for T and rH sensor, (F) balance, (G) tubing for humidity exchanger.

The Microflow facility deals with flow rates between 5 mL/min and 20 nL/min and the capillary beaker contains a vertically mounted capillary (Figure 3). The capillary is filled with water and the contact between the outlet needle and the beaker is a constant water contact zone in the capillary [4]. Due to capillary forces the meniscus between the capillary and the outlet needle remains almost stable even when a strong change in the flow rate occurs. The water enters then the beaker through the capillary and the water level in the beaker is raised without changing the level in the water contact zone.

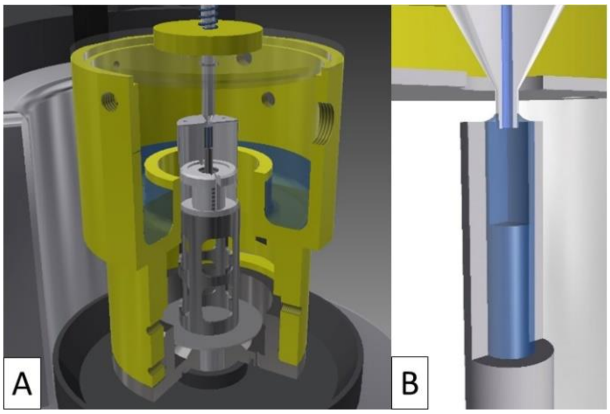

Figure 3: (A) Weighing zone on the balance of the Microflow facility showing outlet needle and beaker with cover. (B) Insight into the contact of the outlet needle in the capillary.

4. Dynamic flow profile changes and instantaneous flow rate determination

Similar to the determination of the steady flow rate the collected weighing data and the data of the linear measuring system are fitted by means of a least square linear fit to obtain the instantaneous flow rate [2, 5]. In this case we have recorded the pair with the position and the timestamp of the linear measuring system using the FPGA to collect each single pulse. The weighing data are continuously collected by a Real Time system (RT), which communicates with the balance at 20 Hz and pairs the weight value directly with the time stamp of the RT. The increase of the weight values and the position of the linear measuring system are shown in Figure 4. Therefore, we are able to choose a fixed time window as short as 0.5 s to perform the least square linear fit to determine the flow rates of the piston prover and the dynamic gravimetric method. By increasing the starting time of the fixed time window by each time step the instantaneous mass flow rates can be determined continuously in time as shown in Figure 5. The vertical orange and cyan lines indicate two fixed time window of 0.5 s at 100 s resp. 200 s in Figure 4 and the resulting flow rate in Figure 5. Additionally, the signal of the DUT is recorded at a frequency of 25 Hz and the averaged mass flow rate over 0.5 s of the DUT is also shown in Figure 5. At first sight, all three data curves collapse on a single curve. However, there is a delay in the build-up of the flow rate along the tubing if the tubing is not well degassed to have an incompressible liquid as shown in a previous paper [3]. Additionally, the electronic response times for the pressure sensors and the Coriolis flow meter have to be taken into account to get the real delay of the build-up of the flow rate. Another point to mention is that at the moment of the strong change in flow rate the gravimetric method reveals a small strong peak upwards, which result from the fact that the capillary forces between the outlet needle and the glass filter slightly change during the strong increase in flow rate. This effect is small, but still worth mentioning.

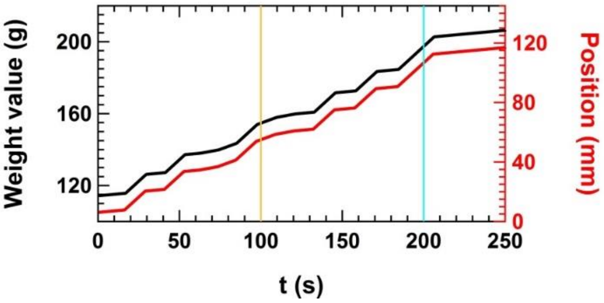

Figure 4: Increase of mass on the balance (black line) and increase of the position of the linear measuring system (red line) as a function of time. The vertical orange and cyan lines indicate two fixed time window of 0.5 s at 100 s resp. 200 s.

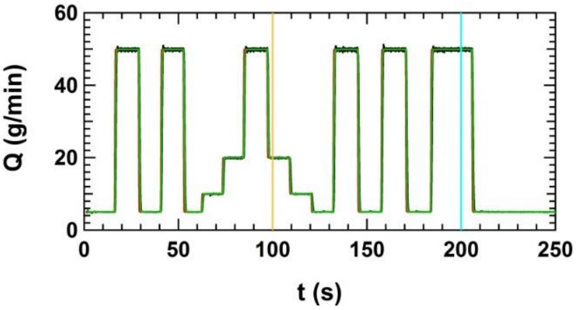

Figure 5: The determined mass flow rate of the balance (black line), the piston prover (red line) and the DUT (green line) as a function of time. The vertical orange and cyan lines indicate two fixed time window of 0.5 s at 100 s resp. 200 s.

5. Response time of Coriolis flow meter with water (incompressible) and oil (compressible)

Measurements were performed with the Coriolis flow meter Cubemass DCI DN01 from Endress+Hauser AG. By filling the tubing with water all the residual air has to be flushed out properly. The measurement shown in Figure 6 was performed with degassed water (incompressible liquid). The curves of the pressure sensors (orange downstream piston, blue upstream Coriolis meter, green downstream Coriolis meter) were corrected with the electronic response time of the pressure sensors (60 ms), which are determined by matching in this case the onset of the increase of the pressure sensors and the onset of the flow generation of the piston prover (red line).

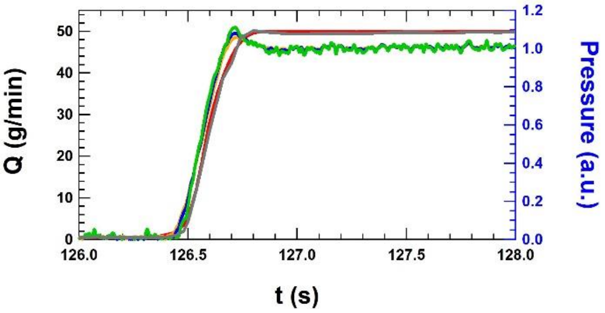

Figure 6: Increase in flow rate generated by the piston prover (red line) using water (incompressible liquid). Curves of the pressure sensors (orange downstream piston, blue upstream Coriolis meter, green downstream Coriolis meter) were corrected with the electronic response time of the pressure sensors (60 ms). The response curve of the Coriolis flow meter (gray line) is shifted by his response time of 210 ms and results in a perfect overlap with the curve of the piston prover.

All the curves of the pressure sensors are shifted in time with the same electronic response time and the pressure values are scaled with the final value after the increase. All the pressure curves show the same behaviour and the effect of the pressure wave created by the generated increase in flow. Reaching the steady flow, the pressure along the tubing gets into equilibrium and the different pressure curves remain constant. The response curve of the Coriolis flow meter (gray line) is shifted by his response time of 210 ms and results in a perfect overlap with the curve of the piston prover (red line). The determination of the response times for this case is only possible when all the tubing and the internal volume of the sensors are perfectly degassed resulting in the detection of the pressure wave caused by the instantaneous increase of the flow rate.

These response times of the pressure sensors and the Coriolis meter are used to evaluate the increase in flow rate with oil (compressible liquid), which was not degassed and therefore behaves like a compressible liquid (see Figure 7). The curves of the pressure sensors and the Coriolis meter are shifted in time with their response times and the curves of the pressure sensors are scaled with the final value for presentation convenience. The curve of the Coriolis (gray line) overlaps perfectly with the curve of the pressure sensor upstream of the Coriolis meter (blue line), which reflect the real increase of the flow rate in the Coriolis meter.

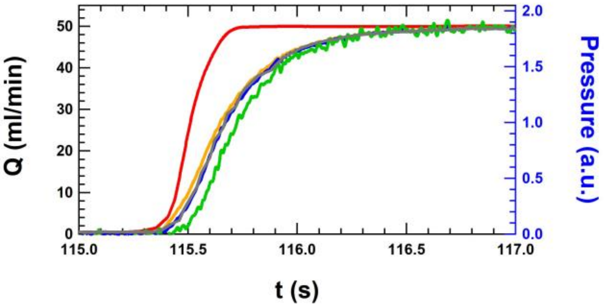

Figure 7: Increase in flow rate generated by the piston prover (red line) using oil (compressible liquid). Curves of the pressure sensors (orange downstream piston, blue upstream Coriolis meter, green downstream Coriolis meter) were corrected with the electronic response time of the pressure sensors (60 ms). The response curve of the Coriolis flow meter (gray line) is shifted by his response time of 210 ms and results in a perfect overlap with the pressure upstream of the Coriolis meter.

6. Dynamic flow profiles below 100 nL/min

Dynamic flow profiles were performed with two thermal flow meters: L01 from Bronkhorst High-Tech B.V. and SLG64-0075 from Sensirion AG. Both thermal flow meters were calibrated with steady flow rates and the dynamic flow profiles below 100 nL/min. The dynamic flow profile consist of cycles with steps of 30 s for 50 nL/min, 80 nL/min, 100 nL/min, 50 nL/min, 30 nL/min and 50 nL/min.

6.1 Flow meter L01 from Bronkhorst High-Tech B.V.

Three cycles were measured after a stabilisation time of 2 h with the L01 as shown in Figure 8. Obviously, the data from the gravimetric method are noisy due to the fact that we use a fit window of only 5 s and that the gravimetric method (black line) is getting to its limits for such short fit windows at these low flow rates. The influence of the variation of the capillary forces at the water contact between the outlet needle and the capillary gets more important than at higher flow rates. First, we focus on the calibration of the L01 with the piston prover including the linear measuring system, which measures directly the position of the plunger and the corresponding instantaneous speed. The deviation of the flow meter is determined for each of the plateaus (constant flow rates) of the three cycles and the average of several deviations at each flow rate is calculated and shown in Figure 9 as full red circles. The measurement uncertainty consist of 2 % from the facility and the repeatability contribution from 3 or more values (plateaus). These deviations from the dynamic flow profile measurements are compared to the deviations obtained from constant flow calibration over several hours (full blue circle). The results are consistent even for these short measurement times.

The average of the flow rates over a full cycle can also be analysed. The deviations determined by the piston prover or the gravimetric method are shown as open red circle or open black circle in Figure 9. These results are also consistent with the constant flow calibration.

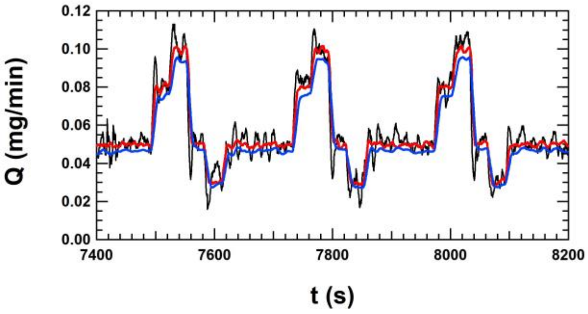

Figure 8: Dynamic flow profile generated by the piston prover including linear measuring system (red line) and measured with L01 from Bronkhorst High-Tech B.V. (blue line). The gravimetric method (black line) is also shown. The fit window is 5 s for the analysis.

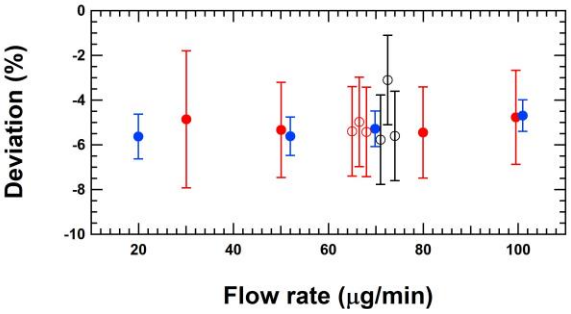

Figure 9: L01 from Bronkhorst High-Tech B.V. Constant flow calibration (full blue circle) and plateau values from dynamic flow profile calibration (full red circle, see text). Calibration for a full cycle with piston prover (open red circle, see text) and with gravimetric method (open black circle, see text).

6.2 Flow meter SLG64-0075 from Sensirion AG

Figure 10 shows the measurement of three cycles after a stabilisation time of 1 h of the SLG64-0075 with the piston prover including the motor encoder signal, which leads to the same flow rate results as the linear measuring system. However, the position is measured indirectly with the signal of the motor encoder and the small fluctuations due to the gear and the mechanics are not visible in the curve of the piston prover, but only in the curve of the SLG64-0075.

The same analysis of the deviation of the flow meter for each of the plateaus (constant flow rates) of the three cycles is performed and shown in Figure 11 as full red circles. These deviations are consistent with the deviations obtained from constant flow calibration over several hours (full blue circle). The analysis over full cycles lead to deviations with respect to the piston prover (open red circle) that are also consistent with the constant flow calibration.

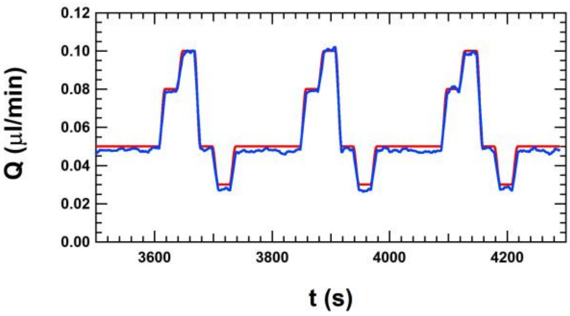

Figure 10: Dynamic flow profile generated by the piston prover including the motor encoder signal (red line) and measured with SLG64-0075 from Sensirion AG (blue line). The fit window is 1 s for the analysis.

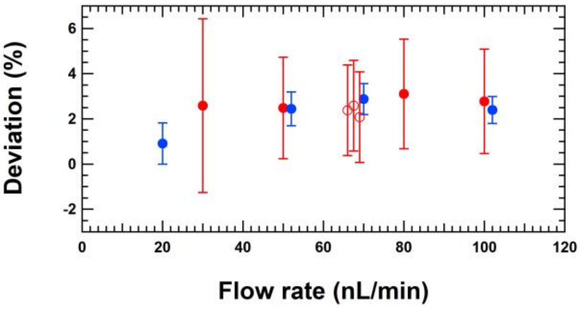

Figure 11: SLG64-0075 from Sensirion AG. Constant flow calibration (full blue circle) and plateau values from dynamic flow profile calibration (full red circle, see text). Calibration for a full cycle with piston prover (open red circle, see text).

6.3 Validation of the stated uncertainties

The calibrations of L01 and SLG64-0075 were part of an inter-comparison in the framework of the project 18HLT08 MEDDII. The stated measurement uncertainties for the constant flow rate and for the dynamic flow profile changes are 1 % and 2 % at 20 nL/min. The measurement results reported here show consistency between the two measurement regimes.

Further validation measurements have been reported in the EURAMET project 1508 report [6], where the results of the inter-comparison validate the stated measurement uncertainties for the constant flow rate and for the dynamic flow profile changes.

7. Conclusion

METAS has developed facilities with METAS piston provers as primary standards to address the issue of measuring non-constant flow profiles for flow rates down to 20 nL/min with process-oriented liquids. The piston provers allow changing the flow rate within seconds and the generated flow rate change is traceable due to the calibrated position measurement and the inner diameter of the piston. The pressure sensor upstream the flow meter indicate the instantaneous increase of the flow rate and allow to characterize the response time of flow meters.

The stated measurement uncertainties for the constant flow rate and for the dynamic flow profile changes are 1 % and 2 % at 20 nL/min and these are validated in an inter-comparison for flow rates from 100 nL/min to 20 nL/min [6].

Acknowledgement

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