Elsa Batista*, Nelson Almeida, Andreia Furtado, Eduarda Filipe, Luis Sousa, Rui Martins, Peter Lucas, Harm Tido Petter, Roland Snijder and Annemoon Timmerman

Assessment of drug delivery devices

Abstract: For critical drug delivery, it is important to have a constant and well-known infusion rate delivered by the complete infusion set-up (pump, tubing, and accessories). Therefore, various drug delivery devices and accessories were tested in this article in terms of their infusion accuracy, start-up delay, response time, and dependency on the viscosity. These measurements were performed as part of the European funded research project MeDD. The obtained results show that the infusion accuracy of the devices is flow rate and accessory depended, especially for low flow rates. Viscosity does not have a significant impact on the flow rate accuracy.

Keywords: compliance; drug delivery; infusion; metrology; pump; standards.

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Abbreviations

EMRP, European Metrology Research Programme; EURAMET, European Association of National Metrology Institutes; GUM, Guide to the Expression of Uncertainty in Measurement; IPQ, Portuguese Institute for Quality; ISO, International Standard Organization; MeDD, Metrology for Drug Delivery; SUD, start-up delay; VSL, Dutch Metrology Institute.

***Corresponding author: Elsa Batista,** Metrology Department, IPQ, Portuguese Institute for Quality, Rua António Gião 2, Caparica 2829-513, Portugal, Phone: +351212948167, Fax: +351213948188, E-mail: ebatista@ipq.pt.
Nelson Almeida, Andreia Furtado and Eduarda Filipe: Metrology Department, IPQ, Portuguese Institute for Quality, Rua Antonio Gião 2,Caparica 2829-513, Portugal
Luis Sousa and Rui Martins: Faculty of Science and Technology, UNIDEMI, Department of Mechanical and Industrial Engineering, New University of Lisbon, Caparica 2829-516, Portugal
Peter Lucas and Harm Tido Petter: VSL-Dutch Metrology Institute, Delft 2629 JA, The Netherlands
Roland Snijder and Annemoon Timmerman: Department of Medical Technology and Clinical Physics, UMC Utrecht, 3584 CX, The Netherlands

Introduction

Drug delivery devices or infusion instruments are widely used in the clinical environment. Their main function is to provide drug therapy, nutrition, and hydration intravenously to patients. Drug delivery is used for almost all hospitalized patients and for those undergoing home care. Several international studies [10] have stated that the dosage of infused pharmaceuticals is subject to uncertainties that may compromise the patient treatment. In infusion applications, the dosage is controlled by the flow rate of the infusion pump and a drug solution of known concentration.

In many cases, the actual flow rate is less important than the total delivered volume. However, if drugs with a very short half-life or a narrow therapeutic range need to be delivered, careful control of the actual flow rate is very important to ensure sound patient treatment. This is particularly the case if low flow rates are required, e.g., for patients who can only tolerate a limited amount of fluid intake, such as neonatal babies. For low flow rate applications, the concentration is typically higher, such that deviations in the infused rate can easily cause overdosing or underdosing. This effect underlines the importance of accurate measurement and control of low flow rates [9]. There are various examples where incidents are believed to be caused by an improper infusion rate, see, for example, [8] where various studies are cited.

The actual infusion rate is dependent on the characteristics of the medical devices used. Typically, when an infusion device is started, it takes some time before the target flow rate is reached, which is also known as the start-up delay (SUD). The SUD is related to system flexibility because the initial volume dispensed will lead to an expansion in the system. This is also known as the compliance of the system. Recent studies [12, 14] show that two known main sources of flow rate deviations are caused by the system compliance and the “push-out effect” (time delay in a multi-pump infusion set when just one of the pumps set-points are changed). This paper investigates how the compliance and the SUD depend on several factors, such as several physical parameters, drug delivery devices, and accessories.

The common infusion solutions used in hospital are aqueous solutions of glucose ($C_6H_{12}O_6$) 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 the case of hypertensive patients, sodium chloride at 0.45 cg/g is used.

The dynamic viscosity ($\eta_{20°C}$) and the density ($\rho_{20°C}$) 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 applied infusion solutions, such as Hespan® and Dextran 40® from BBraun®, which are four times more viscous than water. The dynamic viscosity can be an important parameter, because it directly influences the resistance that can affect the flow rate and its error. The flow rate error will probably be most affected during startup because higher resistance leads to a larger pressure drop which, in turn, leads to a larger volume increase and start-up delay. Furthermore, different drug(s) (solutions) have different viscosities, which make the viscosity a clinically relevant parameter. For that reason, the infusion pumps should be tested with more viscous reference liquids in order to represent the real operational conditions.

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

	$\eta_{20°C}$ (mPa s)	$\rho_{20°C}$ (kg/m³)
Infusion solutions		
5 cg/g $C_6H_{12}O_6$	1145	1017.5
0.9 cg/g NaCl	1020	1005.3
0.45 cg/g NaCl	1011	1001.8
Water	1002	998.2

To meet this need, a metrological infrastructure that can be used by the health care community has since been developed within the European Metrology Research Programme (EMRP) project called "Metrology for Drug Delivery" (MeDD). This infrastructure consists of calibration facilities to determine the flow rate error for varying operating conditions, such as the viscosity, (back) pressure, and temperature (see also [2]). Furthermore, the compliance can be measured as well as the impact of accessories.

There are several types of drug delivery devices. In this work, a syringe pump. Perfusor Space from BBraun® (BBraun central office, Melsungen, Germany; BBraun Portugal, Barcarena, Portugal) was chosen to be tested using different scenarios, flow range, accessories, and various different liquids. In the frame of work package three of the EMRP project MeDD [9], tests were performed by the Portuguese Institute for Quality (IPQ) (Figure 1) and VSL-Dutch Metrology Institute (Figure 2) using the gravimetric method. Both, set-ups and calibration methods used are in accordance with the IEC 60601-2-24 standard [4]. The results are in good agreement with earlier studies [e.g., 11, 16, 17]. However, by taking various accessories and varying operating conditions into account, this current research focuses on additional aspects.

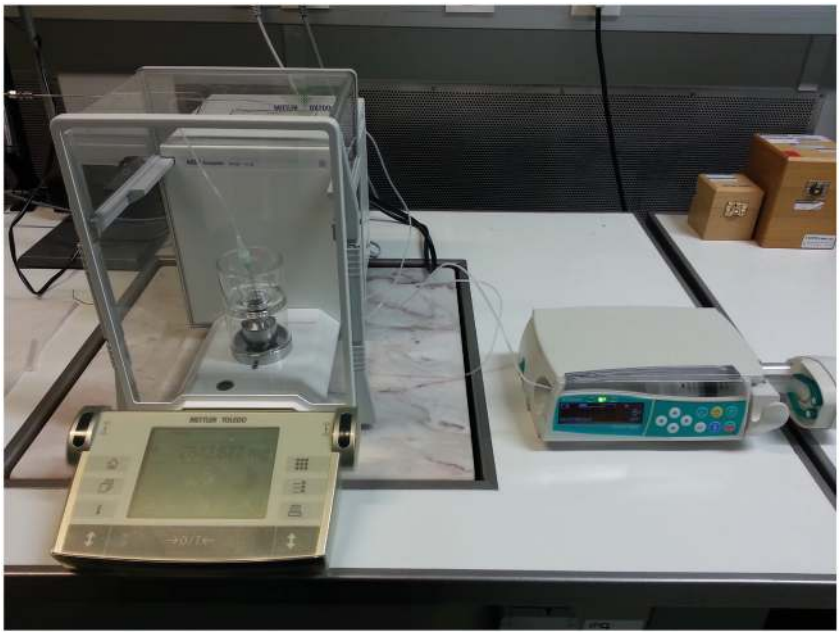

Figure 1: IPQ set-up for syringe pump calibration by gravimetric method.

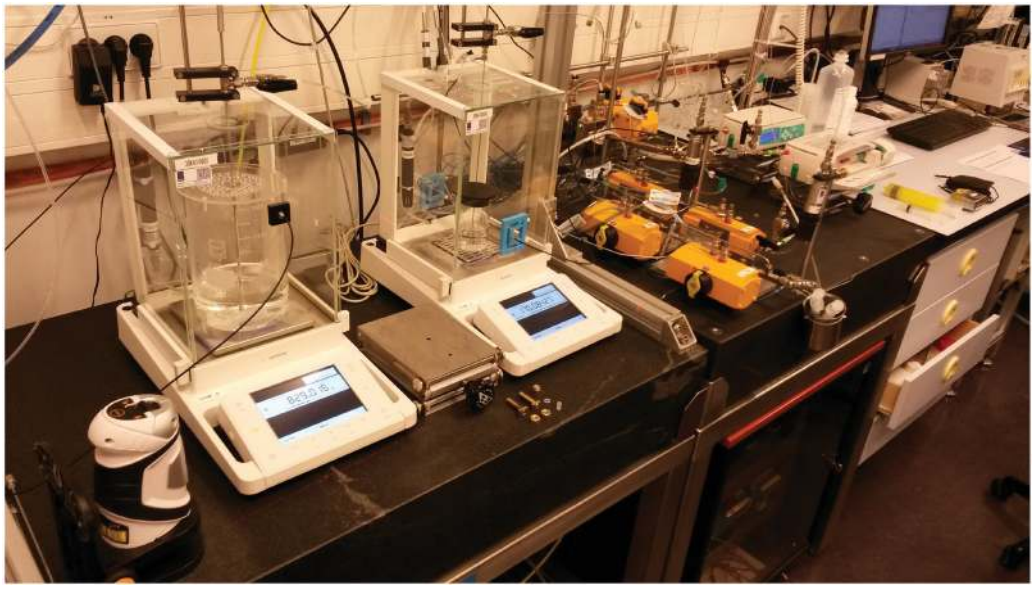

Figure 2: VSL set-up for syringe pump calibration by gravimetric method.

Equipment and scenarios

Three different flow rates were studied for the syringe pump: 0.5 ml/h, 2 ml/h and 10 ml/h, and for plastic disposable syringes of different volumes: 10 ml and 50 ml. Each individual test was repeated three times to determine measurement repeatability.

The accessories tested included the following: an infusion line with a length of 1.5 m BBraun®, REF 8722935), an infusion line of 5.5 m [twice a 2 m line (BBraun®, REF 8722862) and once the earlier mentioned 1.5 m], a filter (BBraun® REF 4184637), and a check valve (Icumedical, REF 011-C3302). Further, glucose aqueous solutions with different viscosities (2 mPa s and 4 mPa s) were used in addition to water. All disposables, infusion lines, filters, and so on, were replaced every day and the syringes were replaced when the plunger reached its end.

The following measuring set-ups (SU) were studied:

- (SU1) Pump with a rigid syringe connected to the default connections of the micro flow set-up, i.e., from the pump directly via rigid tubing and via the default dispersing needle into the measurement beaker;
- (SU2) SU1 with standard syringe;
- (SU3) pump connected to a typical infusion line (with a length of 1.5 m) and then via the default micro flow set-up into the measurement beaker (baseline);
- (SU4) SU3 with elongated infusion line (1 time 1.5 m and twice 2 m infusion lines);
- (SU5) SU2 with a filter installed;
- (SU6) SU2 with a check valve installed;
- (SU7) SU2 with a filling procedure that leads to more entrapped air in the syringe, which resembles the common practice in hospital usage;
- (SU8) SU3 with a typical catheter used in the hospitals to dispense the water in the measurement beaker.

In order to determine the impact of the viscosity on the flow rate error, SU2, SU3, and SU8 were tested with glucose aqueous solutions with different viscosities (2 mPa s and 4 mPa s). The densities of these solutions were determined by an oscillation-type density meter [7], and the nominal viscosity was established through the measured density according to the literature [3, 5]. These two solutions, along with pure water, were then tested with the syringe pump at three different flow rates. Each test was carried out three times.

Procedure

The procedure to test the infusion devices is similar to that described in [4]. In addition, the balance readings were corrected for the buoyancy forces on the measurement beaker, dispensing needle and collected water. The latter two were relative and were in the order of 0.1–0.2% (depending on the equipment used), whereas the first one depended on the stability of the environmental conditions. For low flow rates (e.g., those lower than 1 ml/h), the buoyancy correction for the measurement beaker is deemed significant. For example, for 0.5 ml/h and a

temperature stability of 0.5°C, this term can take on values of up to 0.5%.

In contrast to [4], the back pressure was approximately zero in these tests, because no flow restrictors were used. In the next phase of the project, we plan to determine the impact of the back pressure on the flow rate error, along with compliance and start up delay.

Meanwhile, the syringes were filled with degassed ultra-pure water [4] and the system was rinsed with sufficient water to ensure that there was no air in the system. The intended flow rate was programmed in the syringe pump, after which the water was collected in a vessel standing on the weighing scale. More details on the calibration facilities used can be found in [2].

Flow rate error

The relative error ε obtained in each measurement is calculated by the following formula:

$$\varepsilon = 100\% \frac{q_{\text{pump}} - q_{\text{reference}}}{q_{\text{reference}}} \quad (1)$$

where q_{pump} is the target flow rate (ml/h) set in the pump, and $q_{\text{reference}}$ follows from the balance measurements including corrections.

Response time and compliance

The response time and compliance were determined for set-up SU2 to SU8. For the response time, both the SUD and the delay by doubling or quadrupling of the flow rate were determined. The SUD was defined as the time needed to reach 95% of the target set point after the pump was started. Equally, the delay in doubling the flow rate was defined as the time needed to reach 95% of the new set point (where the new set point was twice the previous set point). The SUD and the delay times in doubling or quadrupling the flow rate were all based on the mass readings of the balance.

The compliance (C) (ml/bar) is given by the ratio between pressure increase (Δp) (bar) due to an applied volume increase (ΔV) (ml) during the occlusion, which is expressed as:

$$C = \frac{\Delta V}{\Delta p} \text{ml/bar} \quad (2)$$

In order to determine the compliance, an occlusion was simulated by closing a downstream valve of the pump (and accessories if used). Thereafter, we measured pressure as function of time. From the measurements, the pressure increase was defined as the maximum pressure that occurs just before the pump gave the occlusion alarm. The pressure was measured with an inline pressure sensor connected via a T-junction. The volume increase followed from the elapsed time to occlusion (response time) multiplied with the flow rate following the set point of the syringe pump. Hence, with this procedure, the compliance can be determined for all pressures that occurred before the occlusion. However, in this work the compliance was only determined for the occlusion pressure, which was approximately 0.65 barg (bar gauge) or 1.65 bara (bar absolute).

The standard ISO-7886-2 [6] describes a similar but more direct way to measure the compliance of a syringe. This is based on adding volume with another syringe and measuring the pressure in a similar fashion. Comparison of both methods revealed that they are in agreement within 30%. This may seem to be a large difference; however, considering the large spread in the measurement results this is a fair number. In this work, the former method is preferred because it offers an easy alternative to determine the flow rate error, stability, response time until occlusion, and compliance all in the same run. Furthermore, standard ISO-7886-2 only takes the compliance due to the syringes into account. The compliance of the syringe pump itself ("pusher") as well as the accessories and infusion lines can be significant and should also be taken into account, too.

With a simulation model of the drug delivery system, the measured compliance can also be used to determine the SUD. This is because an infusion system can be seen as a network of compliant and resistive tubes. When the flows are considered as laminar, the Hagen-Poisseuille law can be used to describe the flow behavior or velocity profile. A laminar flow is a good assumption, because the Reynolds number is typically well below 100. Further, it can be assumed that the flow is fully developed as the inner diameter is small compared with the length of the infusion lines. For now, unsteady effects due to temporal or spatial temperature gradients are neglected. The network can then be modeled using standard network theory and Laplace-transformations, from which the SUD can be determined.

Measurement uncertainty

The overall measurement uncertainty [15] can be derived from the uncertainty of the calibration facility and the

standard deviation of the mean of the repetitions. The measurement uncertainty was evaluated in this study following the Guide to the Expression of Uncertainty in Measurement (GUM) [1]. See [2] for more information on the uncertainty of the calibration facilities used. For the flow rate error, the measurement uncertainty varies between 0.5% for the higher flow rates and up to 2% for the lower flow rates. The standard deviation of the measurement results is the fundamental influencing factor on measurement uncertainty.

Results and discussion

In this section the results obtained for the flow error, response time, and compliance are discussed.

Flow rate error

Figures 3 and 4 show the flow rate errors for the complete set-up (syringe pump including accessories) for 10 ml and 50 ml syringes, respectively, and various accessories. The flow rate error is determined as described in (1). In this case, a positive error indicates that the pump is delivering less than its set point (q_{pump} is larger than $q_{reference}$). Hence, a positive error should be regarded as an underestimation of the drug delivered, or the actual delivered drug is less than predicted from the set point. From these results several statements can be made, as listed below.

- The flow rate error is typically larger for decreased flow rates. This is confirmed by results one would expect, i.e., the lower flow rates are beyond the normal usage of a 50 ml syringe.
- The errors using the 50 ml syringe are generally larger than the errors that occur when using the 10 ml syringe.
- In case a filter is included, the flow rate error is shifted in the positive direction. Hence, the pump is delivering less than its set point. This can be explained by more entrapped air in the filter or by a higher flow resistance due to the filter.
- For flow rates of 2 ml/h and 10 ml/h, it can be concluded that the pump is performing within its claimed accuracy specifications of 2% [13]. However, for a flow rate of 0.5 ml/h, the same conclusion cannot be made because the uncertainty bars cross the 2% error range. Hence, it cannot be concluded (with 95% certainty) whether the pump is performing within or outside its claimed accuracy specifications.
- A larger spread of results can be found at lower flow rates. This is probably caused by varying material properties and/or dimensions of the syringes.

In Figures 5–7, the flow rate error is plotted for SU2, SU3, and SU8 and for different values of the viscosity. In this context "*w*" stands for the viscosity of water, and "*w2*" and

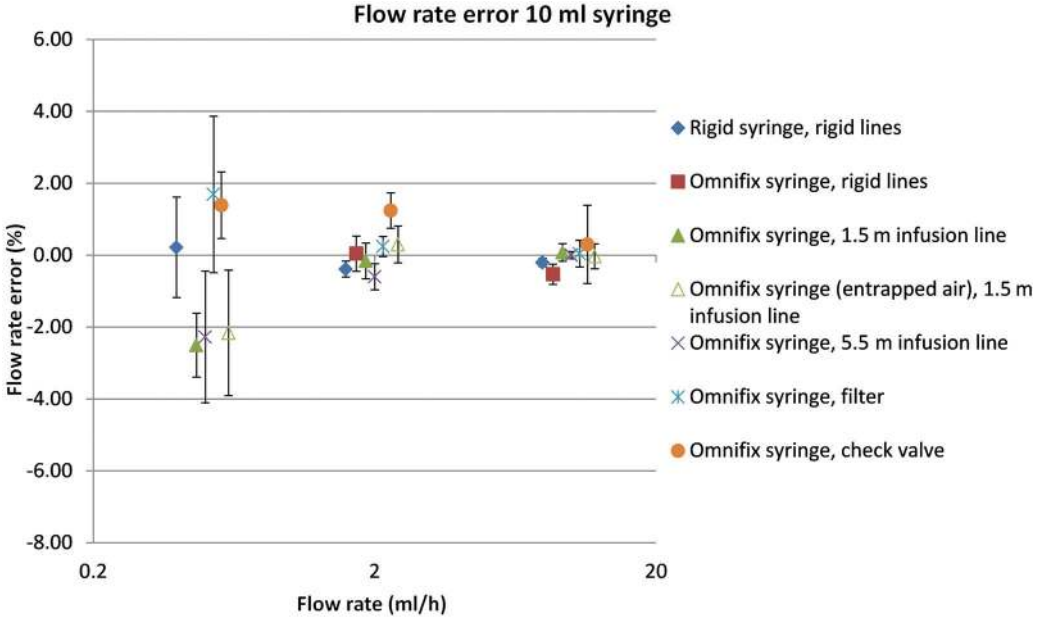

Figure 3: Relative flow rate error as a function of the target flow rate and various accessories for a syringe volume of 10 ml (SU from 2 to 7).

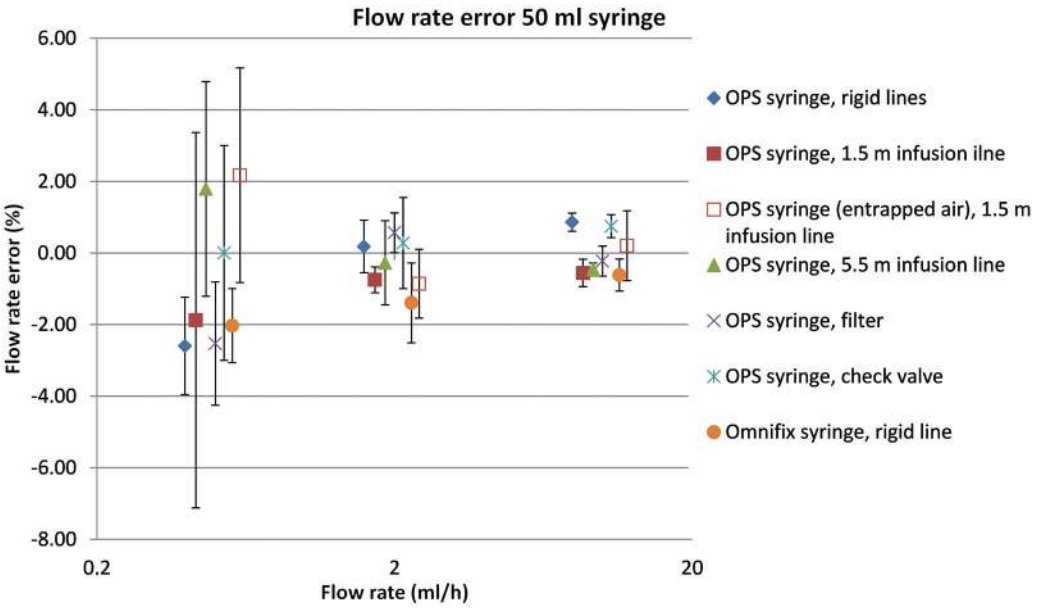

Figure 4: Relative flow rate error as a function of the target flow rate and various accessories for a syringe volume of 50 ml (SU from 2 to 7).

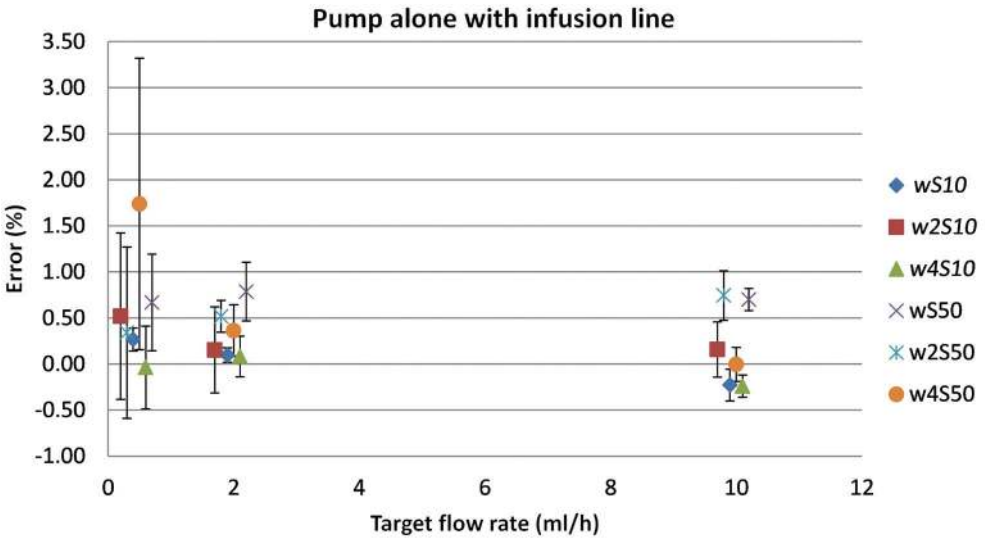

Figure 5: Relative flow rate error as a function of the target flow rate and viscosity and SU8. *wS10* corresponds to water using a 10 ml syringe, *w2S10* corresponds to the 2 mPa s solution using a 10 ml syringe, and *w4S10* corresponds to the 4 mPa s solution using a 10 ml syringe, the same is valid for the 50 ml syringe.

"*w4*" stand for two and four times the viscosity of water, respectively. From the results obtained for the syringe pump several conclusions can be made, as listed below.

- The errors using the 50 ml syringe are generally larger than the errors in the case the 10 ml syringe is used.
- There is no significant difference in the measured error when using solutions with different viscosities, except for the 50 ml syringe in SU8. In all SU for the 50 ml syringe and for the 0.5 ml/h, higher viscosity produces a higher positive error. This means that the measured flow rate is more underestimated when using *w4* solution.
- A larger spread of results can be found at lower flow rates. This is probably caused by varying material properties and/or dimensions of the syringes.
- Larger uncertainties can be found in SU8 due to the set-up's larger instability caused by the flexible infusion line.

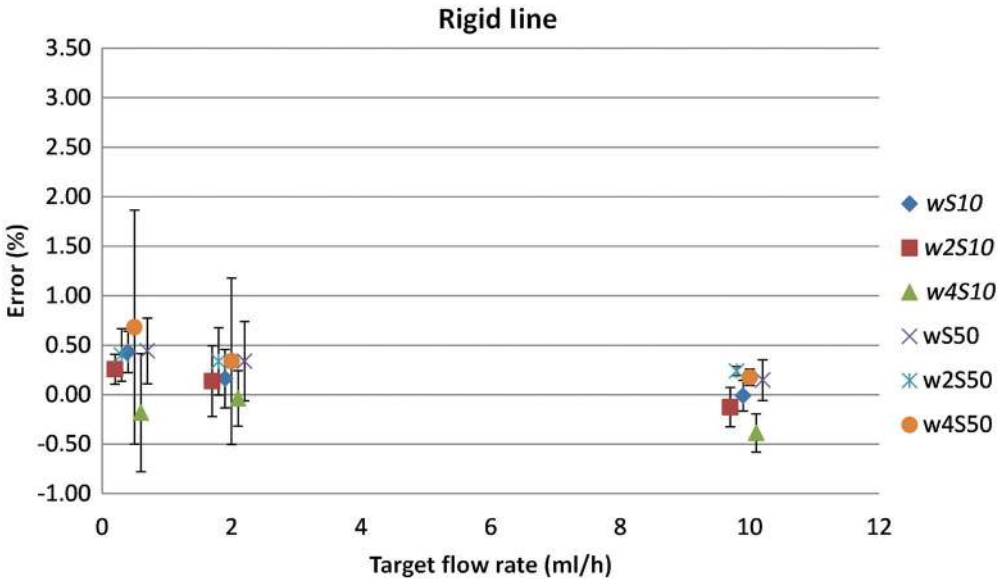

Figure 6: Relative flow rate error as a function of the target flow rate and viscosity and SU2. *wS10* corresponds to water using a 10 ml syringe, *w2S10* corresponds to the 2 mPa s solution using a 10 ml syringe, and *w4S10* corresponds to the 4 mPa s solution using a 10 ml syringe, the same is valid for the 50 ml syringe.

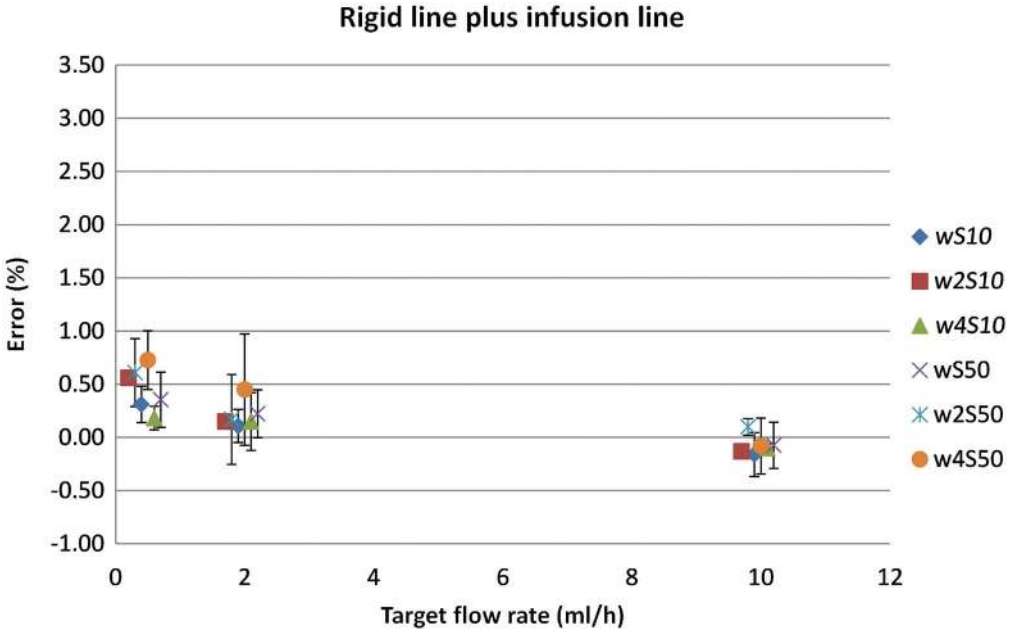

Figure 7: Relative flow rate error as a function of the target flow rate and viscosity and SU3. *wS10* corresponds to water using a 10 ml syringe, *w2S10* corresponds to the 2 mPa s solution using a 10 ml syringe and *w4S10* corresponds to the 4 mPa s solution using a 10 ml syringe, the same is valid for the 50 ml syringe.

Response time and compliance

In Table 2 the compliance for various scenarios and syringe volumes is shown. The flow compliance is determined as described in (2). The larger the compliance, the larger the "elasticity" of the system and the longer the response times (SUD and delay time in doubling or quadrupling the flow rate). From these results several observations can be made, as listed below.

– The much lower compliance for the 10 ml syringe set-ups confirms that the syringe has the largest impact on the overall compliance. Further, for a setup including

Table 2: Compliance for various scenarios and syringe volumes.

Scenario	10 ml syringe (ml/bar)	50 ml syringe (ml/bar)
Rigid syringe	0.24	N/A
Standard syringe	0.21	1.54
Standard syringe, 1.5 m infusion line	0.20	1.54
Standard syringe, 1.5 m infusion line, entrapped air	0.22	1.61
Standard syringe, 5.5 m infusion line	0.44	1.89
Standard syringe, filter	0.52	2.10
Standard syringe, check valve	0.22	1.54

a 10 ml syringe, adding accessories and infusion lines has a much bigger impact in the relative sense.
- For both systems, the inclusion of a filter has the greatest impact when it comes to increasing compliance. This is very likely caused by entrapped air inside the filter. Given that air is more compressible, entrapped air significantly increases the compliance of the system.

Next, the results for the SUD are shown in Figures 8 and 9. From these results, several remarks can be made, as listed below.
- In general it can be stated that, the lower the flow rate, the larger the SUD. The SUD depends on the flow rate because for a lower flow rate, it simply takes longer until the whole system is pressurized (although for the lower flow rates the resistance is slightly lower).
- A larger spread of results can be found at lower flow rates. This is probably caused by varying material properties and/or dimensions of the syringes as well as accessories. Furthermore, it is more difficult to avoid inclusion of air when the accessories are included in the set-up. As air will have a significant impact on the compliance and thus startup delay, this can also result in a larger spread.
- The measured SUD for the 50 ml syringe is comparable to that of the 10 ml syringe, which is in contrast to the measured compliance. This is probably due to the fact that compliance has been determined for the occlusion pressure (approximately 0.65 barg), whereas the required pressure increase during startup is significantly lower. Typically, the compliance increases significantly when the pressure is increased from zero to larger values (thereafter, it levels off or even decreases again). Hence, in case a theoretical model is used to determine the compliance, it is important to have determined the compliance at the right pressure.

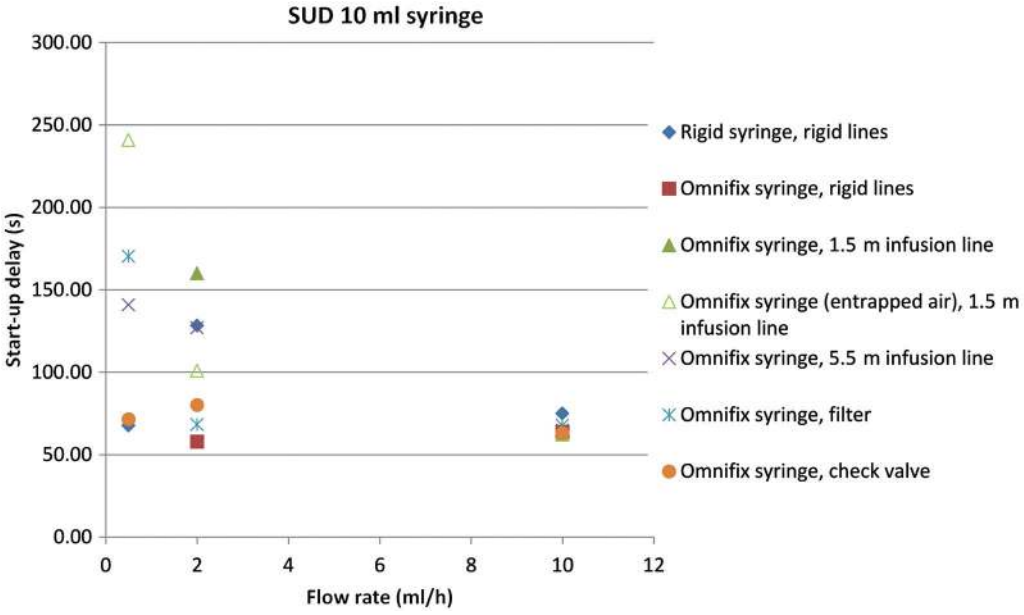

Figure 8: SUD as a function of the target flow rate and various accessories for a syringe volume of 10 ml. Set-up from 2 to 7.

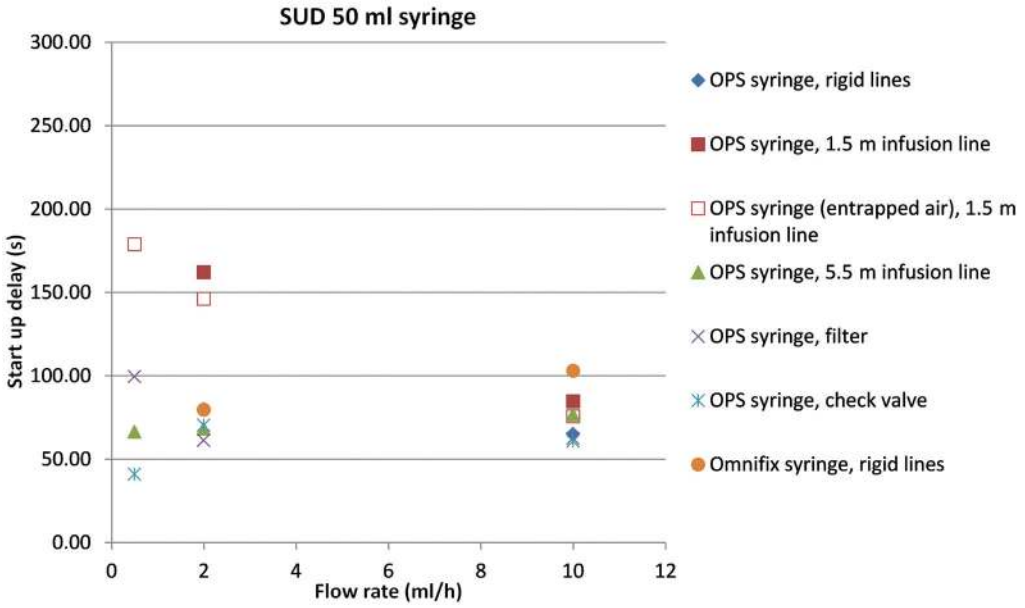

Figure 9: SUD as a function of the target flow rate and various accessories for a syringe volume of 50 ml. Set-up from 2 to 7.

– For both systems, the inclusion of a filter has the greatest impact when it comes to increasing the compliance and start up time. Most probably this is caused by entrapped air inside the filter.

Finally, Figures 10 and 11 show the response times after doubling and quadrupling the flow rate, respectively. These results are obtained for a syringe volume of 10 ml and 50 ml and set-ups SU8 and SU3. From these results, several observations can be made, as listed below.

– The lower the flow rate, the longer the delay time to reach a steady flow rate after doubling or quadrupling the flow. This is as expected and corresponds to the startup delay and compliance.
– For the larger syringe, it takes more time to reach steady flow than for the smaller syringe.

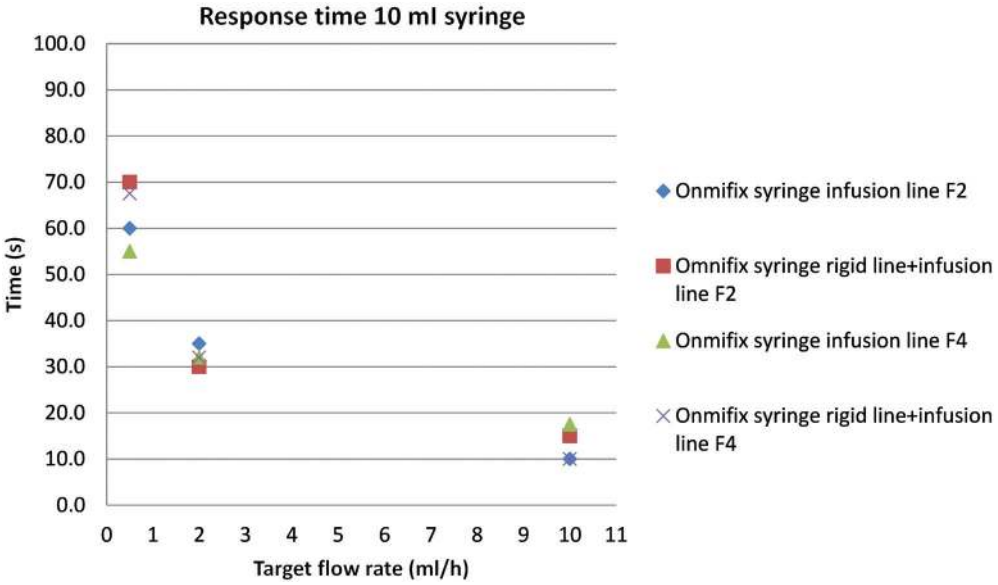

Figure 10: Response time (time to reach 95% of the final flow rate) as a function of the target flow rate, SU 3 and 8 (F2-double flow rate, F4 quadrupled flow rate) for the syringe pump with a 10 ml syringe.

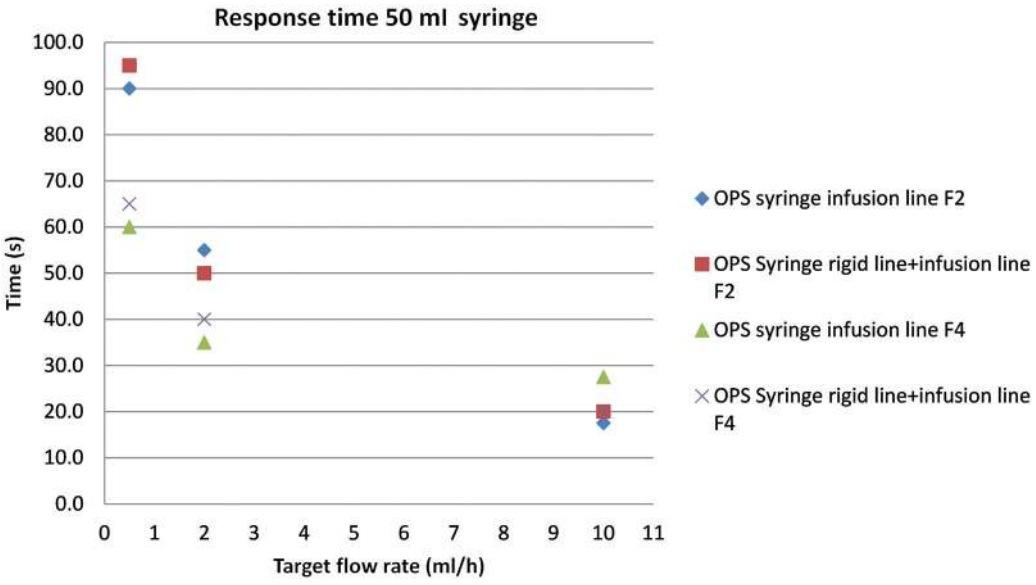

Figure 11: Response time (time to reach 95% of the final flow rate) as a function of the target flow rate, SU 3 and 8 (F2-double flow rate, F4 quadrupled flow rate) for the syringe pump with a 50 ml syringe.

– The type of setup used only has some influence on the lowest flow rate where the variability of the results is larger.

Conclusions and future work

Infusion devices must be reliable when used in drug delivery. However, the normal calibration procedure described in IEC 60601-2-24 does not take into consideration the variations when these instruments are used in field applications, e.g., usage of accessories and varying operating conditions are omitted. Furthermore, not all buoyancy corrections are taken into account. Consequently, calibrations at low flow rates may be subjected to significant uncertainties, which can then lead to undesired patient treatment.

The results obtained in this study show that the devices are sensible to variations in use, particularly at small flow rates and when using large syringes. However, the pump generally performs within its claimed accuracy specifications (i.e., the lower the flow rate, the larger the standard deviation of the results).

System compliance is an important characteristic of infusion devices, which can cause temporary flow rate variations induced by set point changes. Particularly at low flow rates, the (syringe) compliance effects are important, because the temporary deviations with respect to the intended set point values are relatively large. Regulatory authorities and hospitals should therefore consider adopting specific standards and guidelines for system compliance when using high risk medication at low flow rates.

Thus far, IPQ and VSL have tested the infusion devices for the impact of viscosity and accessories. The following research is scheduled: impact of back pressure (METAS, Switzerland), impact of temperature (CETIAT, France) and the impact of various syringes (DTI, Denmark). Furthermore, future works will include other syringe pumps and insulin pumps.

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