MICRO FLOW FACILITY FOR TRACEABILITY IN STEADY AND PULSATING FLOW

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Abstract

Micro and nano flow calibrations are important in several medical applications such as drug delivery where the knowledge of the exact amount of the delivered drug is crucial for efficient health care treatment and safety of the patient. However, international traceability in the micro and nano flow is not validated up to date for flow rate ranges below 33 µl/min. METAS develops in the framework of the EMRP project "HLT07 Metrology for Drug Delivery" a primary standard to cover the flow rate range from 1 ml/min down to 100 nl/min. The setup of the facility and the working principle are addressed in this paper.

Keywords: Micro flow, liquid, dynamic gravimetric calibration, pulsating flow

Introduction

Several applications in biotechnology, medical care, sensor technology and process control involve micro flow wherever mixing, flow or demixing of various fluids or gases are important. METAS develops since 2010 a facility for liquid flow rates from 1 ml/min down to 100 nl/min and participates in the EMRP project "HLT07 Metrology for Drug Delivery" [1, 2] which started in June 2012.
First measurements in steady flow are presented and the determination of the flow rate by means of Orthogonal Distance Regression is discussed [4]. Preliminary results of the flow rate determination of pulsating flow with the gravimetric setup are also shown and compared to the signal of the flow sensor used.

Design of the facility

One of the main issues in the development of the facility is not only to generate a very small flow rate but also to ensure good flow rate stability. To realize this flow rate stability METAS applies the principle of generating the flow by means of a constant pressure drop over a capillary tube according to the law of Hagen-Poiseuille [3]. In the illustrations 1 and 2, the simplified working principle and the facility are shown. A metallic bellow is immerged into the water tank and separates the pressurized air form the pressurized water in the tank to avoid any air absorption in the degased water. To control the water pressure in the water tank the metallic bellow is expanding or compressing by means of adjusting the air pressure inside the bellow with a pressure controller. For this part, the air pressure inside the bellow is adjusted according to the signal of a pressure sensor inside the water tank in order to reach the desired water pressure in the tank. The stability of the water pressure is guaranteed by means of a regulation loop controlled by software. The pressure drop from the water tank to the atmospheric pressure at the outlet needle and the size of the capillary tube determine the flow rate.

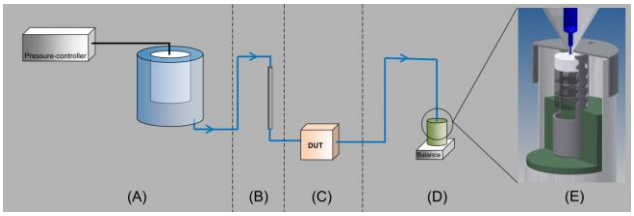

Illustration 1: Simplified drawing of the working principle of the facility. (A) water tank with immerged metal bellow and pressure controller, (B) capillary tube, (C) device under test (DUT), (D) measurement beaker on the balance, (E) detailed cross-section of the top part of the measurement beaker.

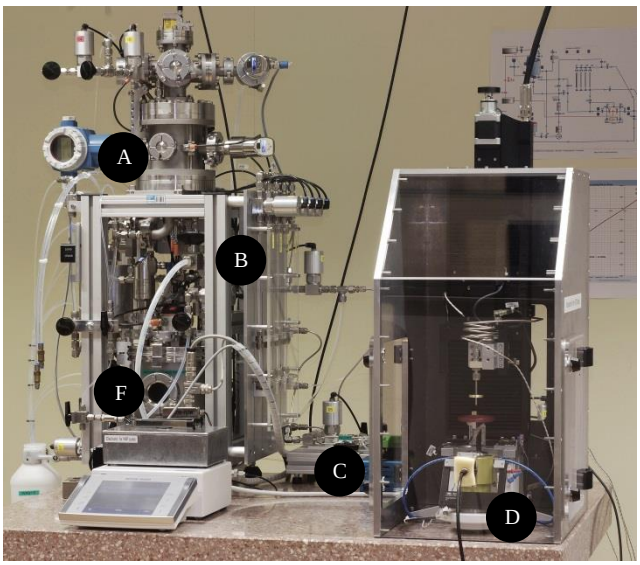

Illustration 2: Photograph of the facility with the main components: (A) water tank with metal bellow, (B) capillary tubes, (C) device under test (DUT), (D) measurement beaker on the balance, (F) main water reservoir.

The facility is designed in such a way that the water pressure upstream the DUT (Device Under Test) can be varied to some extent. In one mode, the water flows from the capillary tube through the DUT and finally in the measurement beaker on the balance. The main pressure drop occurs over the capillary tube and this means that the pressure difference with respect to the ambient pressure upstream the DUT is very small. In a second mode, the water is first guided through the DUT and then through the capillary tube and in the measurement beaker on the

balance. In this case the water pressure upstream the DUT is similar to the water pressure in the water tank.
The installation is filled with degased ultrapure water. Flushing cycles through the various tubing combined with the vacuum in the main water reservoir ensure the ongoing degasing of the water in the piping. In addition, the treatment with UV light during the flushing hampers the growth of bacteria and algae.

Evaporation rate

An important issue is the evaporation rate of the water in the beaker during the measurement. To control this process we apply the conventional method of adding water in an evaporation trap in the weighing zone where the air is then saturated with humidity. Additionally, we have built a special measurement beaker as drawn in the detailed cross-section in illustration 1 (E). The outlet needle is positioned above the glass filters (white discs) where the water enters the measurement beaker. The capillary force in the glass filters sucks the water in before any droplet can be formed at the surface. The water cleaves its way through the glass filters and continues in the water-absorbing foam into the bulk. This prevents the water to be at the surface. With this setup we get stable evaporation rates of (3.15 ± 0.50) µg/min or (3.16 ± 0.50) nl/min respectively and (3.42 ± 1.00) µg/min or (3.43 ± 1.00) nl/min respectively depending on the porosity of the glass filters used.

Gravimetric flying start-stop method

The measurements are performed by means of the gravimetric flying start-stop method. This means that the desired flow rate is set and the data acquisition is only started once the flow rate has reached a steady state. Therefore, the measurement beaker is continuously filled with water and the weighing data are continuously collected with the time stamp of the balance at an acquisition rate of 10 Hz.
An important characteristic of the water flow out of the outlet needle in the measurement beaker is that a connecting water stream builds up. This water stream has a length of 50 µm which is the distance from the outlet needle to the top of the glass filters. The water stream induces a capillary force which remains nearly constant in time and does therefore not influence the relative increase of the weight of the measurement beaker.

Determination of flow rate

The collected weighing data are then fitted by means of the Orthogonal Distance Regression (ODR) [4] where the uncertainties of the weight and of the time are given as input parameters and the slope with its uncertainty is returned. This fitting method has the advantage that at very low flow rates relatively strong fluctuations of the weighing values due to pressure waves or vibrations do not influence the slope.
In Figure 1, the drift measurement of a 200 mg weight is shown. The background noise of the weighing signal of the order of ± 2 µg is due to the fact that the parameter "ambient conditions" of the balance is set to "very stable" and that the command "send the net weight value immediately irrespective of balance stability" is used. To set "ambient conditions" to "very stable" reduces the setting time and therefore the time evolution of the weighing values can be followed without any excessive averaging by the balance.
The sharp peaks of the weighing values are due to the opening of a door or the movement of a person in the laboratory. These influences are observed even though precautions are taken. The influence of vibrations on the balance is reduced by using a weighing table as platform. Additionally, a box made of Aluminum and Plexiglas is placed around the balance to protect from air pressure waves or at least damp important ones (see illustration 2).
The red solid line represents the slope of the drift in the time window from 2.6 h to 3.3 h determined by ODR. The green dashed line indicates the worst case scenario if the slope were determined by the ratio of the differences in weight and time at two distinct moments in time. This slope would not represent the actual time evolution of the weighing values. Obviously, these sharp peaks are much more emphasized at very low flow rates than at higher flow rates as the faster increase of the weighing values would reduce these sharp peaks to background noise.

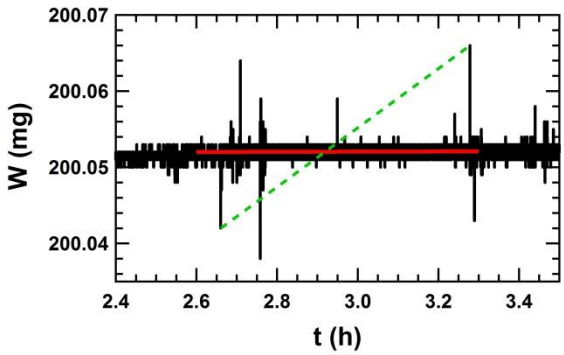

Figure 1: Drift measurement of a 200 mg weight including sharp peaks of the weighing values due to the opening of a door or the movement of a person in the laboratory. (Red solid line) linear fit from 2.6 h to 3.3 h. (Green dashed line) worst case scenario where the slope is determined by the ratio of the differences in weight and time.

Buoyancy correction factor

Another issue of the dynamic measurement is the continuously filling of the measurement beaker with water. Therefore the buoyancy correction for the increasing water volume in the measurement beaker changes in time. To correct for the buoyancy we have the two following possibilities. The first one is that we perform the buoyancy correction of the mass values online by means of the actual air and water density. The mass flow rate $Q(m_{buoyancy(t)})$ is then directly the slope of the fitted data. The second possibility takes into account that these densities do not change significantly during the measurement. We can therefore apply the buoyancy correction factor after the fitting procedure. This means that we calculate the mass flow rate Q_m as the product of the flow rate Q(w) using the real weighing values (not the conventional weighing values) and the buoyancy correction factor $f_{b,d} = \langle 1/(1 - \rho_{air}/\rho_{H2O})\rangle_t$, which is averaged over the measurement time t.

In Figure 2, we compare these 2 approaches. For the first case we determined the mass flow rate $Q(m_{buoyancy(t)})$ and the flow rate Q(w) and calculated the average of the ratio $Q(m_{buoyancy(t)}) / Q(w)$. We performed this for 12 independent experiments and plotted the resulting ratios as the blue squares. For the second case, we determined the averaged buoyancy factor $f_{b,d}$ and plot it as red circles. We can observe a very good overlap of the 2 methods which indicates that the second possibility by means of applying a buoyancy correction factor to the flow rate Q(w) is a simple and valuable method as long as the densities of air and water do not vary significantly in time.

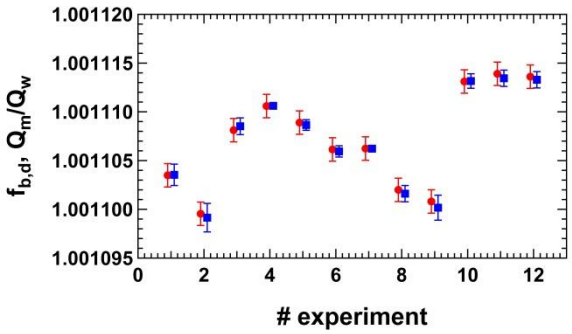

Figure 2: Buoyancy correction factor determined by 2 different methods. (Red circles) the averaged factor $f_{b,d} = \langle 1/(1 - \rho_{air}/\rho_{H2O}) \rangle_t$ using the density values. The error bars indicate their uncertainty (k=2). (Blue squares) the ratio $\langle Q(m_{buoyancy(t)})/Q(w) \rangle_t$ where the mass flow rate is determined by means of the online correction of the mass values due to the continuously increasing water volume in the measurement beaker. The error bars indicate the dispersion 2 σ of the values.

Flow rate stability and uncertainty

As mentioned in the beginning, the flow rate stability is very important. In Figure 3, a flow stability of a mean flow rate of 35.42 µl/min is shown where the deviation from the mean flow rate is plotted. We use a fixed time window to perform a linear fit by means of ODR and increase the starting time of this fixed time window to determine the evolution of the flow rate in time. We can clearly observe that the stability is very good and we obtain a distribution with σ = 0.032 %, as seen in Figure 4.

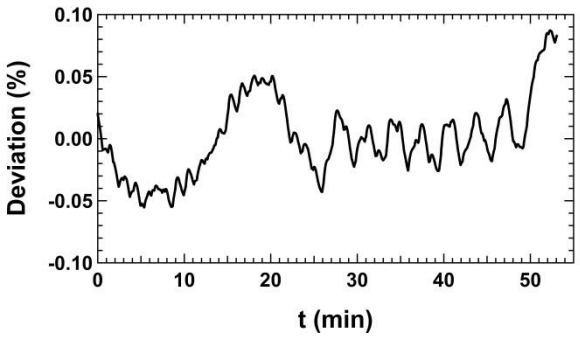

Figure 3: Evolution in time of the deviation of the mass from the mean value of 35.42 µl/min. A fixed time window is used to perform a linear fit by means of ODR and increasing the starting time of this fixed time window leads to the mass flow rate evolution in time.

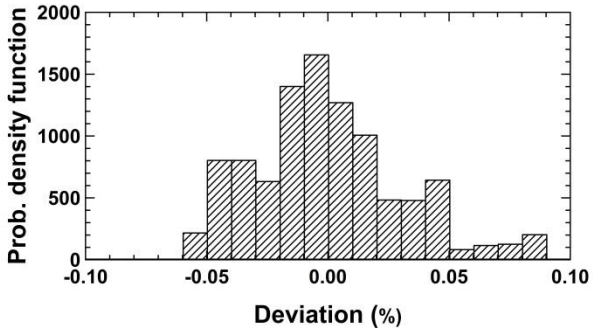

Figure 4: Histogram of the data shown in Figure 3. Distribution with σ = 0.032 %.

The measurement uncertainties of this facility are varying from 0.05 % up to 0.6 % for the flow rate range from 1 ml/min down to 100 nl/min. These uncertainties need to be confirmed during the validation process.

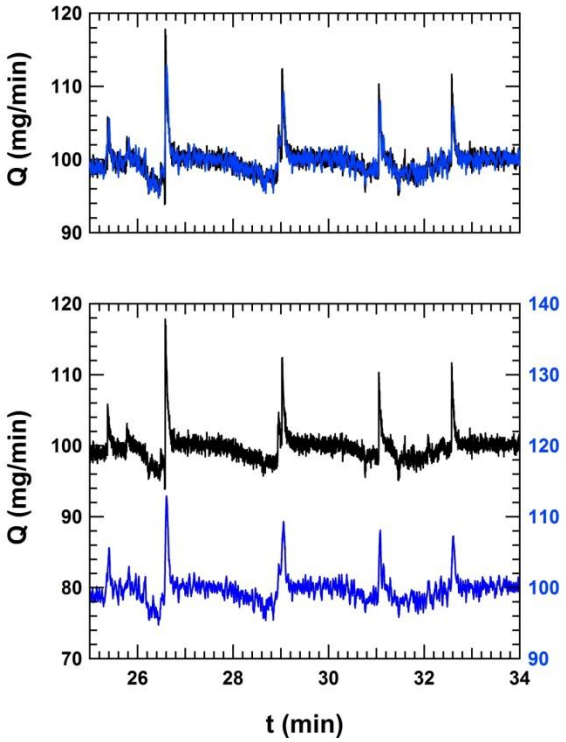

Figure 5: (Blue solid line) mass flow rate determined by means of ODR using a fit window of 4 s and an acquisition rate of 9 Hz -10 Hz. (Black solid line) mass flow rate of a Coriolis mass flow meter with 100 ms integration time and acquisition rate of 10 Hz. (Top) both curves have the same flow rate axis. (Bottom) the flow rate axes are separated by a shift to better visualize the similar trend of the two measuring methods.

Pulsating flow

In addition, the installation is also developed for the determination, characterization and traceability of pulsating flow. First measurements with a Coriolis mass flow meter in the pulsating regime show promising results. A snapshot of the evolution of the flow rate is shown in Figure 5. The signal of the Coriolis mass flow meter is integrated over 100 ms which is also the acquisition rate of

the mass flow rate. We compare it to the mass flow rate determined by our method where we use a fit window of 4 s. We can determine the mass flow rate with an acquisition rate which is equal to the acquisition rate of the weighing values of the balance. We simply increase the starting time of the fit window by one time step of the collected data and get therefore the acquisition rate of 9 Hz -10 Hz.
We clearly see that both signals follow the same trend and that the peaks of the Coriolis mass flow meter are obviously sharper as the integration time is only 100 ms compared to the fit window of 4 s. However, first evaluations of the measurement uncertainty indicate that an uncertainty of 2 % should be reached which is better than the target uncertainty of 3 % as mentioned in the EMRP project [2].

Conclusion

The micro flow facility at METAS is developed to perform calibrations of steady flow rates from 1 ml/min down to 100 nl/min where the measurement uncertainties vary from 0.05 % to 0.6 %. As already mentioned, the uncertainties need to be confirmed during the validation process. In addition, the calibration method for pulsating flow rates from 1 ml/min down to 1 µl/min with an expected uncertainty of 2 % is currently developed. Extension to lower flow rates mainly in pulsating flow regime is part of future investigations. The validation of this facility will be completed by beginning of 2014.

Acknowledgement

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References

[1] EMRP Call 2011 - Health, SI Broader Scope & New Technologies, HLT07 Metrology for drug delivery, www.euramet.org
[2] Website of the EMRP Project HLT07 MeDD, http://www.drugmetrology.com/
[3] Bohl, Elmendorf, Technische Strömungslehre, Verlag Vogel Fachbuch, ISBN 978-3-8343-3129-8, 2008
[4] W. Press, S. Teukolsky, W. Vetterling, B. Flannery, Numerical Recipes in C, New York: Cambridge University Press, 1992, ch. 15.3, pp. 666 – 670.