The role of adequate reference materials in density measurements in hemodialysis

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Abstract. In hemodialysis, oscillation-type density meters are used to measure the density of the acid component of the dialysate solutions used in the treatment of kidney patients. An incorrect density determination of this solution used in hemodialysis treatments can cause several and adverse events to patients. Therefore, despite the Fresenius Medical Care (FME) tight control of the density meters calibration results, this study shows the benefits of mimic the matrix usually measured to produce suitable reference materials for the density meter calibrations.

1. Introduction

Hemodialysis is a renal function replacement therapy. During hemodialysis, the patient’s blood is passed through a filter outside the body and then reintroduced to the patient. Tiny pores in the filter membrane filter out toxins, while vital components, such as proteins, are left in the blood. Excess water can also be removed through these tiny pores. The process is controlled by a dialysis machine that is equipped with a blood pump and monitoring systems that ensure safety. The machine can also administer drugs, e.g. Heparin, to prohibit blood clotting during the treatment [1].

1.1. The role of density measurements in hemodialysis

Dialysate consists of purified water and various substances dissolved in it. With the exception of glucose, the substances dissolved in the dialysate are all electrolytes. Their concentration (besides potassium and the buffer substance) closely resembles the concentration of the electrolytes occurring naturally in the blood. Dialysate regulates the electrolyte and acid-base balance of the dialysis patient and removes waste products. Dialysate is produced by the hemodialysis machine combining purified water, acid concentrated solution and bicarbonate concentrated solution. Acid concentrated solution can be obtained in each Hemodialysis Center through a first dilution certified process using certified mixtures of needed electrolytes in ultra-pure water. The final product, i.e. the dialysate, must be validated by a calibrated portable oscillation-type density meter. A wrong dilution means a product that is not conform to be used in patient treatments. If the oscillation-type density meters are not properly calibrated, then a wrong mixture of electrolytes will be used for patients’ treatments causing several and adverse events to them. A second dilution of these concentrated electrolytes will take place in the dialysis machine. Normally ratios 1:35 or 1:45 are used [2]. To be sure that the final dialysate is adequate for the treatment based on the medical prescription, the maximum permissible error given by the calibration certificate of the density meter, on the first dilution process, is set to 0,001 g/cm³.
1.2. Oscillation-type density meters

The working principle of an oscillation-type density meter is based on the law of harmonic oscillation, in which a U-shaped tube, i.e. the measuring cell, is completely filled with the sample to be analysed, and subjected to an electromagnetic force. The measurement of the frequency and duration of vibration of the tube filled with the sample allows the determination of the density value of the sample. This measuring principle is based on the Mass-Spring Model [3].

Like all measuring instruments, the results obtained by an oscillation-type density meter may vary in time. Errors may be due to: instrumental changes due to physical changes in the U-tube (mass, volume or elasticity coefficient); changes in the electronic operation of the instrument; damage due to mishandling; instrument movement during measurement, especially if at a different angle to the horizontal; effects of liquid on the surface of the tube, such as deposition of material, or erosion by the sample or by the cleaning method. Therefore the calibration is an essential key to understand and take into account the measuring behaviour of the measuring instruments.

1.3. The National Metrology Institute and the calibration of the FME density meters

Density, \( \rho \), is defined as the mass per unit volume of a fluid or a solid [4], and depends, in general, on both temperature and pressure. It is a property of extreme importance, as it is routinely applied in the control of industrial processes, but also used in fields such as biomedical diagnostics, fiscal control and basic research. The uncertainty requirement in a density measurement depends on its specific application and can vary from better than 0.1 % to 1 % [5].

Calibration is an operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication [6]. Reference materials are often used in calibration operation as measurand generator. According to ISO Guide 34 [7], a reference material can be described by a material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process.

In the Laboratory of Properties of Liquids (LPL) of the National Metrology Laboratory of Portuguese Institute for Quality (IPQ), density determination of liquid samples can be performed with an oscillation-type density meter DMA 5 000 (Anton Paar). An internal procedure based on the ISO 15212-1 [8] is used for these measurements. The uncertainty budget according to GUM methodology [9], previously established [10], comprises four major uncertainty components: the uncertainty associated with the measurements repeatability, the uncertainty due to the density meters resolution, the uncertainty related to the standard density meter calibration, which depends on the uncertainty of the Certified Reference Materials used, and the uncertainty of the temperature and pressure measurement of the sample inside the measuring cell. The calibration of portables oscillation-type density meters in IPQ is performed by comparative method using reference materials that are measurand generators (Figure 1). These reference materials are characterized with IPQ standard density meter (DMA 5 000, Anton Paar). The density and temperature measurement results of IPQ’s standard density meter are traceable to SI units by means of calibration with certified reference materials. The reference solutions are then used in the Fresenius Medical Care (FME) density meters and its indication are compared with the reference values. The measurement error results from the difference between the measured quantity value, i.e. the density value indicated in the FME density meter for a reference solution, and the reference, i.e. the density of the reference solutions determined in IPQ standard density meter. The measurement uncertainty is the non-negative parameter.
characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used [10]. FME acceptance criterion is given by the modulus of the sum of the measurement error with the expanded measurement uncertainty obtained in the calibration. For a calibration to be acceptable for FME, this sum should be lower or equal to 0.001 g/cm$^3$.

![Schematic representation of FME oscillation-type density meters calibration by comparative method in IPQ.](image)

**Figure 1.** Schematic representation of FME oscillation-type density meters calibration by comparative method in IPQ.

### 1.4. Calibration of FME oscillation-type density meters by IPQ

Since 2006, IPQ has been performing the calibration of the FME density meters at 20 ºC, for two different densities (1.141 g/cm$^3$ and 1.163 g/cm$^3$). Earlier IPQ used standard solutions of sucrose, similar to those used in the Metrological Control of refractometers (OIML R124: 1997), whose stability and homogeneity had been evidenced. But, in 2011, due to the high calibration rejection rate of the density meters, IPQ along with FME began trying to unravel what was the origin of these high failure rates. Then, FME provided to IPQ a sample of acid concentrated solution for further tests.

### 2. Experimental procedure

#### 2.1. Characterization of acid concentrated solution solution

According to the label the major components of the acid concentrated solution were sodium chloride (~78 % of the solid residue) and anhydrous glucose (~13 %). The coefficient of thermal expansion within the [10, 30] C temperature interval was determined in order to be compared with the temperature correction used by FME.

#### 2.2. Development of new reference material

As the major components of the acid concentrated solution were sodium chloride, two new aqueous solutions of sodium chloride were prepared (mass fraction of 19.2 cg/g and 21.9 cg/g) in order to produce the two points of density desired by FME (1.141 g/cm$^3$ and 1.163 g/cm$^3$, respectively).
2.3. Oscillation-type density meters calibration by comparative method in IPQ

The FME density meters were tested with the old reference material (sucrose aqueous solutions with 33.5 cg/g and 38 cg/g), with the new reference materials (sodium chloride aqueous solutions with 19.2 cg/g and 21.9 cg/g) and with the acid concentrated solution.

3. Results

The coefficient of thermal expansion of the acid concentrated solution used by FME ((0.50 ± 0.10) kg m$^{-3}$ K$^{-1}$) was confirmed by IPQ ((0.48 ± 0.06) kg m$^{-3}$ K$^{-1}$). The results obtained in the tests with the different solutions showed the similarity of the measuring error obtained with the acid concentrated solution together with the sodium chloride aqueous solutions. Indeed the errors displayed using the previous reference solutions are one order of magnitude lower than the one using the acid concentrated solution or the new reference materials (Table 1). The viscosity ($\eta$) of the two kinds of reference solutions shown to be different (Table 1), and this fact could cause errors due the oscillation damping of measuring cell that occurs for viscosities higher than 2 mPa·s. This type of error in the portable density meters cannot be quantified.

| Solution tested                        | Calibration results / kg/m$^3$ |
|----------------------------------------|-------------------------------|
|                                        | $\rho$ / kg/m$^3$ | $X$ / cg/g | $\eta$ / mPa·s | Error | $U (k=2,00)$ |
| sucrose aqueous solutions               | 1141              | 33.5       | 3.89            | -0.4  | 0.2         |
|                                        | 1163              | 38.0       | 5.89            | -0.6  | 0.2         |
| sodium chloride aqueous solutions      | 1141              | 19.2       | 1.52            | -2.2  | 0.2         |
|                                        | 1163              | 21.9       | 1.67            | -2.4  | 0.2         |
| acid concentrated solution             | 1159              | -          | -               | -2.5  | 0.2         |

Table 1. Calibration results of FME density meters.

With the use of the sodium chloride aqueous solutions as reference material for the calibration of the FME density meters, the calibration rejection rate was reduced from 23 % to 4 %.

4. Conclusions

The present study allowed us to demonstrate the correct adaptation of the reference material used in calibration methods in order to reproduce the real operational conditions of the measuring instrument. It was showed that is not enough to guarantee the basic requirements of the reference material, such as homogeneity and stability and specified property [7] (in this case the required density) to obtain acceptable calibration results, as it is also necessary to know the characteristics, such as composition and viscosity of the liquids with which the density meters are intended to be calibrated.

For FME Portugal, the adaptation of the reference material used in the calibration of their density meters allowed an increasing of the stability of the dilution and treatment support process. An important reduction on cost was verified on transport, re-calibration and repairing. The total number of needed density meters was reduced and consequently IPQ response time was shorter. All these performance enabled a more stable global process.
5. References

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