Testing micro-flow devices for medical applications

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Abstract

Almost every medical department at hospitals all around the world uses infusion devices to administrate fluids, nutrition, and medications to patients for the treatment of numerous different diseases and ailments. Depending on the intended use of the equipment e.g., if it is used for anaesthesia of adults or for medical treatment of premature infants, the accuracy of the equipment can be more or less important. A well-defined metrological infrastructure can help to ensure that infusion devices function properly and are as accurate as needed for their use. However, to establish a metrological infrastructure an appropriated knowledge about infusion devices in use is necessary that enables calibration and testing procedures to be properly defined. This paper summarises the results of various tests conducted with three types of devices – a syringe pump, an infusion device analyser and an insulin pump.

1. Introduction

Infusion therapy is one of the most commonly used forms of therapy in health care. Almost every hospital department use infusion equipment to administer important medical drugs. Infusion therapy can also be used to deliver fluids or nutrition to a patient. Infusion equipment cover a wide range of devices and applications from implantable pumps for pain treatment, to bags in IV (intravenous) poles. In general, infusion devices are used to provide a steady flow rate or to administrate a certain volume (bolus) of fluid, nutrition, or drug into the patient.
Depending on the use of infusion devices the intended flow rate indicated by the device or application is more or less important. For general anaesthetics in adults the accuracy of the flowrate may not be a critical factor as the variety in response to anaesthetics varies greatly among individuals. However, for infusion treatment of premature or new-born infants a correct and accurate administration of drug may be vital [1, 2].
The earlier EMRP project HLT07 MeDD (Metrology for Drug Delivery) published a review listing the potential medical errors associated with flow rate variability in drug delivery devices [3]. These errors can have serious health consequences for the patient including severe health damage or death.

Regardless of the type of treatment or patient group the infusion device is used for, it is of great importance to know what accuracy one can expect from a device. Therefore, a well-defined metrological infrastructure is needed to ensure that the precision and the accuracy of the pump flow rate error are within expected limits specified by the manufacturer or by the user of the pump, as the metrological infrastructure ensures a traceability to a commonly agreed standards as the SI units [4].
This paper describes part of the test program of the EMPIR project 18HLT08 MeDDII - Metrology for drug delivery [5] which has been conducted with the aim of getting knowledge about several selected medical flow devices in order to define the best calibration practices for them. Particularly, the tests of a syringe pump, an infusion device analyser (IDA) and an insulin pump are described. The tests have been performed using calibration facilities based on various principles such as the gravimetric principle, piston prover or syringe pump volumetric method, optical interface tracking method or μ-PIV method. The methods are briefly described in this paper.

For each tested device we briefly summarize the performed tests and their results and we show a more detailed analysis for one of the tests per device as an example. More details on all of the tests can be found in publication series which are just under preparation [15].

2. Instruments under test

2.1 Syringe pump

Syringe pumps are motor-driven pumps that uses one or more syringes to provide a steady flow rate or to administrate a certain volume (bolus) of drugs into a patient. The motor in a syringe pump drives a spindle that pushes the plunger (piston) into the syringe. Depending on the quality of the stepper motor, the spindle, etc. a more or less smooth movement of the plunger is achieved. These pumps are used with disposable plastic syringes or with reusable glass or metal syringes. There is a wide variation in the quality and the flow rate ranges offered by these pumps.
In the project 18HLT08 MeDDII the syringe pump BBraun Perfusor Space (Fig. 1) was tested in a flow range from 0.01 mL/h to 30 mL/h with disposable plastic syringes. Two syringe sizes were used for the tests in this project specifically a 10 mL and 50 mL syringes, which are mostly used in clinical applications.

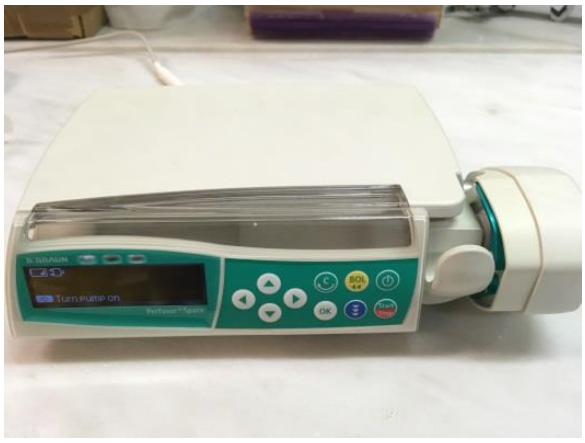

Figure 1: Syringe pump for use with disposable syringes

2.2 Infusion device analyser

Infusion devices analysers (IDA) are used to analyse the performance of a variety of infusion pumps. They measure both average and instantaneous flow and also check the occlusion alarm on the infusion devices by measuring the occlusion pressure. IDAs are often used by the users or maintenance officers at the hospitals maintenance department to check the performance of a drug delivery device. These devices are usually calibrated by the manufacturer before they are sold. In many cases, subsequent calibrations are not considered and there is no documentation explaining how to perform them. To maintain the traceability chain of an IDA its calibration should be performed by a recognized laboratory, accredited or national metrology institute (NMI) using well defined calibration procedures.
In this project the infusion device analyser Fluke IDA-1S has been tested (Fig. 2).

Figure 2: Infusion device analyzer.

2.3 Insulin pump

Insulin pumps offer a flexible treatment of diabetes. They can have different working principles and can operate at different flow rates. One working principle is an elastomer (like a balloon) that is filled with insulin and pumped through a capillary, providing a stable but fixed flowrate. Another principle is based on a stepper motor that moves a plunger incrementally and forces the piston into a container to push out the insulin. In this case, small amounts of liquids are delivered at a specific time interval and the flow is quasi-continuous. The volume increment is often called a single dose.
In this project an insulin pump of the latter type has been tested with flow rate range of (0.25-10) µL/h with single dose of 500 nL for the flow rate of 10 µL/h and 250 nL for lower tested flow rates.

3. Calibration methods

The following sections describe the methods used to calibrate and test the different medical infusion devices that were evaluated in this project. A more detailed description can be found in [6].

3.1 Gravimetric method

The gravimetric principle is based on measuring the mass delivered by an infusion device, also denoted DUT (Device Under Test), in a beaker placed on a laboratory balance, as described in [7]. For flowrates below 1 mL/h the balance should have a resolution of micrograms (6 decimal places). The mass flowrate is determined as the mass collected in the beaker divided by the time needed to collect the mass. Demineralized degassed water should be used as fluid to avoid bubble formation in the small tubing. The mass flowrate is converted to a volume flow rate by dividing with the water density. The density is determined from water temperature using a commonly

accepted formula from literature, e.g. [8]. Many parameters must be taken into account, corrected or included in the measurement uncertainty budget. These parameters include among others, evaporation, water degassing, flow stability, time measurement, temperature stability, buoyancy correction of the delivered liquid, buoyancy correction for the immersed tube (needle) into the liquid, jet force from the immersion tube, stick/slip of liquid on tube (needle), drift and linearity of the balance, etc.
In the present project, all devices were, beside other approaches, also tested with the gravimetric method.

3.2 Syringe pump/piston prover

High precision syringe pumps with glass or metal syringes and a piston prover [9, 10] were used to achieve an accurate flowrate for calibration and testing of the IDA. The syringe pump or piston prover can be calibrated either using a primary gravimetric standard as described above or by calibrations of a plunger shift, piston cross-sectional area and a clock.

3.3 Optical interface tracking method

The interface tracking method consists of measuring the position of the meniscus of a liquid-air interface in a capillary as a function of time. The data of the position and time allows to calculate the speed of the meniscus and by multiplying with the cross section of the capillary to obtain the flow rate as a function of time. The measurement setup uses high precision capillaries in combination with a high-speed camera and telecentric lenses [11, 12].
This method was used to test the insulin pump.

3.4 μ-PIV method

μ-PIV is an optical method of flow visualisation used to determine instantaneous fluid velocity measurements. The flow is seeded with tracer particles that are imaged to cross-correlate their displacement at two different time points with a defined interval to determine their velocity. A typical μPIV system includes an optically transparent microchannel with flowing fluid seeded with tracer particles, an illumination source and camera to record a sequence of images to cross-correlate and determine the velocity [6].
This method was used to test the insulin pump.

4. Tests of the syringe pump

4.1 Tests summary

Several tests have been conducted to characterise the flow rate behaviour of the syringe pump using the gravimetric reference method in various laboratories.
The first test investigated the pump's performance for various liquids. The average flow rates generated by the syringe pump have been compared with the syringe filled with: distilled water, saline solution, dopamine, dobutamine, propofol and gelaspan, at a set flow rate of 1 mL/h. No significant differences were found in the resulting flow rates related to the different liquids. This shows that the test with distilled water, as specified in the standard [16], is representative for the group of considered liquids.
Next the average flow rate generated by the syringe pump was measured for different plunger positions in a 50 mL syringe. These tests were carried out to verify if it is possible to restrict the flow rate tests to specific syringe segments, which are representative for the entire syringe volume. The syringe was divided into ten segments, and it was found that the maximal difference from the generated average flow rates over all the segments was about 1.4% for the lowest tested flow rate of 1 mL/h. The test has been performed for the BBraun Original-Perfusor syringe only.
In the next test, two methods for assessing short-term flow variability of the syringe pump were compared. The first is based on the standard [13], which defines the so-called trumpet curves. The second is based on the recently published technical information report [14], which uses a single-compartment pharmacokinetics model to define an alternative methodology for evaluating the effect of flow rate instability. It was shown that the predictions of the "flow rate variability" of the first approach (in terms of standard deviation of an average flow rate instead of its minimum and maximum) and the "compartment volume variability" of the second approach are quantitatively similar when the "observation window" in the first approach is about 2.5 times the "drug decay time" in the second approach (for details of definitions see [13, 14]).
Next the performance of the syringe pump and of the gravimetric reference methods of several laboratories have been tested for extremely low flow rates of 0.1 mL/h and 0.01 mL/h, approaching the lower range of the syringe pump as it is specified by the manufacturer. A software unlock from the manufacturer is necessary to use the device at the 0.01 mL/h flow rate. More details of the tests at the low flow rates are discussed below.

4.2 Tests at the extremely low flow rates

The extremely low flow rates of 0.01 mL/h and 0.1 mL/h have been tested with a 10 mL syringe in three laboratories – IPQ, RISE and NEL. Average flow rates have been measured by three laboratories over the time periods summarised in Table 1. The percentage deviation of the average flow rate from the set point value are shown in Fig. 3, including the error bars representing the expanded uncertainties with confidence level of 95%, as reported by the laboratories. The uncertainties also include a 1% contribution resulting from variability of diameters of the syringes used. Fig. 3 shows that the results of all laboratories agree if the stated uncertainties are taken into account. This is a confirmation of the different test methods and uncertainty assessments used by the laboratories. Furthermore, the uncertainty intervals given by all laboratories overlap with the

accuracy interval of ± 2% as specified by the manufacturer. Moreover, the flow rate deviation itself is within the accuracy specification for the laboratory with the lowest stated measurement uncertainty.

Table 1: Test times over which the flow rates have been averaged

Laboratory	RISE		IPQ (long)		IPQ (short)		NEL
set flow rate (mL/h)	0.01	0.1	0.01	0.1	0.01	0.1	0.1
test time (h)	72	40	24	16	2	2	2

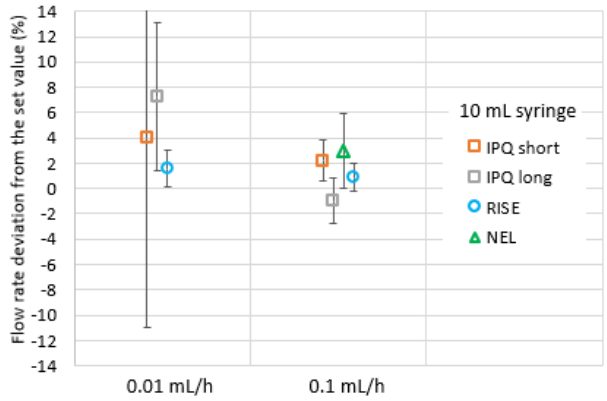

Figure 3: Comparison of calibration results for average flow rate obtained in various labs. The bars represent the expanded uncertainty of the resulting flow rate deviation which is calculated as (ref value – set value)/set value*100%.

In addition to the long-time average flow rate values, it is also interesting to look at the dynamic behaviour of the syringe pump at low flow rates. At RISE, the actual balance readings have been logged every second during the tests. The data was used to calculate 5 s averages of the reference flow rate and their dependence on time, which is shown in the upper part of Fig. 4. From the figure, a pulsating character of the flow can be observed. Averaging over a long period (Tab. 2) leads to small deviations of the resulting average flow rate from the setpoint. However, reducing the averaging time (period) would possibly result in larger deviations. To quantify this effect, the trumpet curve method of [13] can be used. Using an averaging period (observation window) and shifting the start of the averaging time to different points in time over the entire test period, various average flow rates Q_{avg} are obtained which lie in a range of $E_{P\,min} \leq Q_{avg} \leq E_{P\,max}$. If the ranges $E_{P\,min}$ and $E_{P\,max}$ are plotted as functions of the averaging period, the so-called trumpet curves are obtained. The trumpet curves for averaging period with a duration from 2 min to 31 min are shown in the lower panel of Fig. 4. The average flow rate variability given by the range width $E_{P\,max} - E_{P\,min}$ exceeds 10% for averaging times below approx. 5 min at 0.1 mL/h and below approx. 25 min at 0.01 mL/h. To achieve the flow rate variability below 4% required to meet the accuracy specification of ± 2%, approx. 18 min averaging time for 0.1 mL/h and 80 min for 0.01 mL/h are needed. (Plots for the 0.01 mL/h flow rate can be found in the prepared paper series [15].)

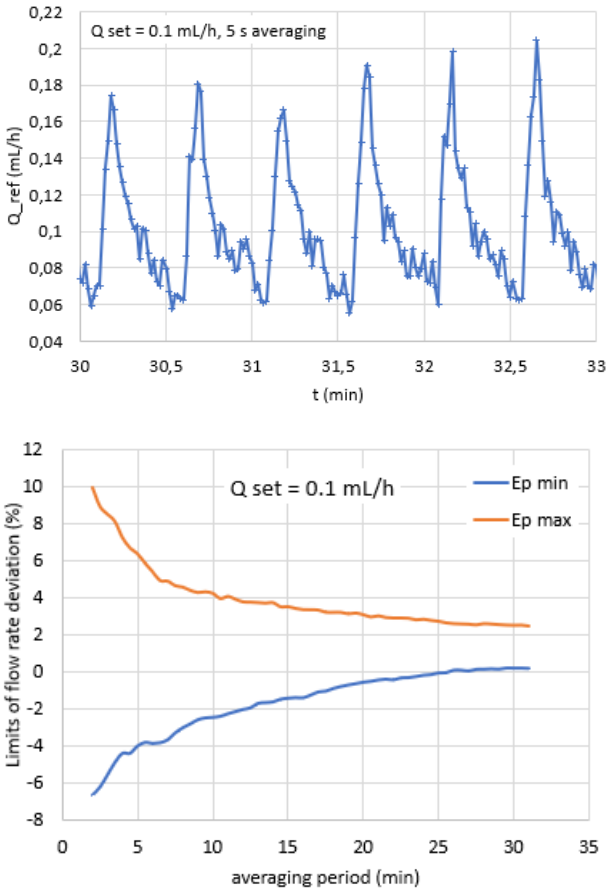

Figure 4: The upper part of the plots shows flow rate (5 seconds average) as a function of time for 0.1 mL/h. The lower part shows a range of the averaged flow rate for a given duration of the averaging period (trumpet curves).

5. Tests of the infusion device analyser

5.1 Tests summary

In order to determine the best calibration procedure for both flow and pressure of an Infusion device analyser, several tests have been performed, mainly: flow rate measurement error determination, use of different acquisition times (volumes), use of different calibration liquids (water, saline solution, dobutamine, dopamine), reproducibility test and comparison of several methods with various reference flow rate realisations. Detailed description of the uncertainty components has been provided.

The first two tests are described in more detail below. The observed differences of flow rate errors for various liquids were an order of magnitude smaller than the uncertainties of the results for particular liquids indicating that the IDA is not affected by the properties of the calibration liquid.

To determine the reproducibility of the IDA, one laboratory performed a calibration of the flow rate on three different days. For 10 mL/h and above, the largest deviation between the repetitions was 0.15 %, which is less than the calibration uncertainty of 0.61 % for 10 mL/h. Below 10 mL/h, the deviation increases to 1 %, but is still within the claimed uncertainty of 2.59 %.
Different methods can be used to calibrate the IDA with respect to flow. The most common method is to use a high-quality reference syringe pump with metrological traceability ensured. Other methods use a calibrated reference flowmeter or direct gravimetric measurements, however, the latter may not be the best option, because the outlet of the IDA is not a continuous flow. All methods were compared in this work. The use of a reference syringe pump method is recommended.

5.2 Flow rate measurement error determination

The flow rate measurement error was determined by six laboratories (METAS, IPQ, CMI, RISE, NEL, DTI) at different flow rates: 0.5, 1, 5, 10, 25, 50 and 100 mL/h. The results can be seen in Fig. 5. All calibrations performed by the laboratories were based on the method with a syringe pump as a reference. Good agreement between the calibration results was observed taking into account the reported uncertainties. The largest deviations between the laboratories are observed at the lower flow rates.

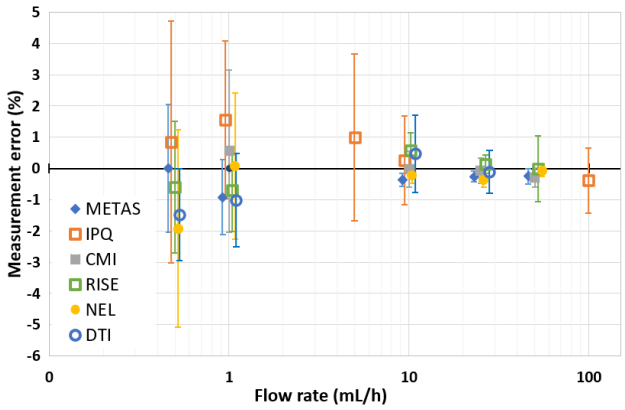

Figure 5: Flow rate measurement error of the IDA. The error is determined as (IDA value – ref value)/ref value*100 %.

5.3 Effect of acquisition time (volume)

The manufacturer specifies the instrument accuracy as 1 % or reading ± resolution (0.01 mL/h) for flow of 16 mL/h to 200 mL/h for volumes over 20 mL or otherwise 2 % of reading ± resolution (0.01 mL/h) for volumes over 10 mL. At very low flow rates the measurements with 10 mL or 20 mL volumes take many hours which may not be feasible for a calibration laboratory. Therefore, the flow rate error of IDA was determined at different flow rates with different delivery volumes and thus different acquisition times. From the results presented in Fig. 6 one can see that the error variations for volumes larger than approximately 4 mL are already below the lowest calibration uncertainties reported in the paragraph 5.2.

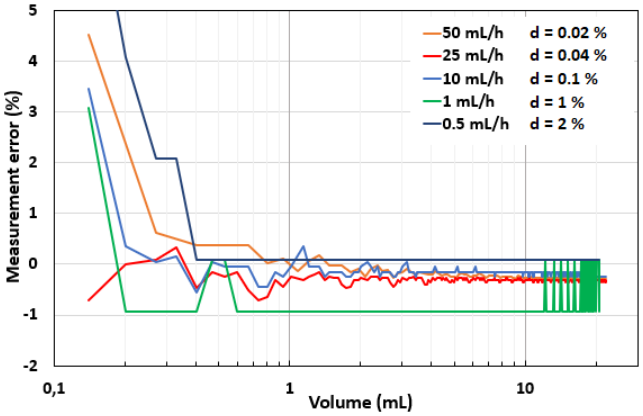

Figure 6: Dependency of the obtained flow rate measurement error of the IDA on the liquid volume used for the calibration. The smallest digit of the IDA display is 0.01 mL/h corresponding to a percentual flow rate increment *d* given in the legend.

6. Tests of the insulin pump

6.1 Tests summary

The gravimetric and optical methods described in this paper allow a detailed analysis of the delivery mechanism of insulin pumps delivering discrete doses at given cycle times. In this case the average flow rate can be characterized by two methods – the discrete dose analysis method (described below) and the common method based on linear regression of the mass-time or volume-time data.
The discrete dose analysis method allows for detailed follow-up of dose cycle time and delivered doses as a function of time, and to investigate the short- and long-term performance of insulin pumps. For the linear regression it has been shown that the method is appliable with additional requirements: it is advantageous to choose the fitting window to be five times the cycle time and the averaging time frame to be at least ten times the cycle time of the delivery of the single doses in order to obtain a representative result for the calibrated average flow rate of the insulin pump.
Calibration results for average flow rate obtained with various calibration principles and with both data analysis methods have been compared. Long-term fluctuations of the pump have been evaluated in a 60 hours test showing that the basal flow rate can change within ±5 %.
The discrete dose analysis method is also suitable for determining of bolus sizes. Due to the long-term fluctuations caused by the pumping mechanism, it is advisable to determine the bolus size at different positions of the piston in the container in order to compensate these long-term fluctuations. The bolus

calibrations have been performed by several laboratories and the results have been compared.

6.2 Discrete dose analysis method

The method described in the standard IEC 60601-2-24:2012 – Clause 201.12.1.104 [13] analyses the discrete volumes of the single doses at a constant cycle time. The method used in this work to analyse the discrete doses is very similar, except that the constant cycle time is replaced by the time stamps that identify the step increase in weight for the gravimetric method or the step increase in position for the interface track method. The data of the gravimetric method are used to explain the discrete dose analysis method. First, the times of the step increase must be determined by identifying the local maxima in the slope of the curve of the weighing data. The slope of the curve of the weighing data (Fig. 7, black line) has been calculated using the linear regression method over a fitting window of 2 s, as shown in Fig. 7 (green line). The local maxima of the gradient indicate the times of the step increase, whereby the weight value in the gradient is represented by the green diamond. To calculate the step increase, the weight values prior to the increase must be identified. Therefore, the weight values from -15 s to -10 s are averaged with respect to the time stamp of the local maxima in order to reduce the measurement noise. These averaged values are shown as red circles in Fig. 7 and are used to determine the weight increment of the single doses by subtracting two consecutive values. At the same time, the corresponding cycle time is also determined and analysed for irregularities. The histogram of the weight increments is shown in Fig. 8, where the average of the discrete dose volume is 496.6 nL with a standard deviation of 21.2 nL, resulting in a deviation of +0.68 %. Furthermore, the corresponding cycle times of the discrete doses range between 179.80 s and 180.30 s with a mean value of 180.00 s.

Another issue arises from the starting point of the discrete dose analysis method, which is even more important for the similar method described in the standard IEC 60601-2-24:2012, where no requirements for the starting point of the data analysis are specified and a fixed cycle time is applied. Several starting points are chosen, whereby the starting point for the discrete dose analysis lies prior to the increase (Fig. 7, red circle), whilst the step increase (green diamond – +12 s) or after the step increase (blue square – +20 s; orange triangle up – +30 s; pink triangle down – +60s). The average over the discrete dose volumes has always been calculated over the same acquisition time in to obtain the average over the same number of discrete doses. The results (for the full data set please see the prepared publication series [15]) show no significant dependence on the starting point for both the discrete dose analysis and the method according to IEC 60601-2-24:2012. It is also important to note that for this data set, the deviations of both methods are consistent and only a minor variation is observed. Averaging the weight values over 5 s slightly differs the results from the method in IEC 60601-2-24:2012, where only single weight values are taken for the analysis without reducing the reading noise of the balance. However, the difference is negligible compared to the measurement uncertainty.

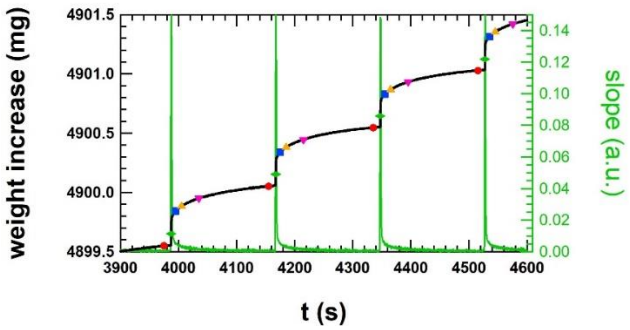

Figure 7: Smooth step increase of the weight of single doses of the order of 500 nL at cycle times of 180 s for a flow rate of 10 µL/h (black line). Average of weight values for 5 s prior to the increase (red circle), in the step increase (green diamond – +12 s), after the step increase (blue square – +20 s, orange triangle up – +30 s, pink triangle down – +60 s). The slope of the step increase of weight for finding the local maxima (green line, right axis) is shown and corresponds to the time of the green diamonds.

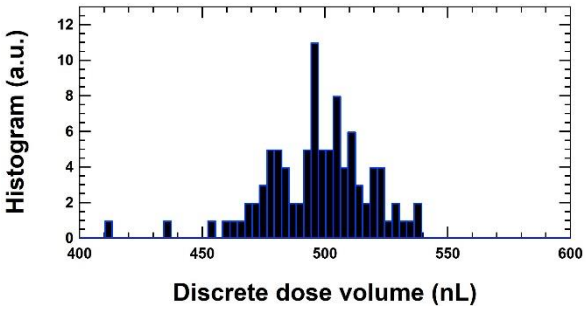

Figure 8: The dose volumes at 10 µL/h for the measurements at METAS are represented in a histogram. The average of the dose volumes from 3975 s to 20895 s is 496.6 nL leading to a deviation of +0.69 %. The corresponding cycle times of the discrete doses are between 179.80 s and 180.30 s with an average of 180.00 s.

7. Conclusion

Tests of three flow devices used in health care have been performed, namely a syringe pump, infusion device analyser and an insulin pump. The test programme was planned with the aim to define recommendations and the best practices for calibration of the instruments and for ensuring their metrological traceability.

On top of this conference paper which briefly summarises the work done and shows several examples the series of papers is in preparation with detailed data sets [15].

The knowledge gained by this work will also be used to formulate the corresponding Euramet Calibration Guidelines on drug delivery devices.

ACKNOWLEDGMENTS

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