OPEN ACCESS

Journal of Diabetes and Treatment

Batista E, et al. J Diabetes Treat 4: 1075.

DOI: 10.29011/2574-7568.001075

Review Article

Calibration of Insulin Pumps

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Citation: Batista E, Sousa JA, Martins RF (2019) Calibration of Insulin Pumps. J Diabetes Treat 4: 1075. DOI: 10.29011/2574-7568.001075

Received Date: 01 October, 2019; **Accepted Date:** 30 October, 2019; **Published Date:** 05 November, 2019

Abstract

Nowadays, several types of infusion pumps are commonly used for medical drug delivery, such as insulin pumps, and present different measuring features and capacities according to their use and therapeutic application. In order to ensure the metrological traceability of these equipment, it is necessary to use suitable calibration methods and standards.

During the research herein presented, two different calibration methods were used to determine the flow rates of an insulin pump. One of these was the gravimetric method, considered as a primary method, and commonly used by the National Metrology Institutes; the other calibration method used was an optical method, which relies on the measurement of the variation of volume of a drop during a period of time.

The suitability of each calibration method mentioned earlier was assessed by testing an insulin pump at a flow rate of 10 µL/h and for a volume of 10 µL, that in the tested device corresponds to 1 unit of insulin. Experimental results revealed a non-continuous functioning of the insulin pumping device under test, which was unexpected, and could lead the patient not to receive a continuous dose of medicine.

Keywords: Calibration, measurement, microflow, insuline pump, gravimetry, optical method

Introduction

Subcutaneous insulin infusion is a standard therapy for a person with Diabetes Type I. In such a case, insulin pump delivers insulin continuously, simulating the natural internal secretion of insulin from the pancreas [1]. Insulin pumps have a reservoir where the insulin is stored, and this is connected to a capillary tube, with a caterer at its end, that will be connected to the patient subcutaneously (Figure 1).

Figure 1: Equipment under calibration, where 1 is the insulin pump and 2 is the volume chamber with the capillary tube.

The continuous delivery of insulin into a patient has a significant advantage regarding the multiple daily injections because it can deliver precise amounts of insulin, as needed, and there is better control over background or "Basal" insulin dosage to meet all the body's non-food-related insulin needs. Besides, the insulin pump is assisted by software that automatically determines the bolus infusion dosage. This value can also be programmed on the machine [2]. Hence, it is crucial that the volume and flow generated by these devices be the most accurate and precise as possible. To ensure this, it is necessary to have appropriate calibration methods.

Calibration Methods

Gravimetric method

The gravimetric method is considered as a primary method and is commonly used by the National Metrology Institutes [3,4] to calibrate the flow rate delivered by the equipment, such as insulin pumps. This relies on weighing the mass of liquid delivered during a specified time. The flow rate is then determined by the quotient of the mass of reference liquid, usually water, and time interval, including some corrections (Equation 1) [3].

$$Q = \frac{1}{t_f - t_i}\left[\left((I_f - I_i) - (\delta m_{buoy})\right) \times \frac{1}{\rho_W - \rho_A} \times \left(1 - \frac{\rho_A}{\rho_B}\right) \times [1 - \gamma(T - 20)]\right] + \delta_{evap} \quad (1)$$

Although evaporation is kept to a minimum value via technical means - by using an evaporation trap, for instance, the determined mean evaporation rate (δ_{evap}) is required as a correction term in the volume flow rate (Q) (Eq. 1). More information is described in [3].

Other contributions to the model are the density of the reference liquid, i.e. water (ρ_W); the time interval of the weighing, i.e. the final time (t_f) minus the initial time (t_i); the mass of the displaced reference liquid, i.e. the difference between the final (I_f) and the initial (I_i) indication of mass in the scale (Figure 2); the density of the air during the tests (ρ_A); the density of the mass standards used to calibrate the balance (ρ_B): coefficient of thermal expansion of the material (γ), the temperature of the water during the tests (T) and the repeatability δQ_{rep}. The term δm_{buoy} accounts for the buoyancy contribution of the dispensing needle immersed in the weighing vessel (Eq. 1).

In addition, the calibration methodology used at the Portuguese Institute for Quality (IPQ), namely at Laboratory of Volume and Flow, and validated in a range down to 120 µL/h, with uncertainties of 3%, was adapted for this work.

The procedure implied the use of an experimental setup consisting of an insulin pump, serving as the flow generator, that has a removable volume chamber (Figure 1). Additionally, this volume chamber had attached a plastic tube that was connected to a reservoir placed on an environmental protected chamber (evaporation trap) inside a Mettler Toledo AX26 scale's plate (Figure 2); the tip of the tube was inserted below the water line contained in the reservoir in order to have a Continuous mass reading.

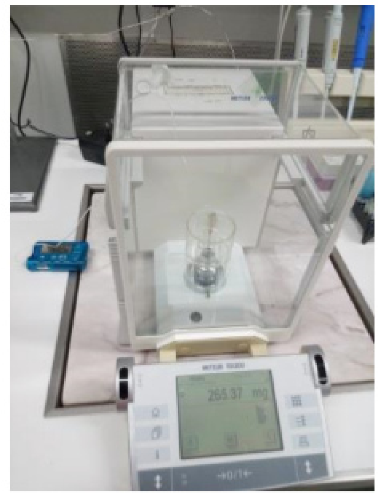

Figure 2: Picture of the assembling for calibration of an insulin pump by gravimetric method in IPQ: balance Mettler Toledo AX26 with evaporation trap (on the right) and a syringe pump (on the left).

Concerning the flow rate, and according to the manufacturer's nomenclature, the insulin pump was tested at 1 U/h, which represents 10 µL/h, and U means a unit of insulin. Moreover, to remove any remaining air in the tube, the system was purged during 10 minutes before starting the measurements. Therefore, only when the volume chamber and the tubes were full of the calibration liquid (water) the measurements started.

The data acquisition of mass was taken directly from the scale every 250 ms using a customised application developed in *Lab view*, while the measurement of time registered by the computer was carried out simultaneously. Hence, the flow rate was determined every 30 s, having into account a minimum of 23 instantaneous flow measurements.

During the calibration procedure, the temperature of water and air, the relative humidity and the atmospheric pressure were continuously measured and recorded.

Optical method

As an alternative to the gravimetric method, a novel methodology based on the application of optical technology was developed to measure flow rates.

After the insulin pump was set at 1 U/h (10 µL/h), the delivered liquid flow was determined by observing the volume increase of a drop at the end of the polypropylene tube (Figure 3a) placed inside an evaporation trap. This observation was performed at a specific time by using photographs taken by a Veho VMS-004 USB digital microscope shown in Figure 3b.

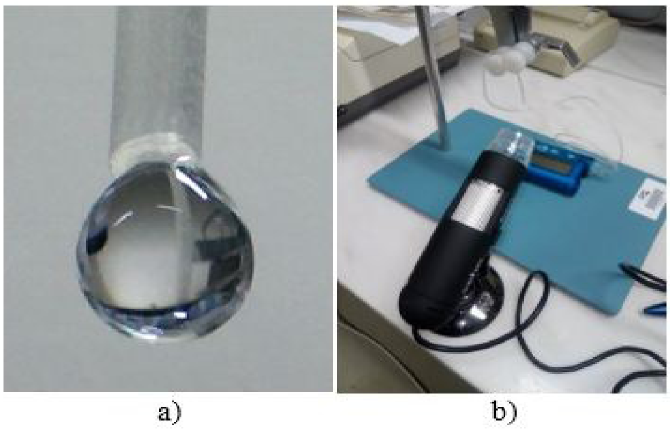

Figure 3: a) Magnified view of a drop captured by USB digital microscope Veho VMS-004; b) Experimental setup for calibration of an insulin pump using a photometric method.

The projected area of the drop was obtained geometrically with the assistance of a 3D CAD software (Figure 4) by defining boundary polylines on its highly magnified picture, with pixel resolution, and considering the tube diameter, 1,49658 mm, measured by interferometry, as the reference value for length. This value was then converted to an equivalent sphere volume and later to a flow rate based on time acquired and on volume change.

Figure 4: Magnified view of a drop with its boundary defined in a CAD software (SolidWorks 2018).

Besides, evaporation tests were performed at different sizes of the drop at the same working conditions of the flow tests and where it can be seen that the larger the drop radius, the larger the evaporation rate (Figure 5). The obtained equation can then be use to correct the determined flow rate.

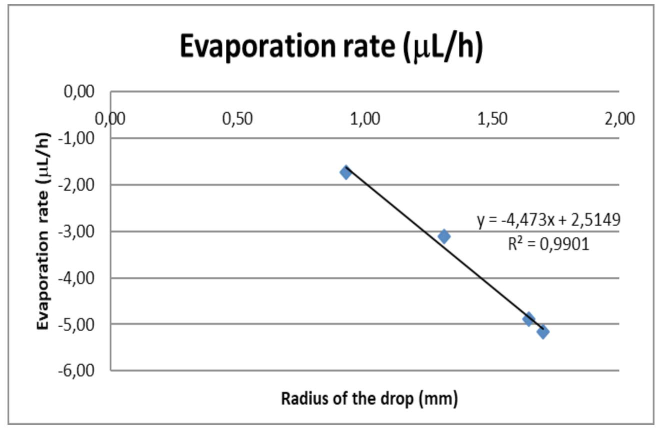

Figure 5: Evaporation rate

Results and Discussion

Gravimetric method results

Five tests were carried out on different days. The volumetric flow rates and corresponding uncertainties obtained are presented in Figure 6.

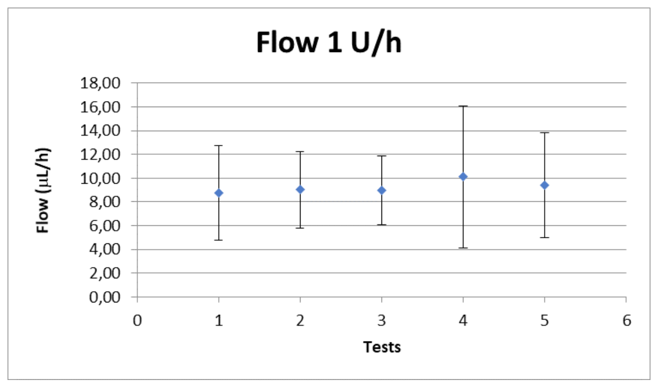

Figure 6: Gravimetric calibration results of insulin pump.

The average error obtained from these 5 measurements was - 8% and the uncertainty 44%. No information on accuracy of the device is given by the manufacturer, so it is not possible to evaluate the determinate error by comparison with specifications.

Uncertainty calculation followed the GUM [5] and the model described in equation. 1 [6,7]. Detailed information regarding the uncertainty components used in the calculation of volumetric flow rate uncertainty is described in Table 1.

After analysing all uncertainty components, it was verified that the flow variability of the insuline pump (repeatability) is the largest source, one can even say the only source, since the others are negligible. This variability can also be observed in Figure 7.

Uncertainty components	Estimation	$u(x_i)$	c_i	$(c_i \times x_i)^2$
Final mass (g)	1,60	$3{,}78\times10^{-05}$	$4{,}08\times10^{-04}$	$1{,}13\times10^{-36}$
Water density (g/mL)	0,997556	$6{,}28\times10^{-04}$	$-4{,}10\times10^{-06}$	$8{,}85\times10^{-37}$
Air density (g/mL)	0,001180	$2{,}89\times10^{-06}$	$3{,}59\times10^{-06}$	$2{,}32\times10^{-49}$
Balance weight density(g/mL)	8,00	$2{,}50\times10^{-03}$	$7{,}54\times10^{-11}$	$2{,}53\times10^{-53}$
Temperature (˚C)	22,9	0,906	$-9{,}82\times10^{-10}$	$1{,}26\times10^{-38}$
Expansion Coefficient (/˚C)	$2{,}40\times10^{-04}$	$6{,}93\times10^{-06}$	$-1{,}20\times10^{-05}$	$9{,}59\times10^{-46}$
Initial mass (g)	1,59	$3{,}78\times10^{-05}$	$-4{,}08\times10^{-04}$	$1{,}13\times10^{-36}$
Evaporation (mL/s)	$1{,}04\times10^{-07}$	$1{,}47\times10^{-08}$	1	$9{,}26\times10^{-36}$
Initial time(s)	0,250	$7{,}00\times10^{-04}$	$1{,}67\times10^{-09}$	$3{,}69\times10^{-50}$
Final time (s)	2460	$7{,}00\times10^{-04}$	$-1{,}67\times10^{-09}$	$3{,}69\times10^{-50}$
Buoyancy (g)	0,0001	$1{,}74\times10^{-06}$	$4{,}08\times10^{-04}$	$5{,}16\times10^{-42}$
Repeatability (mL/s)	$3{,}90\times10^{-06}$	$5{,}41\times10^{-07}$	1	$1{,}68\times10^{-27}$
Flow (µL/h)	10,1 (Eq. 1)			
u_{comb} (µL/h)	2,0			
U_{exp} (µL/h)	4,0			

Table 1: Uncertainty contributions in gravimetric insulin pump calibration.

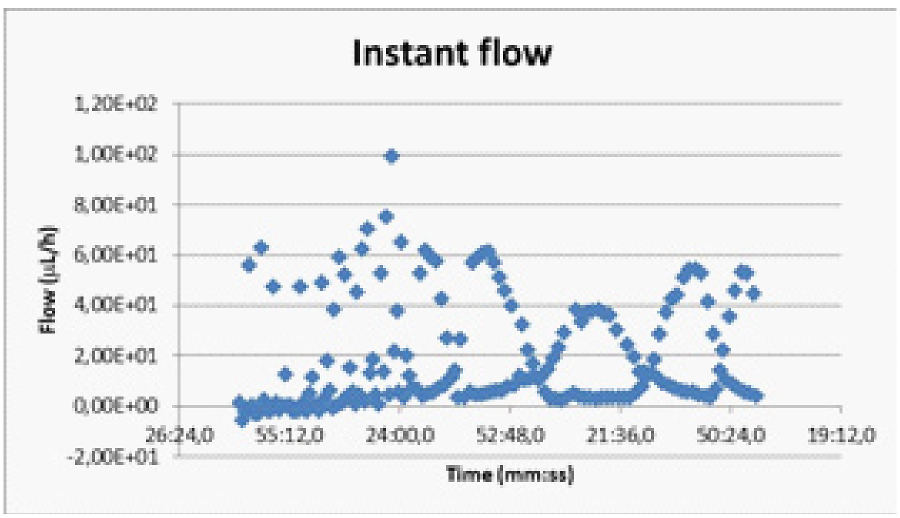

Figure 7: Instant flow in insulin pump calibration.

Optical method results

The experimental conditions and the results obtained using the optical method is summarised in Table 2. ΔT is the difference of time between snapshots, and the evaporation correction described in Figure 5 was applied to the average results.

Test	Time (hh:mm:ss)	Δ*T* (s)	Area (mm²)	Radius (mm)	Volume (µL)	Δ*V* (µL)	Flow (µL/h)
1	16:15:48		5,01	1,262827	843,568		
2	16:15:58	10	5,50	1,323142	970,304	126,73	12,67
3	16:16:06	8	5,54	1,327945	980,908	10,60	1,32
4	16:16:14	8	5,61	1,336308	999,558	18,64	2,33
5	16:16:30	16	5,82	1,361089	1056,205	56,64	3,54
6	16:16:42	12	6,29	1,414980	1186,696	130,49	10,87
7	16:16:54	12	6,30	1,416105	1189,527	2,83	0,23
						Average	5,16
						Corrected value with evaporation	8,68
						U (µL/h)	3,92

Table 2: Calibration of the insulin pump using an optical method.

The uncertainty calculation was determined according to the GUM approach considering equation 2, which describes the volume of a sphere over time variation, ΔT:

$$Q = \frac{4\pi \times r^3}{3\Delta T} \quad (2)$$

Hence, the uncertainty contributions to the model are the radius of the drop (r), which depends on the calibration of the measurement device of the radius, the microscope alignment and the operator effect; the time interval (ΔT); evaporation δQ_{evap} and repeatability δQ_{rep} (Table 3).

Uncertainty components	**Estimation**	$u(x_i)$	c_i	$(c_i \times x_i)^2$
Radius (cm)	$1,35\times10^{-03}$	$3,82\times10^{-06}$	$2,08\times10^{-06}$	$6,30\times10^{-23}$
Time (s)	11	$7,00\times10^{-03}$	$-8,50\times10^{-11}$	$3,54\times10^{-25}$
Evaporation (mL/s)	-0,000977	$8,03\times10^{-10}$	1	$6,44\times10^{-19}$
Repeatability (mL/s)	$5,45\times10^{-07}$	$5,45\times10^{-07}$	1	$2,97\times10^{-13}$
Flow (µL/h)	8,68			
u_{comb} (µL/h)	1,96			
U_{exp} (µL/h)	3,92			

Table 3: Uncertainty contributions in optical insulin pump calibration.

Results confirm that there is significant variability of flow rate with time, which was also observed in the gravimetric test (Figure 7). When both results from the gravimetric method and optical method are compared, it can be seen that they are consistent with each other (Figure 8) since they are within the uncertainty values obtain for each method.

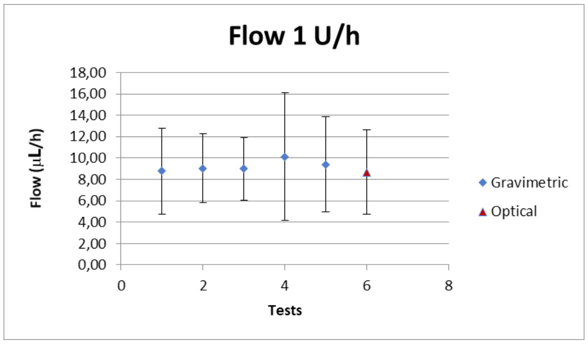

Figure 8: Comparison results between gravimetric and optical methods.

Conclusions

Insulin pumps deliver insulin to a person with diabetes continually simulating the natural internal secretion of insulin from the pancreas. The calibration of the insulin pump pursued during this work showed beyond doubt that the patient would not get a continuous dose of insulin due to the pump flow rate variability, and this can potentiate a severe health problem. At these small flow rates, the infusion is imposed in short positive-displacement pulses, probably via a lead screw connected to a stepper motor, which instead of continuously, operates for only short time intervals.

In addition, the new optical method implemented revealed promising results, if compared with the gravimetric method, at least for the instrument under test. The results of both methods were consistent, and the uncertainties were in the same order, being smaller for the optical method.

Acknowledgement

This work has received funding from the EMPIR programme co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation programme.

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