Low flow measurement for infusion pumps: implementation and uncertainty determination of the normalized method

J Cebeiro, A Musacchio, and E Fernández Sardá

Departamento de Tecnología Médica, Hospital de Pediatria Prof. Dr. Juan P. Garrahan. Combate de los Pozos 1881, Buenos Aires, Argentina.

E-mail: jcebeiro@garrahan.gov.ar

Abstract. Intravenous drug delivery is a standard practice in hospitalized patients. As the blood concentration reached depends directly on infusion rate, it is important to use safe devices that guarantee output accuracy. In pediatric intensive care units, low infusion rates (i.e. lower than 10.0 ml/h) are frequently used. Thus, it would be necessary to use control programs to search for deviations at this flow range. We describe the implementation of a gravimetric method to test infusion pumps in low flow delivery. The procedure recommended by the ISO/IEC 60601-2-24 standard was used being a reasonable option among the methods frequently used in hospitals, such as infusion pumps analyzers and volumetric cylinders. The main uncertainty sources affecting this method are revised and a numeric and graphic uncertainty analysis is presented in order to show its dependence on flow. Additionally, the obtained uncertainties are compared to those presented by an automatic flow analyzer. Finally, the results of a series of tests performed on a syringe infusion pump operating at low rates are shown.

1. Introduction

Continuous drug therapy is generally administered via the intravenous pathway with a delivery system regulating drug concentration in blood in order to achieve and maintain a desired result. In order to achieve the adequate therapeutic dose, the device is set at a specific flow rate. Although underinfusion may not provide sufficient therapy, overinfusion can produce serious toxic side effects. The therapeutic range and risks associated with under- and overinfusion are highly drug and patient dependent [1]. In pediatric patients, low infusion rates, often less than 10 ml/h, are used. This fact significantly reduces the admissible range of flow deviations of the device that should reach the highest required performance standards for neonatal care.

Several reports on the failure of infusion pumps have been published [2], [3] and the FDA (Food and Drug Administration) has initiated recalls of different infusion devices [3]. In order to prevent accidents or failure to accomplish clinical expectancies, periodic trials have been proposed. As it stands for other medical devices, it is necessary to include infusion pumps in a scheduled testing program aimed at risk reduction [4], [5]. Procedures, guidelines, and recommendations written by manufacturers and medical technology agencies exist to investigate if factory specifications are achieved over the whole useful life of the device. The Biomedical Benchmark™© published by ECRI (Emergency Care Research Institute) introduces testing techniques and establishes intervals for
assessing flow accuracy [6]. In this study, we have followed the method specified in the IEC/ISO60601-2-24 standard: Particular requirements for the safety of infusion pumps and controllers [7]. It provides a detailed description of the gravimetric procedure, including instrument set up, equations for performance parameters calculation, and graphical representation. An in-depth analysis of some interesting aspects of the implementation, such as weight loss due to evaporation, stability settings, temperature drift, environmental vibration, balance level, time capture, and load symmetry can be found in the study performed by Clarkson [8]. Although this study states that balance resolution is the dominant error (i.e. uncertainty) source in testing infusion devices using the gravimetric method, there are other components, such as balance linearity and repeatability [9], that can increase the final uncertainty of the method. Furthermore, these uncertainties can individually exhibit higher values than the resolution and be different among balances with the same resolution but from different manufacturers. Definition of the weighing uncertainty is the basis for the final method uncertainty calculation necessary for method selection and a mandatory requirement of the ISO 17025 standard for testing and calibration laboratories [10], [11].

Different techniques exist for flow measurement: gravimetric [6], [7], [8], [12], volumetric [6], and automatic [13], [15]. The automatic methods rely on optical-volumetric analyzers that simply require connecting the infusion line to an inlet port and show flow and volume readings on their screens [13], [14]. Some of them can simultaneously test several infusion devices and transmit samples to the PC via an RS-232 interface, thus allowing digital storage and further numeric analysis [15].

The present study describes the implementation of a normalized method for infusion-pump-accuracy determination for low flow delivery (1.0-25.0 ml/h). Uncertainty sources are revised together with a numeric and graphic analysis performed in order to show its dependence on flow rate. Additionally, the obtained uncertainties are compared to those presented by an automatic flow analyzer. Finally, as an example, the results of a series of tests performed on a syringe infusion pump operating at low rates are shown.

In the present study we use the concept of uncertainty as defined by the GUM (Guide to expression of uncertainty in measurement) [16], [17] whereas the word error may either refer to the numerical parameters indicated in section 2.1 (equation 3 and 4) or to a spurious distortion on a measurement process. The uncertainty specification in weighing for balances is referred to as precision.

2. Materials and methods

2.1. Method description

The procedure indicated for syringe infusion pumps in the ISO/IEC 60601-2-24 standard was used [7]. However, the analysis discussed here is also valid for other types, such as rotary peristaltic, linear peristaltic, and cassette infusion pumps. Being a gravimetric method, it consists of the recording of the weight contained by a collector recipient placed on a precision balance which receives the flow delivered by the infusion pump being tested. Sample values are transmitted to a PC at a fixed time interval. The assay lasts two hours and is conducted for a fixed flow set in the infusion pump. While the first-hour samples are rejected, the second-hour samples are used to calculate different parameters of interest, such as mean and errors. The weight difference between consecutive samples is converted to flow \( F_i \) through the density value and time interval according to equation (1).

\[
F_i = \frac{60(w_i - w_{i-1})}{sd}
\]  

Where \( F_i \) is flow expressed in ml/h units, \( d \) is the infused liquid density, \( S \) is the time interval in minutes, and \( w_i - w_{i-1} \) is the weight difference between consecutive samples separated by time interval \( S \).

Figure 1 shows the assay scheme for the syringe infusion pump: flow coming from the pump arrives in the collector recipient on the balance through the plastic tube – infusion line – connected to the syringe and the needle. The pump and the liquid must have the same level to prevent pressure
differences that hinder or facilitate flow because of hydrostatic factors. The needle size should be 18G (gauge) in order to generate standard pressure drops depending on diameter, flow, and liquid viscosity. For example, an 18G, 6-9 cm catheter generates a mean pressure drop of 14.1–17.9 mmHg h l\(^{-1}\) for flows in the 100-300 ml/h range. For low infusion rates, drop formation in the needle may cause a stepwise increment (steps of approximately 0.05 ml). In order to avoid this increase, the tip of the needle should be immersed in the liquid, allowing it to flow in a continuous fashion.

![Image](image.jpg)

**Figure 1:** The ISO 60601-2-24 procedure setup.

A Pioneer 214 analytical balance (Ohaus, USA) with a full capacity of 210 g was used. Table 1 shows its specifications according to the manufacturer’s certification. Distilled water was used as infusion liquid (Braun, Argentina) with a density of 0.998 g ml\(^{-1}\) (+0.001 g ml\(^{-1}\)) at 20° C. Weight samples were collected in a notebook at 30-second intervals [7] via an RS-232 serial port protocol using a graphical user interface developed with Borland Builder® C++. Data transferred to the PC were stored in text files and later imported into the Matlab® numerical computing environment to develop numeric and graphic analyses including error calculation in several observation windows.

| Variable        | u\(_c\) | Units  |
|-----------------|--------|--------|
| Resolution      | 0.1    | mg     |
| Linearity       | 0.3    | mg     |
| Repeatability   | 0.05   | mg     |
| Interval (S)    | 130    | msec   |
| Density (d)     | 0.001  | g ml\(^{-1}\) |

Interval time uncertainty was not specified in the balance data sheet; therefore, it was assessed by measuring the time between consecutive samples received by the software. The histogram of these time intervals over a 2-hour acquisition showed a maximum deviation of 130 ms. Additionally, this software-assessed uncertainty was instrumentally confirmed by measuring the time interval between consecutive data sets sent by the balance through the DB9 Tx pin using a digital oscilloscope TD2 2012B (Tektronix, USA). The high sensitivity of precision balances may produce distortions caused by tension and movement of the components shown in figure 1. Hoses made of soft and elastic materials, such as PVC, are often subject to movements and exert forces when under pressure. In order to provide physical isolation we
used a cylindrical (diameter 9 cm, height 12 cm, volume ~800 cm$^3$) acrylic mechanical isolation chamber covering the central volume of the balance case, including the weighing pan (figure 1). Every mechanical effort is supported by the chamber and discharged over the balance floor, thus reducing the weighing deviation. The present study has been developed under ISO/IEC 60601 atmospheric conditions (table 2).

**Table 2. Environmental conditions.**

| Variable               | Value      | Unit       |
|------------------------|------------|------------|
| Atmospheric pressure   | 1013±10    | hPa        |
| Temperature            | 22.0 ± 2.0 | °C         |
| Relative humidity      | 60 ± 10    | %          |

In high precision weighing it may be necessary to consider the force exerted by air buoyancy, even though in our working conditions and balance precision the effect was less than 0.1 %.

2.2. Evaporation

A recipient containing water on the weighing pan has a weight loss due to water evaporation. The effect depends on the size of the exchange area between water and air and relative humidity of the peripheral atmosphere. The magnitude of this exchange is represented by the evaporation rate; it is expressed in units of µl/min. In order to quantify this magnitude, we conducted preliminary trials with different recipients and conditions. A total number of six combinations were studied (table 3). Trials consisted of the recording of weight samples of a recipient containing distilled water at two samples per second during two hours, the ISO/IEC standard assay time for testing flow accuracy [7]. The duration selected allows an accurate estimate of the water loss during the entire period of the assay. The aim was to investigate how the results may be influenced by recipient shape and relative humidity. Ideally, evaporation rates should be independent of environmental conditions; therefore, we used an engine oil film covering the recipient area in order to avoid water evaporation [8]. An additional trial in a saturated atmosphere was performed using a wet cloth inside the chamber (described in 2.1) in order to evaluate the behaviour in a saturated atmosphere (a relative humidity of 100%).

**Table 3. Evaporation assays**

| Recipient             | Volume (cm$^3$) | Exchange area (cm$^2$) | Mechanical Isolation Chamber | Humidity at onset |
|-----------------------|-----------------|------------------------|-------------------------------|-------------------|
| Beaker                | 100             | 15.2                   | No                            | Ambient           |
| Beaker                | 100             | 15.2                   | Yes                           | Ambient           |
| Beaker                | 100             | 15.2                   | Yes                           | 100%              |
| Beaker                | 250             | 34.2                   | No                            | Ambient           |
| Graduated cylinder    | 25              | 5.0                    | No                            | Ambient           |
| Beaker + Oil film     | 100             | 0                      | Yes                           | Ambient           |
2.3. Uncertainty estimation

Section 2.1 describes an indirect method where weight is measured to subsequently calculate flow through equation (1). The GUM of the BIMP (Bureau International des Poids et Mesures) states that combined standard uncertainty for indirect measures is calculated as follows [16]:

\[ u_c(F) = \left( \sum_{k=1}^{N} \left( \frac{\partial F}{\partial x_k} \right)^2 u^2(x_k) \right)^{\frac{1}{2}} \]  

(2)

Where \( F \) is the indirectly measured flow, \( u_c(F) \) is the combined standard uncertainty of the indirect measurement, \( x_k \) represents every single variable in equation (1), \( u(x_k) \) is the corresponding standard uncertainty to every single variable, and \( \frac{\partial F}{\partial x_k} \) is the partial derivate of equation (1) with respect to each given variable \( x_k \). The value \( N \) is the number of variables combined to calculate the flow. The following four direct measure values are involved: density, time, and two weights. The weighing standard uncertainty may be considered twice in equation (2), so a value of \( N=4 \) was used. Individual standard uncertainties were calculated according to the data in table 1. Standard weight uncertainty is the result of the quadratic addition of the three uncertainties: resolution, linearity, and repeatability adjusted according to the type of distribution and coverage factors [16]. For time uncertainty calculation, a square distribution function with a half-width of 130 msec was assumed. For density uncertainty calculation a square distribution was also used.

2.4. Trumpet curves

Performance parameters were calculated for several observation windows according to:

\[ E_p(\text{max}) = \max_{j} \left[ \frac{S}{p} \sum_{i=j}^{p} \frac{F_i-r}{r} \right]^{100} \]  

(3)

\[ E_p(\text{min}) = \min_{j} \left[ \frac{S}{p} \sum_{i=j}^{p} \frac{F_i-r}{r} \right]^{100} \]  

(4)

where \( F_i \) is the flow calculated according to equation (1), \( P \) the observation window size in minutes, \( r \) the set flow rate on the infusion pump, \( S \) the sampling period, and \( m \) the maximum number of observation windows for this window size \( P \) [7].

These errors represent the maximum and minimum of the mean flow error for a given observation window, usually between 2 and 31 minutes. These values are helpful for the assessment of pump performance and may be the basis to determine if an infusion pump is indicated for an intended use according to the infused drug half life.

3. Results

3.1. Evaporation assay

Figure 3 shows the weight loss for the different recipients and environmental conditions listed in table 3. Evaporation rates are indicated in table 4 for each combination together with a linearity estimator: the correlation coefficient. Additionally, the percentage represented by the evaporation rate with respect to three infusion rates is shown in order to illustrate how the result is influenced by this effect.
3.2. Uncertainty

Figure 4 plots the combined standard uncertainty (calculated according to equation 2) together with the individual contribution of each component as a function of flow for a range between 0.1 and 25.0 ml/h. Figure 5 plots the percentages represented by these magnitudes as a function of the measured flow. Table 5 shows the percentage uncertainty for particular flow rates covering the mentioned range for the studied method and the widely-used IDA4-Plus Flow Analyzer. Additionally, the table shows the time required by the IDA4 to reach the volume necessary in order to achieve the uncertainty specified by the manufacturer at the corresponding flow rate [14].

Table 4. Evaporation loss for different containers. The percentage of error shows the portion that evaporation loss represents for different flow rates.

| Recipient                  | Capacity (ml) | Evaporation rate (µl/min) | Flow rate (ml/h) | Percentage of error (%) |
|----------------------------|---------------|---------------------------|------------------|-------------------------|
|                            |               |                          | 0.50             | 1.0                     | 10.0                    |
| Beaker                     | 100           | 0.77                      | 9.3              | 4.6                     | 0.5                     |
| Beaker                     | 100           | 0.48                      | 5.8              | 2.9                     | 0.3                     |
| Beaker                     | 250           | 1.21                      | 14.5             | 7.2                     | 0.7                     |
| Beaker + oil film          | 100           | <8.3 \times 10^{-4}      | <0.1             | <0.05                   | <0.005                  |
| Graduated cylinder         | 25            | 0.06                      | 0.7              | 0.4                     | 0.04                    |

*With mechanical isolation chamber, the others without.
Figure 4: Individual source contributions (time, weight, and density) and combined standard uncertainty.

Figure 5: Percentage individual source contributions (time, weight, and density) and percentage combined standard uncertainty.

Table 5. Percentage uncertainties at different flow rates calculated for the studied method (uc) and the IDA4 flow analyzer (uc IDA4). Time values expressed in hours represent the measuring time needed by the IDA4 to reach the specified uncertainties.

| Flow (ml/h) | uc (%) | uc IDA4 (%) | IDA4 time (h) |
|------------|--------|-------------|---------------|
| 0.5        | 7      | 4           | 20.0          |
| 1.0        | 3      | 3           | 10.0          |
| 1.5        | 2      | 3           | 6.7           |
| 2.0        | 2      | 2           | 5.0           |
| 5.0        | 1      | 2           | 2.0           |
| 10.0       | 1      | 2           | 1.0           |
| 25.0       | 1      | 1           | 0.8           |
3.3. Performance assays

In order to show the results presented by the method, a series of trials was conducted. An Activa22 syringe infusion pump (Adox, Argentina) was tested with set infusion rates of 2.0, 5.0, 10.0, and 20.0 ml/h. More than 8 hours of data were recorded. Figure 6 plots trumpet curves for Activa22 at different rates. Collected data were used for error calculation for different observation windows according to equations (3) and (4). Trumpet curves are shown for observation windows in the range of 2 to 31 minutes together with the mean flow.

![Trumpet curves for set infusion rates of 2.0, 5.0, 10.0, and 20.0 ml/h](image)

**Figure 6:** Trumpet curves for set infusion rates of 2.0, 5.0, 10.0, and 20.0 ml/h

4. Discussion

Evaporation test results present an increased water-loss rate in recipients with wider transversal sections (tables 3 and 4, figure 3). Peripheral atmosphere saturation produces erratic behaviour with moisture condensation over the beaker walls increasing weight at the first hour but exhibiting a low decrease towards the second. For the other cases, water evaporation takes place with constant rates strongly related to the area of liquid in contact with ambient air. For some rates, the percentage represented by evaporation is significant, consisting of an important portion of overall flow (up to 7%...
for flows of 1.0 ml/h or smaller); therefore, water loss cannot be neglected. Correlation coefficients presented indicate a linear dependence between time and volume, supporting the idea of a constant evaporation rate for the whole period of two hours. The introduction of a mechanical isolation chamber only partially reduces water loss by evaporation, which still remains significant and above some currently sold infusion pump specifications. The addition of a thin (2-3 mm) engine oil film over water surface reduced the evaporation making it undetectable (<0.1 mg in 2 hours), and the evaporation curve remained zero.

Uncertainty of the normalized method proved to be lower than 1% for flows of 5.0 ml/h and higher, decreasing as flow increased. For flows of 1.0 ml/h uncertainty was 3% (table 5). The differences in balance resolution, time interval, and period of assay make it difficult to compare our results with those obtained by Ilfeld et al. [12].

The method performance is comparable to, or even better than some commercially-available infusion pump analyzers [13], [14]. At low flow rates, the normalized method presents the advantage of requiring less trial times as shown in table 5. While a 10-hour test is needed to reach a specification of 3% with a flow of 1.0 ml/h [14] using an IDA4 Plus flow analyzer, two samples are enough for the normalized method to obtain similar or better performance. Moreover, although the ISO/IEC standard recommends a two-hour test, for low flow measurement this time continues to be shorter than some IDA4 times. In any case, times longer than 31 minutes will be required by IDA4 to obtain trumpets curves for the longest window. This analyzer presents other kinds of advantages, such as demanding less work from the department staff, and some models allow testing of four infusion pumps simultaneously.

The sampling time used (30 sec) is that indicated by the standard. It can be increased to 2 minutes in order to reduce relative uncertainty without affecting the trumpet curves, even though some distortion may appear in flow-time curves due to aliasing effects.

The uncertainty analysis performed is also valid for higher flows, although in this case some previous considerations become less important, such as evaporation and balance precision. Some others, such as balance capacity, appear as limiting parameters.

Performance assays show a classic syringe pump result with smaller differences between $E_P(max)$ and $E_P(min)$ towards longer observation windows and higher flows: as flow rate increases error reduces and $E_P(max)$ and $E_P(min)$ tend to each other in the classic trumpet shape (figure 6).

5. Conclusion

A normalized method based on the ISO/IEC 60601-2-24 standard was used. Flow measurement is affected by several factors, such as air currents, movements, and evaporation.

Covering water with an engine oil film allowed to make the assay independent of environmental conditions, reducing evaporation rate until making it undetectable.

Method uncertainty turned out to be equivalent to other alternatives presenting an important additional advantage: considerable shorter testing times for low infusion rate analysis. Another interesting feature of the normalized method is cost. Even when using two balances of different capacities and precision to cover the full range of currently-available infusion pumps (0.5-1500 ml/h) it is still significantly less expensive than a flow analyzer. Calibration services for analytical balances are available everywhere and cheaper than those for infusion pump analyzers.

The normalized method proved to be an interesting alternative for testing accuracy in infusion pumps used for low flow delivery in hospital intensive care units, anesthesiology, and on wards.

For lower flows, such as those delivered by implantable infusion pumps, even more precise balances should be used (0.01 mg). Such balances are more sensitive to environmental-mechanic perturbations than the one used for this study. These flow rates cannot be measured by IDA4 according to specifications [13].

For higher infusion rates it is necessary to use higher-capacity balances, but less precision is required. In these cases, the uncertainty analysis presented in section 2.3 and 3.2 may be applied.
6. Future studies

The next step is investigating the method repeatability by performing series of trials and comparing trumpet curves obtained in several measurements under the same conditions. In order to contrast the performance of the method against flow analyzers, an experimental study including statistical tests and comparison among trumpet curves should be performed.

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