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Calibration of infusion pumps using liquids whose physical properties differ from those of water

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Abstract. Infusion medical devices are used in field applications, namely in clinical environments, here are used several types of liquids, according to the therapeutic to be administrated into the patient. In order to determine the influence of the fluids physical properties, such as viscosity and density and to produce an adequate reference liquid, tests were performed with a syringe pump, using the gravimetric method as reference calibration method.

1. Introduction

Infusion pumps are measuring instruments that are widely used in clinical environment for nutrition and hydration of patients and for controlled drug delivery. There is a large variability of used liquids in these pumps, namely parenteral nutrition, insulin, cardiogenic amines, analgesics and antibiotics. These liquids have different physical properties that can influence the total delivered volume and the flow rate.

Usually the calibration of flow measuring devices is performed with water as reference liquid [1]. Despite common infusion solutions used in the infusion pumps are low viscous aqueous solutions, some are approximately four times more viscous than water. This fact suggests that the infusion pumps behaviour should be tested with more viscous reference liquids in order to reproduce the real operational conditions.

2. Microflow measurements and calibration of infusion devices

The Volume Laboratory (LVO) of National Metrology Laboratory (LNM) of the Portuguese Institute for Quality (IPQ), in collaboration with FCT/UNL-DEMI, developed a gravimetric system for microflow measurements and calibration of infusion devices [2] in the frame of the European Metrology Research Programme (EMRP), through the participation in the Joint Research Programme - Metrology for Drug Delivery (MeDD) [3].

3. Liquids physical properties

The Laboratory of Properties of Liquids (LPL) of LNM-IPQ, together with LVO, has been performing studies related with the influence of the liquids physical properties in the volumetric instruments accuracy [4]. Therefore, for dynamic measurements of volume, physical properties such as viscosity and density have particular importance in the flow behaviour.



3.1 Density

Density, ρ , is defined as the mass (m) per unit volume (V) of a fluid or a solid [4], and depends on both temperature and pressure. It is a property of extreme importance, applied in the control of industrial processes, biomedical diagnostics, legal control and research. In the LPL, the determination of liquid's density is performed with an oscillation-type density meter DMA 5 000 from Anton Paar, with a best expanded uncertainty of $0,010 \text{ kg/m}^3$ ($k = 2$). An internal procedure based on the ISO 15212-1 [5] is used for these measurements.

3.2 Dynamic viscosity

The dynamic viscosity, η , is a measure of the internal resistance of a fluid to the flow and is obtained from the ratio of the shear force (τ) and the velocity gradient or shear rate ($\dot{\gamma}$) and it is also the product of fluid density by its kinematic viscosity (ν). The measurement of the kinematic viscosity of a liquid through a capillary with a viscometer is based on the measurement of the time that a fixed volume of liquid takes to flow, in laminar flow regime and only, due to gravity, through the capillary at controlled temperature. The kinematic viscosity of the liquid tested is then obtained from the product of the measured flow time and by the constant of the viscometer used [6, 7].

4. Characteristics of the commonly infusion solutions

The common infusion solutions used in hospital are aqueous solutions of glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) with a mass fraction of 5 cg/g and sodium chloride (NaCl) at 0,9 cg/g. When there is an incompatibility with the drugs to be administered or in case of hypertensive patients, sodium chloride at 0,45 cg/g is then used (Table 1).

Table 1. Physical properties of the hospital infusion solutions and water.

	dynamic viscosity @ 20 °C / mPa·s	density @ 20 °C / kg/m ³
Infusion solutions		
$\text{C}_6\text{H}_{12}\text{O}_6$ (5 cg/g)	1,145	1017,5
0,9 cg/g NaCl	1,020	1005,3
0,45 cg/g NaCl	1,011	1001,8
Water	1,002	998,2

The viscosity and the density of these solutions (Table 1) are similar to the ones for water, which is used as reference liquid in the calibration of the syringe pumps. However, there are some commonly infusion solutions, like Hespan® and Dextran 40®, that are four times more viscous than water. This fact suggests that the infusion pumps should be tested with more viscous reference liquids in order to reproduce the real operational conditions.

5. Experimental procedure

5.1 Standard calibration of infusion pumps

The calibration of infusion devices was performed by gravimetric method [1]. A syringe is filled with degas ultra-pure water [8] and a purge is done by passing a sufficient amount of water through the extension line to ensure that there is no bubble in the system. The intended rate flow is programmed in the syringe pump and the water is then collected in a flask inside the evaporation trap in the balance plate (Mettler, AX26). Through the difference between the apparent mass of the liquid displaced into the flask (I_L) and the empty flask (I_E) in the measuring time interval ($t_f - t_i$) the volumetric flow (Q) is then calculated by a LabVIEW® program using Equation 1 [2].

$$Q = \frac{V}{t_f - t_i} \left[\left((m_f - m_i) - (\rho_B V_{\text{imm}}) \right) \times \frac{V}{V_{\text{imm}} - V_{\text{air}}} \times \left(\rho_A - \frac{\rho_B}{\rho_w} \right) \times [T - \rho_B (V_{\text{imm}} - V_{\text{air}})] \right] + \rho_B V_{\text{imm}} \quad (1)$$

Where: ρ_w - water density; ρ_A - air density; ρ_B - mass standard density; γ - expansion coefficient; T_0 - measured water temperature; δV_{evap} – evaporation; δm_{imp} - correction due to tube immersion.

5.2 Calibration of the infusion pumps with viscous liquids

Five aqueous solutions with different viscosities (1,5 mPa·s, 2 mPa·s, 2,5 mPa·s, 5 mPa·s and 10 mPa·s) were prepared gravimetrically using two different compounds - glycerol and glucose. The density of these aqueous solutions was determined as described in 3.1, and the nominal viscosity was established through the measured density according to the literature data [9].

These five solutions, along with pure water, were then tested with a Nexus 3000 pump at three different flow rates of 1 mL/h, 5 mL/h and 10 mL/h. Each test was carried out 3 times and the uncertainty of the average was determined based on the pooled standard deviation and the uncertainty method. The error for each test solution was obtained in relation to the difference from the pure water flow results.

A Perfusor® Space infusion pump was also tested at three different flow rates with water and glycerol solutions with a viscosity of 5 mPa·s and 10 mPa·s.

The calibration results were analyzed according one-way ANOVA (Excel®) assuming a Gaussian distribution for the data.

5.3 Calibration uncertainty budget

The calibration uncertainty budget was established according to GUM methodology [10] and comprises the uncertainty components described in Table 2.

Table 2. Uncertainty components for flow determination by gravimetric method.

Uncertainty source	Standard uncertainty	Evaluation process
final mass	$u(I_L)$	1/2 mse (mean square error)
initial mass	$u(I_E)$	1/2 mse
water density	$u(\rho_w)$	Literature [10]
air density	$u(\rho_A)$	Literature [11]
mass pieces density of the	$u(\rho_B)$	Calibration certificate
temperature	$u(T)$	Calibration certificate
expansion coefficient	$u(\gamma)$	Literature [1]
evaporation	$u(\delta V_{\text{evap}})$	Polynomial adjustment
final time	$u(t_f)$	Estimation (1 μ s)
initial time	$u(t_i)$	Estimation (1 μ s)
buoyancy	$u(m_{\text{imp}})$	Calibration certificate
repeatability	$u(\text{rep})$	Standard deviation of the measurements

6. Results

From the data presented in Table 3 and Figure 1 one can observe that there is no evident trend in the general results either in flow and viscosity range tested. For the glycerol solutions with a higher viscosity an increasing uncertainty was observed and generally at least two times higher than the ones obtained for the glucose solutions.

Table 3. Resume of the calibration results of the Nexus 3 000 infusion pump for the different flows and aqueous solutions tested assuming water as reference.

Nominal Flow / ml.h ⁻¹	η / mPa·s	Sol.	Error / %	U / %	Nominal Flow / ml.h ⁻¹	η / mPa·s	Sol.	Error / %	U / %	Nominal Flow / ml.h ⁻¹	η / mPa·s	Sol.	Error / %	U / %
1	1,5	Gly	-1,3	1,7	5	1,5	Gly	-0,1	1,1	10	1,5	Gly	-0,08	0,84
		Glu	0,1	1,3			Glu	0,06	0,97			Glu	0,0	1,4
	2	Gly	-0,6	2,1		2	Gly	0,5	1,2		2	Gly	0,44	0,82
		Glu	-0,6	1,4			Glu	0,13	0,91			Glu	0,1	1,1
	2,5	Gly	-0,7	4,4		2,5	Gly	0,2	1,2		2,5	Gly	-0,1	1,0
		Glu	-0,1	1,4			Glu	0,27	0,91			Glu	0,1	1,4
	5	Gly	-3,2	4,4		5	Gly	0,1	1,3		5	Gly	0,4	1,3
		Glu	-0,5	1,5			Glu	0,23	1,1			Glu	0,3	1,2
	10	Gly	-2,6	9,1		10	Gly	0,1	2,4		10	Gly	-0,5	2,2
		Glu	-0,2	1,3			Glu	0,0	1,1			Glu	0,1	1,3

Legend: Flow – nominal flow tested; Sol. – Solutions; Gly – Glycerol; Glu – Glucose; η - Nominal dynamic viscosity @ 20 °C; Error – Relative difference between tested solution and water; U – Relative expanded uncertainty of the measured flow.

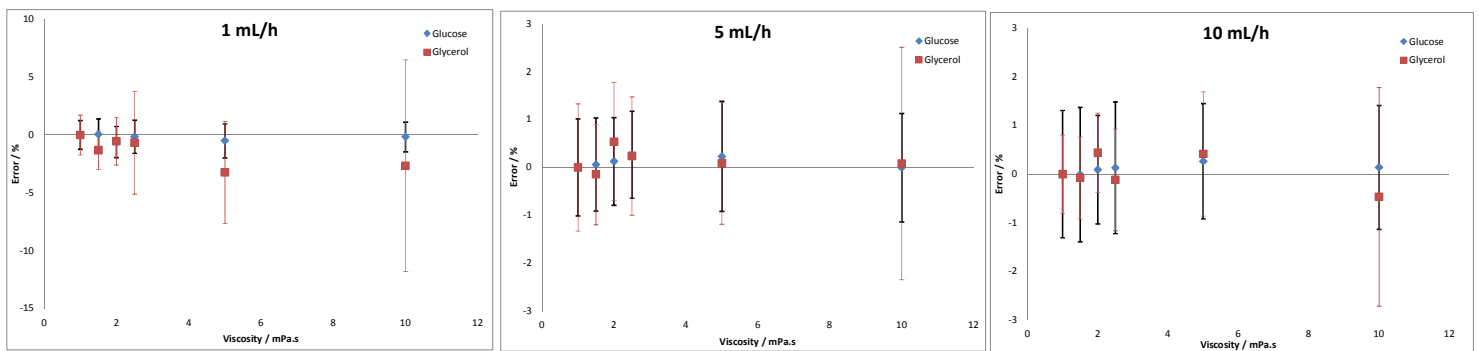


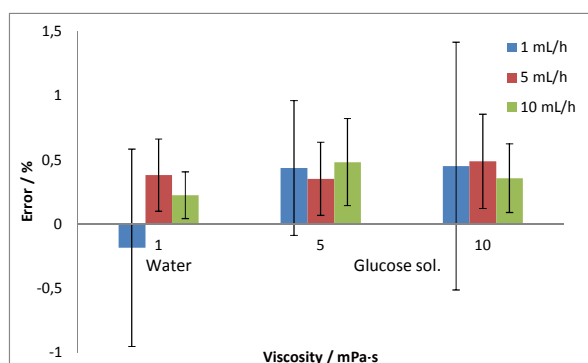
Figure 1. Flow measuring error from water results of the Nexus 3 000 infusion pump for the different flows and for the aqueous solutions tested. (the vertical bars represent measurement uncertainty)

The results of the one-way ANOVA for the effect of the flow and viscosity on flow error of the Nexus 3 000 infusion pump (Table 3) shows that the viscosity of the samples tested (from 1,5 mPa·s to 10 mPa·s) has no effect neither on the error of the resulting flow (p -value > 0,05 %). For the flow, the null hypothesis is reject for a significance level of 0,05 %, therefore we can concluded that the flow produces a significant effect on the error of the calibration results.

Table 3. Resume of the one-way ANOVA results for the effect of the flow and the viscosity on the flow error of the Nexus 3 000 infusion pump.

Liquids / Effect	<i>p</i> -value ($\alpha = 0,05 \%$)
Water	
Flow effect	0,03
Glycerol	
Flow effect	0,00
Viscosity effect	0,74
Glucose	
Flow effect	0,00
Viscosity effect	0,92

The flow measuring errors from the nominal flow and measuring uncertainty of the Perfusor® Space infusion pump for the different flows and viscosities also shown no evident trend in both (Figure 2).

**Figure 2.** Flow measuring error from the nominal flow of the Perfusor® Space infusion pump for the different flows and for the aqueous solutions tested (the vertical bars represent measurement uncertainty).

The results of the one-way ANOVA for the effect of the flow and the viscosity on the flow error of the Perfusor® Space infusion pump (Table 4) shows again that the viscosity of the samples tested has no effect on the error of the resulting flow (p -value $> 0,05 \%$).

Table 4. Resume of the one-way ANOVA results for the effect of the flow and the viscosity on the flow error of the Perfusor® Space infusion pump.

Effects	<i>p</i> -value ($\alpha = 0,05 \%$)
Flow	0,65
Viscosity	0,15

7. Conclusions

Based on the results obtained during the calibration of the two syringe pumps tested it can be verified that there are no significant differences between the measured flow for the different liquids tested and no influence of the viscosity in the final flow, within the interval of 1 mPa·s to 10 mPa·s.

The increasing uncertainty observed for the glycerol solutions with the increasing viscosity in the Nexus 3 000 infusion pump can be related with the low vapour pressure of glycerol (0,001 hPa at 20 °C [10]) compared with water (2 300 hPa at 20 °C [10]). This fact should lead to a higher evaporation rate in the more viscous glycerol solutions. It can also be concluded that glucose solutions

seems more suitable for these kinds of tests leading to a better repeatability and therefore a lower measuring uncertainty.

The statistical analysis of the flow measuring error by means of ANOVA has shown that the viscosity of the samples tested (from 1,5 mPa·s to 10 mPa·s) has no effect on the error of the resulting flow for both pumps. On the other hand the flow produces a significant effect on the error of the calibration results as confirmed by the one obtained for water for the Nexus 3 000 infusion pump. For the Perfusor® Space infusion pump no significant effect was observed on the flow errors obtained with the tested liquids. We can assume that these different results in the flow effect must be related with different mechanical behaviors of these infusion pumps.

This work leads to the conclusion that water is suitable reference calibration liquid in the case of this equipment within the flow range of 1 mL/h to 10 mL/h. We can also assume that different types of viscous liquids used in hospital environment have no significant influence in the final delivered flow.

8. References

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