Assessment of drug delivery devices and accessories

A few show cases

Flow rate error, compliance and impact of operating conditions

Working document

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Contents

1 Introduction

This report is written as part of MeDD [3], in particular for deliverables 3.1.1 to 3.1.3, 3.2.1 to 3.2.2 and 3.3.1 to 3.2.5. In drug delivery, the flow rate and concentration determine the pharmaceutical dosing. In this report we focus on the flow rate only.

In this report it is studied whether typical infusion pumps perform within specifications. That is, whether the actual flow rate error is equal or less than what the manufacturer claims. 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). This is a very important parameter because it defines how long it takes before the patient receives the infusion doses that it needs. Therefore, it will also be investigated how the compliance and start up delay depend on several physical parameters, drug delivery devices and accessories. The following aspects are considered:

- accessories: infusion line, filter and check valve;
- pump types: syringe and peristaltic;
- syringe types: Omnifix and OPS;
- syringe volumes: 10 mL and 50 mL;
- operating conditions: viscosity, back pressure and temperature.

In addition to determining the compliance and start up delay, it will be investigated whether the compliance can simply be obtained via occlusion measurements, which are much simpler to perform than flow rate measurements. Finally, the flow rate error and flow rate stability are studied.

The set up and calibration methods used are in accordance with standard 60601-2-24. Furthermore, the investigations are in line with earlier performed investigations, e.g. [1]. By taking into account various accessories and equipment and varying operating conditions, this research goes beyond the already available literature [1].

The structure of this report is as follows. In Section 2 and 0 the used equipment and planning are discussed, respectively. In Section 3 the measurement protocol is discussed, whereas in Section 4 to 9 the tests results are discussed. Finally, in Section 0 some recommendations are given how one can fill a syringe and accessories.

2 Equipment and settings

For the assessment of the drug delivery devices, the following equipment is used (manufacture Bbraun unless indicated otherwise):

- Syringe pump Bbraun serial number 49682
- Syringes:
    - Syringe volume 10 mL, Omnifix, REF 4617100V, LOT3A02048 (used for scenarios 2 tot 8)
    - Syringe volume 10 mL, Perifix, REF4638107, LOT3L04048 (used for scenario 1)

    - Syringe volume 50 mL, Omnifix REF, LOT
    - Syringe volume 50 mL, OPS REF8728801F, LOT14B1082017 (used for scenarios 2 tot 8)
- Peristaltic pump serial number 267771
- Peristaltic infusion line:
    - Peristaltic line REF8700127SP LT3F25340000
- Serum bag 1000 ml
- Accessories:
    - Infusion line 1.5 meter, REF 8722935, LOT 8A11219SC5 (used for scenario 3 and 4).
    - Infusion line 2 meter, REF 8722862, LOT 14A22E8SB4 (used for scenario 4)
    - Filter, REF4184637, LOT2B20340000 (used for scenario 5)
    - Check valve, Icumedical, REF 011-C3302, LOT 2833910 (used for scenario 6)
    - Potentially: catheter, 0.6x25mm, Gr16
    - Potentially: valve block VYCON REF 5827.93

For the assessment of drug delivery devices liquids with various densities are required. These densities will be realized by making different mixtures of glucose and water. The following relative densities compared to water will be used: 1, 2 and 4. The settings for the upstream and occlusion pressure are as follows:

- Upstream pressure
    - Peristaltic pump: level 5
    - Syringe pump: not available.
- Occlusion pressure
    - Peristaltic pump: level 9
    - Syringe pump: level 5

The following flow rates are used for the syringe pump: 0.5 mL/h, 2 mL/h and 5 mL/h. For the peristaltic pump the following flow rates are used: 2 mL/h, 10 mL/h and 50 mL/h. The infusion devices are investigated using set ups that rely on balance measurements. Furthermore, it will be investigated whether commercially available flow meters can be used.

3 Protocol syringe pump and peristaltic pump measurements

In this section the measurement protocol for the syringe and peristaltic pump is discussed. Two different types of tests can be distinguished:

1. Start up delay (SUD) and responds to occlusion (RTO).
2. Doubling flow rate delay (DFD).

The protocols to quantify these parameters are discussed in the next two sections.

3.1 Start up delay and responds to occlusion

The protocol to quantify the SUD and responds to occlusion is given below. The responds to occlusion is used to determine the compliance for the given occlusion pressure. See Section 0 for some advice on how to fill the syringes and accessories.

1. Unless otherwise required, set the occlusion value to level 5 for the syringe pump and level 9 for the peristaltic pump.
2. Replace the disposables when required[1].
3. Prime the complete set up and make sure there are no air entrapments. Both pumps can be used to prime automatically by using the 'Bolus function'. Press bolus (wait a few moments) and press prime. Recommendation: verify whether the bolus volume matches the increase in weight on the balance[2]. The syringes and accessories can easily introduce air bubbles in the system, hence it is recommended to be extra cautious on entrapped air.
4. Check for leakages.
5. Place the pump at the same height as the liquid level in the measurement beaker. For the peristaltic pump, place the infusion bag such that the liquid level in this bag is 1 meter above the pump.
6. Set the correct flow rate and set the duration to a sufficient long time (say 10 hours).
7. After priming, make sure there is zero flow.
8. Start the balance read out.
9. Start the pump exactly 60 seconds after the balance read out has started.
10. Close the downstream valve after 1 hour (for the peristaltic pump 30 minutes can be used). Wait for the occlusion alarm to sound. Open the valve again and stop the test after 5 minutes (omitted in case occlusion is not studied).
11. Check integrity of the disposables.
12. Repeat each measurement 3 times (two in case there is insufficient time)
13. The following parameters need to be measured during the experiment:
    - Elapsed time (time is zero is defined when the pump is started);
    - Reference flow rate;
    - Pressure in the line;
    - Water temperature;
    - Ambient temperature and humidity.

In case the syringe is full enough for the next run, one can restart from point 6. However, perform a bolus to make sure there is no air entrapment. For the analysis, the following parameters need to be determined:

- Time to reach 50% of the flow rate $t_{50\%,start}$;
- Time to reach 95% of the final flow rate $t_{95\%,\ start}$;

[1] Infusion lines, filters, etc. need to be replaced every day. A syringe needs be replaced when the plunger has reached its end.

[2] For some tests the indicated mass significantly jumps when the test is started, which might be caused by using the bolus function. Turning on the pump for just a few moments seems a good remedy.

- Flow rate stability between $t_{95\%}$ and t_{end} (where t_{end} is the time when the downstream valve was closed) ;
- Relative deviation between target flow rate and reference flow rate;
- Compliance (only when occlusion is studied).

The compliance is defined as:

$$C = \frac{\Delta V}{\Delta p}$$

where ΔV is the volume increase due to an applied pressure increase Δp. From the measurements, the pressure increase is defined as the maximum pressure that occurs just before the pump gives the occlusion alarm. The pressure is measured with an inline pressure sensor connected via a T. Note, this sensor in itself will also have some compliance (to do).

The volume increase follows from the responds time to occlusion multiplied with the flow rate. Note, the actual volume increase may be different than the dispensed volume indicated by the pump due to play. However, in reality this will happen too, hence is included in the evaluation. The compliance is a function of the pressure increase because the pressure increases not linearly in time (because of nonlinear elastic effects, see also Section 4), hence:

$$C = C(\Delta p)$$

The measured compliance will later be used to estimate the SUD, see [2] for details. Estimating the SUD via this approach would be much easier than using the balance. Next, the relative flow rate deviation follows from:

$$\varepsilon = 100\% \frac{q_{pump} - q_{actual}}{q_{actual}}$$

where q_{pump} is the target flow rate set in the pump and q_{actual} follows from the balance measurements. Remarks:

- The final flow rate is defined as the flow rate achieved after possible over and under shoots have been damped out. Hence, the final flow rate is obtained once a steady state flow has been achieved.
- The above parameters may depend on the plunger level. However, this effect probably small and therefore ignored.

3.2 Delay time in doubling the flow rate

The protocol for investigating the delay time in doubling the flow rate is very similar to the earlier discussed protocol. The differences are:

- The occlusion bit is discarded;
- Rather than starting the pump, the flow rate is doubled (or quadrupled) at a defined start point. Note, the flow rate should only be increased after the pump has more or less reached steady state (usually about 15 minutes is sufficient).

For the analysis, the following parameters need to be determined:

- Time to reach 50% of the final flow rate $t_{50\%,,double}$
- Time to reach 95% of the final flow rate $t_{95\%,\ double}$
- Flow rate stability between $t_{95\%,,double}$ and the end of the test

3.3 Scenarios

One or more of the following test set ups, or scenarios, will be investigated:

1. Pump with glass/ rigid syringe and connected to the default connections of the micro flow set up. That is, from the pomp via rigid tubing via a dispersing needle into the measurement beaker.
2. Same as 1, however with a standard syringe (OPS or Omnifix).
3. Pump connected to a typical infusion line (1.5m) and then via the default micro flow set up into the measurement beaker (baseline).
4. Same as 3, however elongated infusion line (achieved by 1 time 1.5 m and 2 times 2 m infusion lines)
5. Same as 3, however with also a filter installed.
6. Same as 3, however with also a check valve installed
7. Same as scenario 2, however with a filling procedure that more resembles the usage in hospitals (see Section 10.2).
8. Same as 3, however instead of standard infusion line a neonatology line is used.
9. Same as 3, however filling procedure is such that there are air bubbles present.

Remark, one could argue that all scenarios should mimic hospital usage. However, by using the above scenarios one can easily distinguish between the impact of air bubbles and the accessories.

4 Impact of drug delivery accessories

4.1 Motivation and goal

The goal of these series is to investigate how various accessories influence the compliance. Accessories will directly influence the compliance and are therefore important for the compliance of the total system.

4.2 Equipment and scenarios

The following equipment will be used for the tests:

- One syringe pump, two syringes
  - 10 mL, Bbraun Omnifix;
  - 50 mL, Bbraun OPS and Omnifix.
- One peristaltic pump.
- Various combinations of accessories: infusion line, elongated infusion line, filter, check valve, neonatology line.

Scenarios 1 to 7 will be studied. Furthermore, three different target flow rates will be used (the pump set points, see protocol). For the investigations the micro fluidic set up

of VSL is used. For a measurement time of 60 minutes and a flow rate of 0.5 mL/h, the measurement uncertainty is 0.9%. For a measurement time of 30 minutes and a flow rate of 2 mL/h and 10 mL/h, the uncertainty is 0.5% and 0.1%, respectively.

4.3 Results and discussion

Figures 1 and 2 show the flow rate error for the complete set-up (syringe pump including accessories) for a 10 ml and 50 ml syringe and various accessories. The flow rate error is determined as described in Section 3.1. 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 the following statements can be made:

- 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 in general larger than the errors occurring in case the 10 ml syringe is used.
- 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 % [17]. For a flow rate of 0.5 ml/h this conclusion can in general not 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 general, for the syringe pumps and the syringes used, the measured flow rate stability (not shown) is lower than the inter-syringe variances.

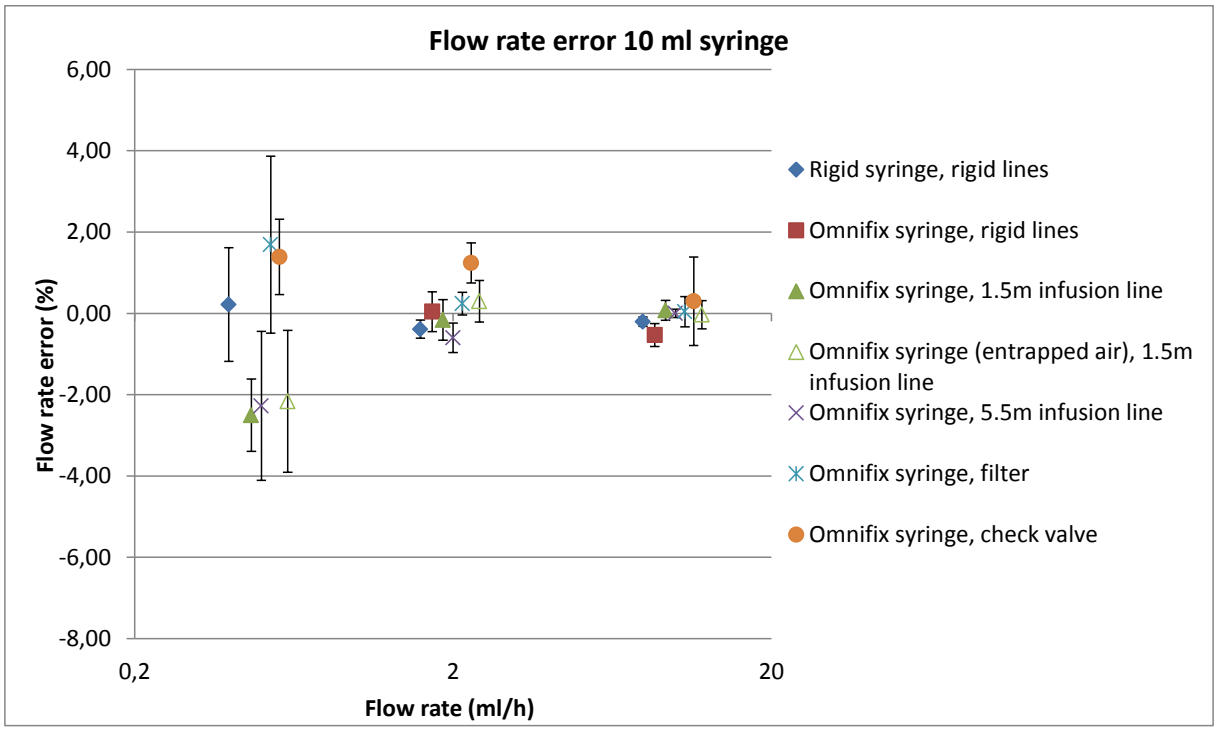

Figure 1 - Relative flow rate error as function of the target flow rate and various accessories for a syringe volume of 10 ml. SU from 2 to 7.

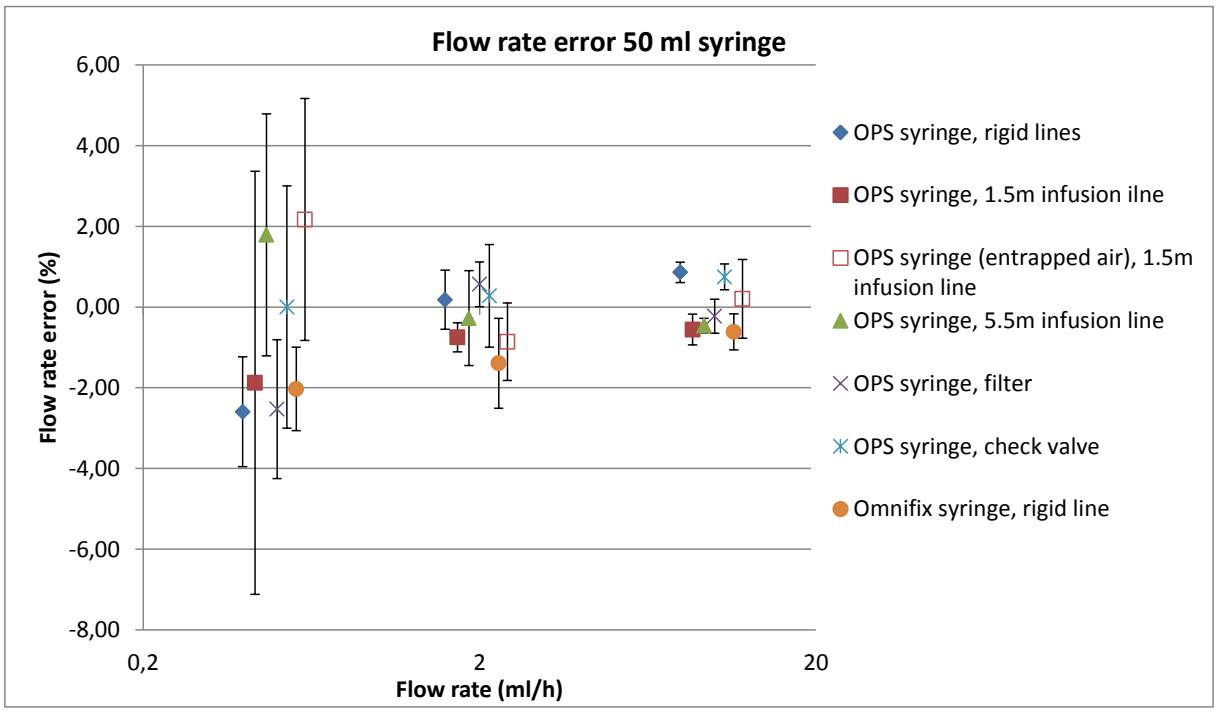

Figure 2 - Relative flow rate error as function of the target flow rate and various accessories for a syringe volume of 50 ml. SU from 2 to 7.

In Table 1 the compliance for various scenarios and syringe volumes is shown. The flow compliance is determined as described in Section 3.2. The larger the compliance, the larger the 'elasticity' of the system and thus also the longer the response times (start-up

delay and delay time in doubling or quadrupling the flow rate). From these results the following observations can be made:

- The much lower compliance for the 10 ml syringe setups confirms that the syringe has the biggest impact on the overall compliance. Further, for a setup including a 10 ml syringe, adding accessories and infusion lines has a much bigger impact in the relative sense.

- For both systems, including a filter increases the compliance the most. Very likely this is caused by entrapped air inside the filter. Because air is more compressible, entrapped air significantly increases the compliance of the system.

Table 1. 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, 1.5m infusion line	0.20	1.54
standard syringe, 1.5m infusion line, entrapped air	0.22	1.61
standard syringe, 5.5m infusion line	0.44	1.89
standard syringe, filter	0.52	2.10
standard syringe, check valve	0.22	1.54

Next, the results for the start-up delay are shown in Figures 3, 4 and 5. From these results the following remarks can be made:

- In general it can be stated that, the lower the flow rate is, the larger is 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 proved to be 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 because the 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.

- For both systems, including a filter will increases the compliance and start up time the most pronounced. Most probably this is caused by entrapped air inside the filter.

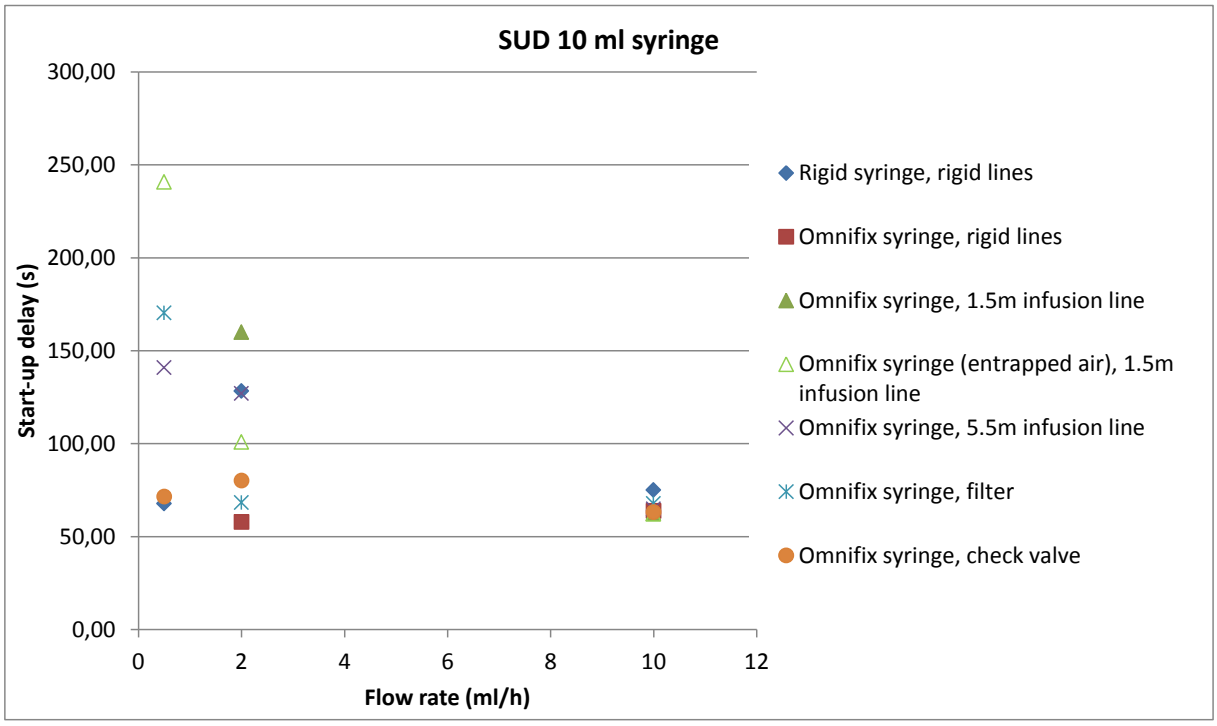

Figure 3 - Start-up delay (SUD) as function of the target flow rate and various accessories for a syringe volume of 10 ml. Set-up from 2 to 7.

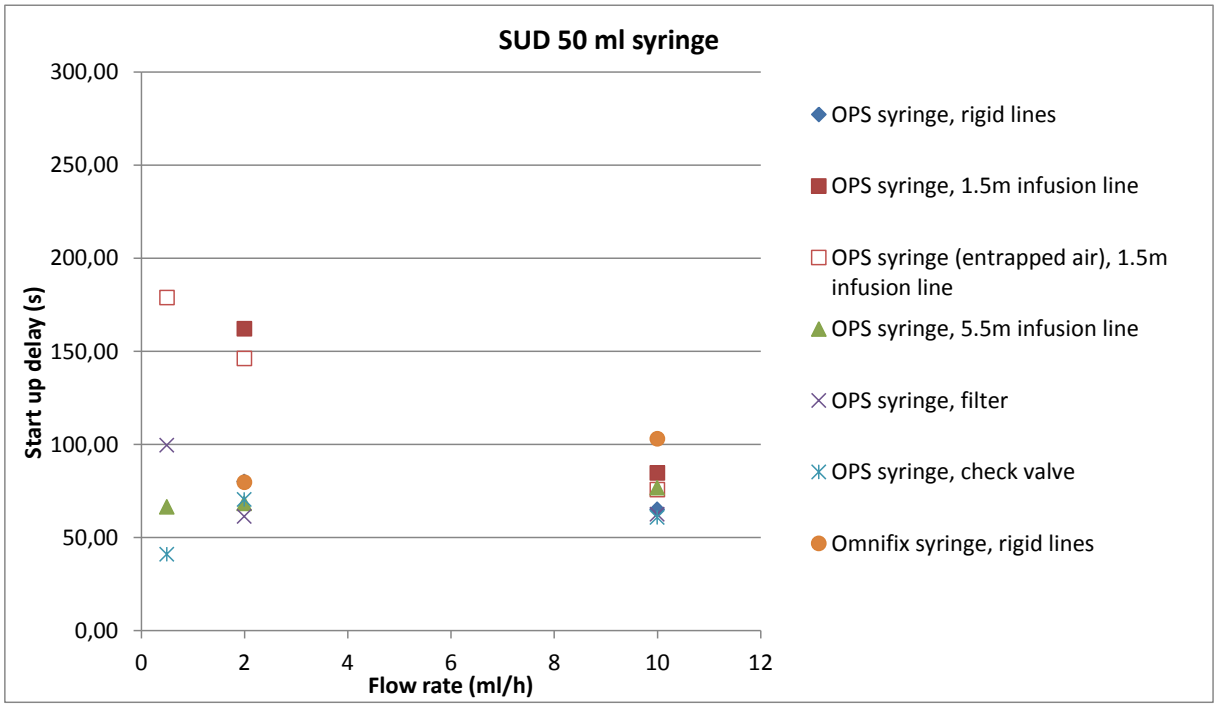

Figure 4 - Start-up delay (SUD) as function of the target flow rate and various accessories for a syringe volume of 50 ml. Set-up from 2 to 7.

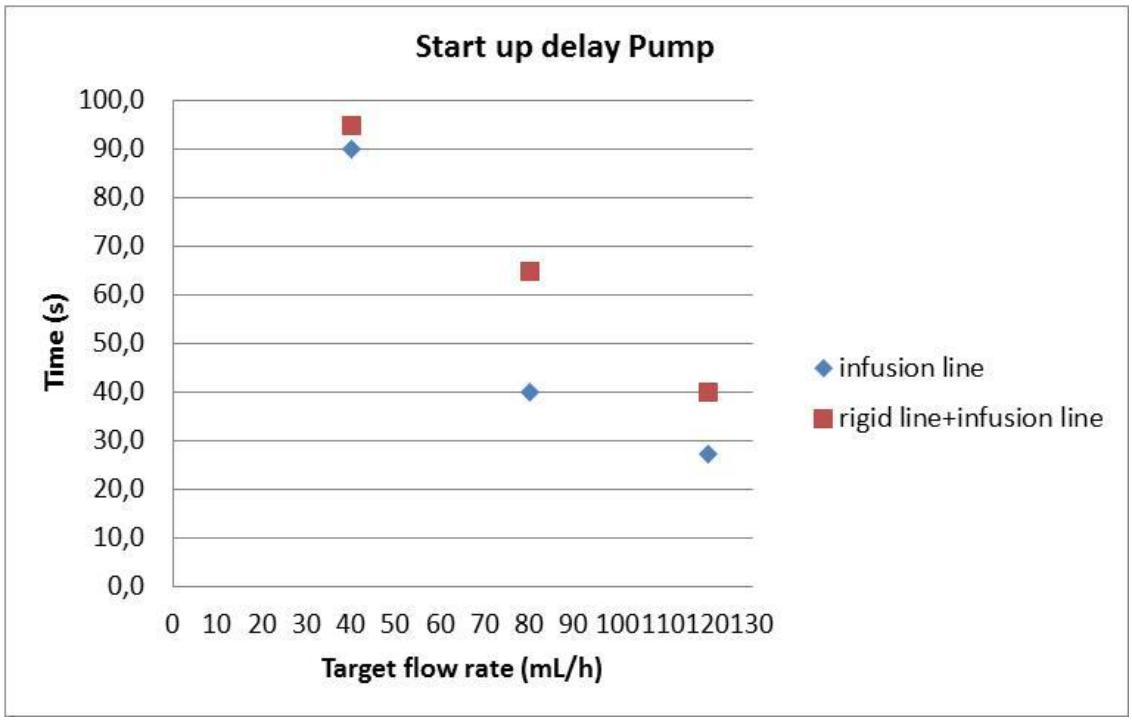

Figure 5 - Start-up delay (SUD) as function of the target flow rate for the peristaltic pump.

5 Impact of viscosity

5.1 Motivation and goal

Viscosity is one of the physical parameter that can influence the pressure drop in a tube, hence also the delivered flow rate. Additionally, the pressure build-up depends on the viscosity, hence it plays a role in the startup delay, flow rate error and stability.

Infusions solutions generally used in drug delivery devices can have a relative viscosity range from 1 up to 4, when compared with the water. In order to study the influence of viscosity in flow rate of drug delivery devices several test will be performed using mixtures of water and glucose with different viscosities.

5.2 Equipment and scenarios

The following equipment will be used for the tests:

- One peristaltic pump and one syringe pump with two different syringes, 10 ml (Omnifix) and 50 ml (OPS).
- Various combinations of accessories (see below).
- Three different solutions, water (w), glucose mixture with 2 times the viscosity of water (w2) and glucose mixture with 4 times (w4) the viscosity of water.

The following combinations for the two pumps and accessories will be made:

1. Pump alone connect to the infusion line directly to the balance

2. Pump alone and connected to the default connections of the micro flow set up. (scenario 2)
3. Pump connected to the default infusion line and then via a typical catheter into the measurement beaker. (scenario3)

The 3 setups described before will be tested using 3 different liquids. The tests will be performed at various flow rates: 0.5 mL/h, 2 mL/h and 10 mL/h for the syringe pump and 2 mL/h, 10 mL/h and 50 ml/h for the peristaltic pump. In case of sufficient time, the pump measurements can be repeated for a different infusion line diameter and also using a filter or check valve.

5.3 Results and discussion

The results are shown in figure 6 to 8 for the syringe pump.

From the results the following can be observed:

- The errors using the 50 mL syringe are always larger than the 10 mL syringe.
- There is no significant difference in errors when using solutions with different viscosity.
- A larger variability can be found at lower flow rate.

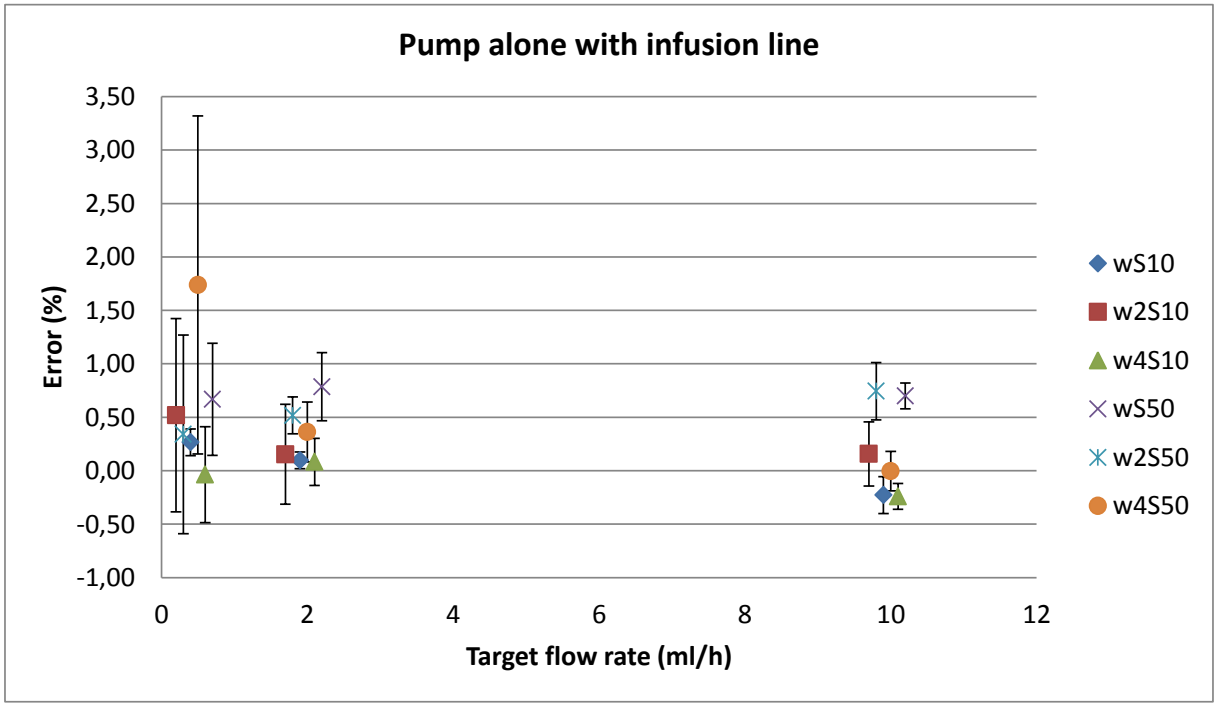

Figure 6 Relative flow rate error as function of the target flow rate and viscosity of the used liquid using only the pump with the infusion line. The relative flow rate error follows from the relative difference between the target flow rate and actual flow rate which is measured with the balance).

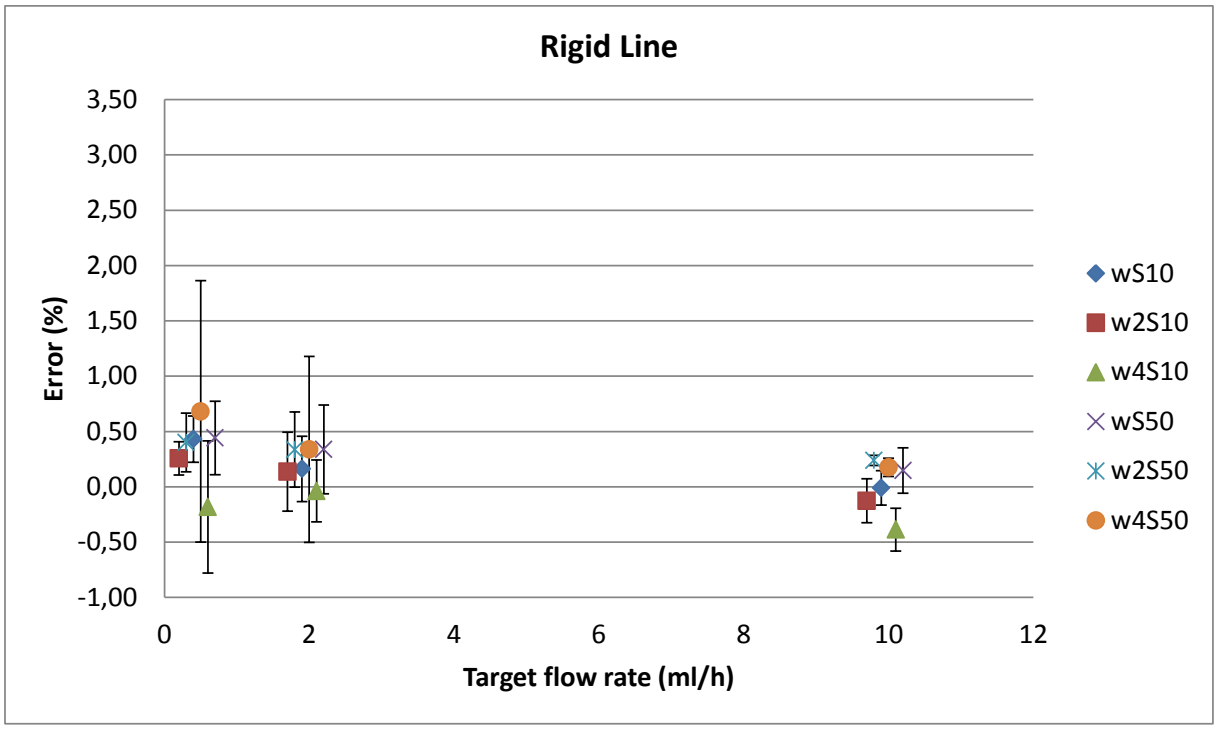

Figure 7 Relative flow rate error as function of the target flow rate and viscosity of the used liquid the pump connected directly to the microflow setup . The relative flow rate error follows from the relative difference between the target flow rate and actual flow rate which is measured with the balance).

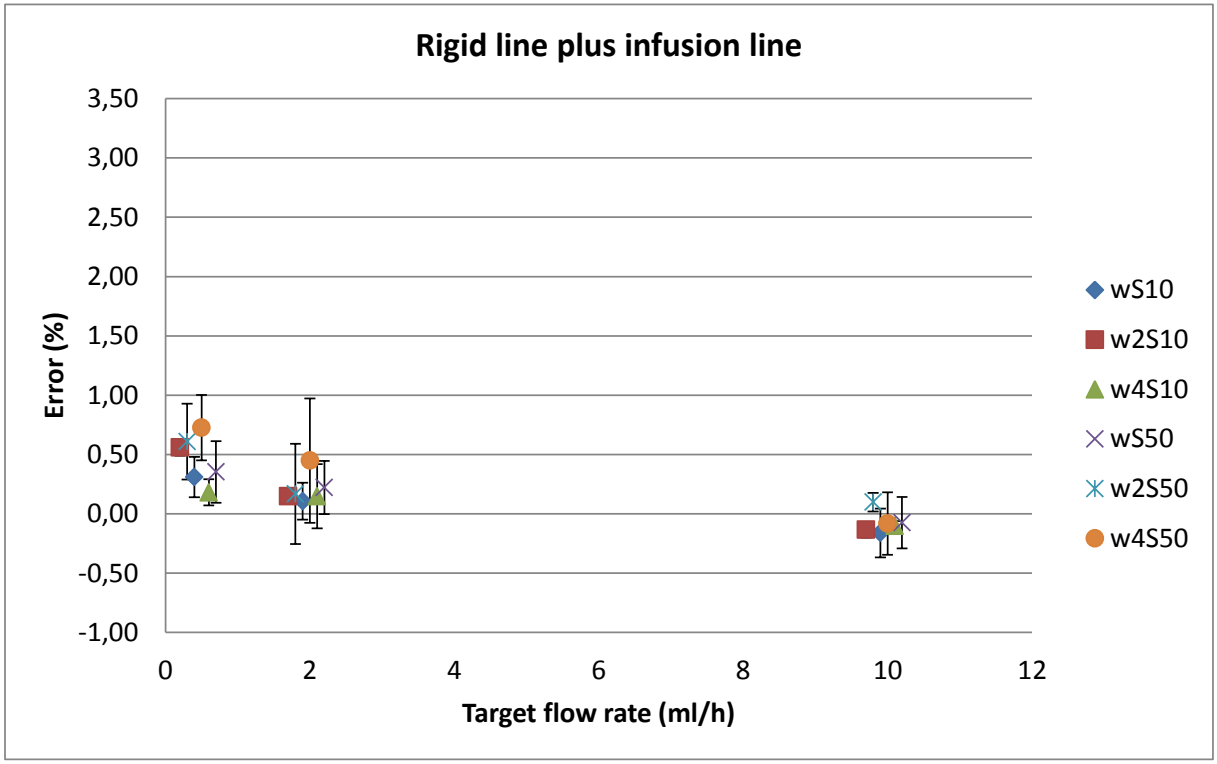

Figure 8 Relative flow rate error as function of the target flow rate and viscosity of the used liquid the pump connected to an infusion line and to the microflow setup. The relative flow rate error follows from the relative difference between the target flow rate and actual flow rate which is measured with the balance).

The results are shown in 9 and Figure 10 for the peristaltic pump.

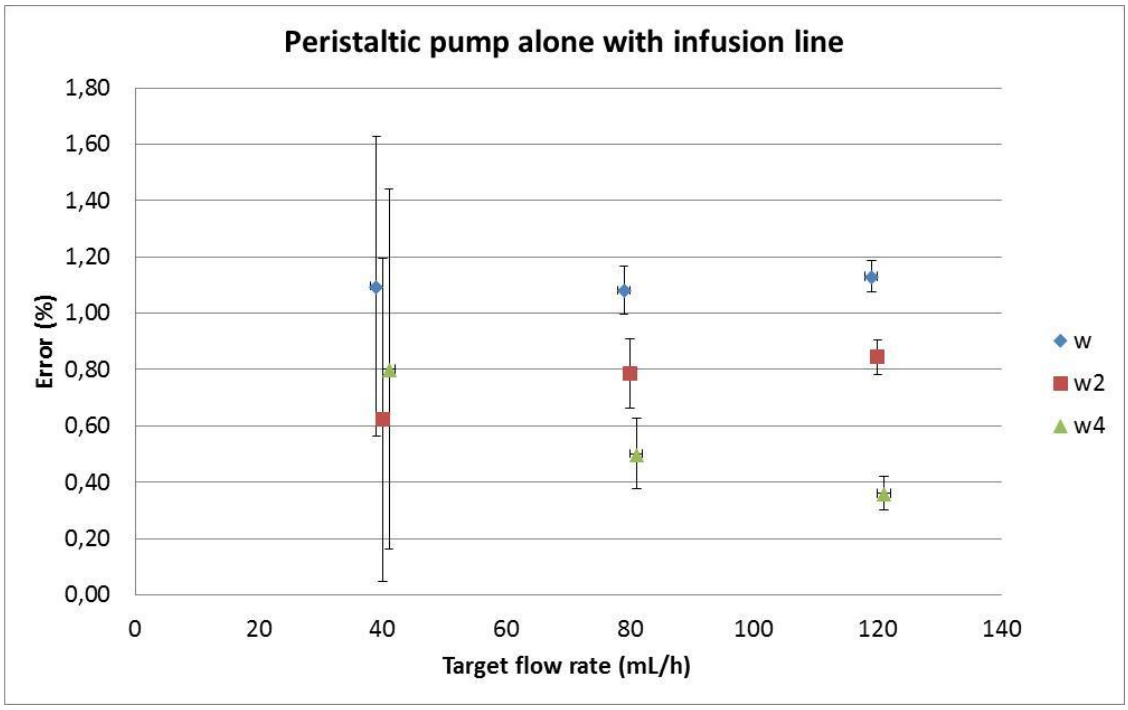

Figure 9 Relative flow rate error as function of the target flow rate and viscosity of the used liquid using only the peristaltic pump with the infusion line. The relative flow rate error follows from the relative difference between the target flow rate and actual flow rate which is measured with the balance).

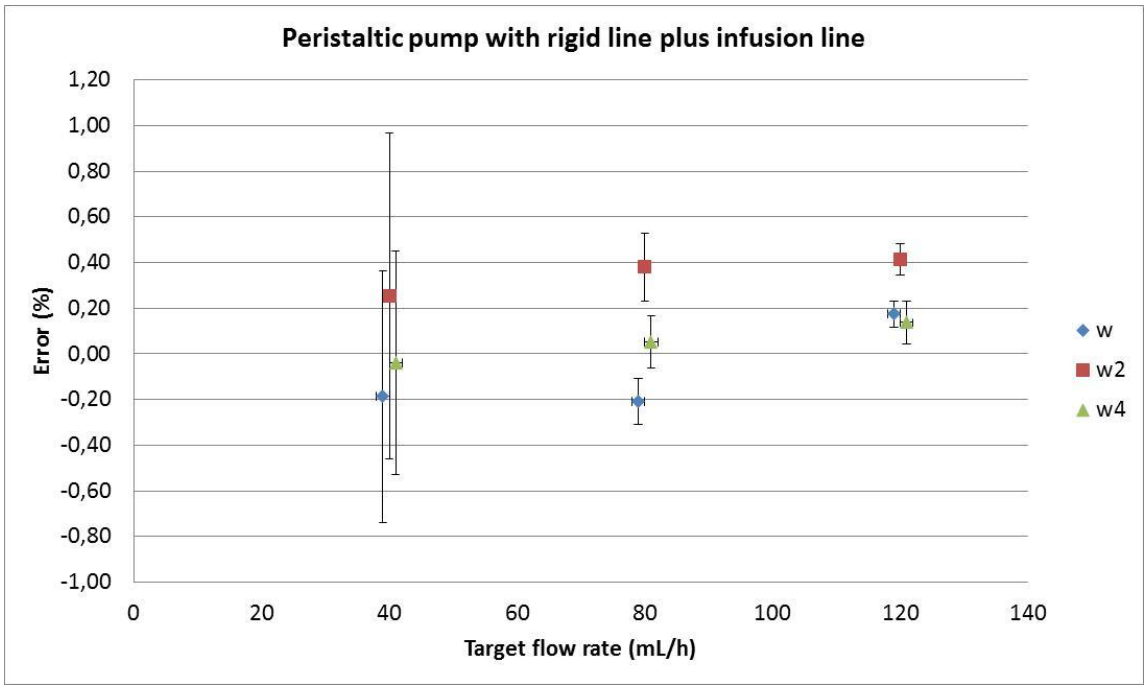

Figure 10 Relative flow rate error as function of the target flow rate and viscosity of the used liquid the peristaltic pump connected to an infusion line and to the microflow setup. The relative flow rate error follows from the relative difference between the target flow rate and actual flow rate which is measured with the balance).

The main conclusion are that the more viscous the liquid the less dead volume and therefore the larger the flow, the smaller the error.

6 Back pressure dependency

6.1 Motivation and goal

The goal of these series of tests is to determine the impact of the back pressure on the flow rate error. This is important to study because the compliance depends on the pressure. Note, the patient back pressure is roughly 13 mmHh, which corresponds to 17 mbar or 180 mmH20.

6.2 Equipment and scenarios

A syringe pump with two syringes: 10 mL (Omnifix) and 50 mL (OPS) is used for the investigations. The infusion pump will be directly connected to the rigid lines of the calibration bench such that the only source of compliance is from the syringe. The following back pressures are used: 24 mbar and 170 mbar, where the former roughly corresponds to the patient pressure.

6.3 Results and discussion

The results of the relative flow rate deviation as a function of the target flow rate and the applied back pressure at the outlet of the syringe are shown in Figures 11 and 12.

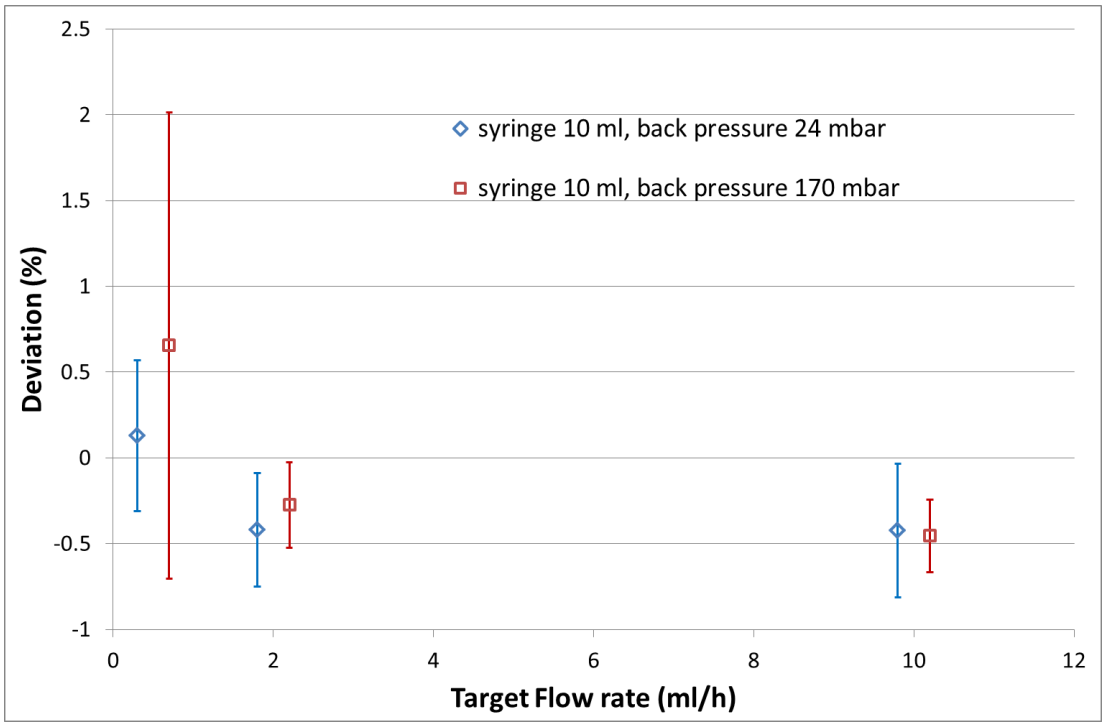

Figure 11 Relative flow rate deviation as function of the target flow rate and the applied back pressure at the outlet of the syringe of 10 ml.

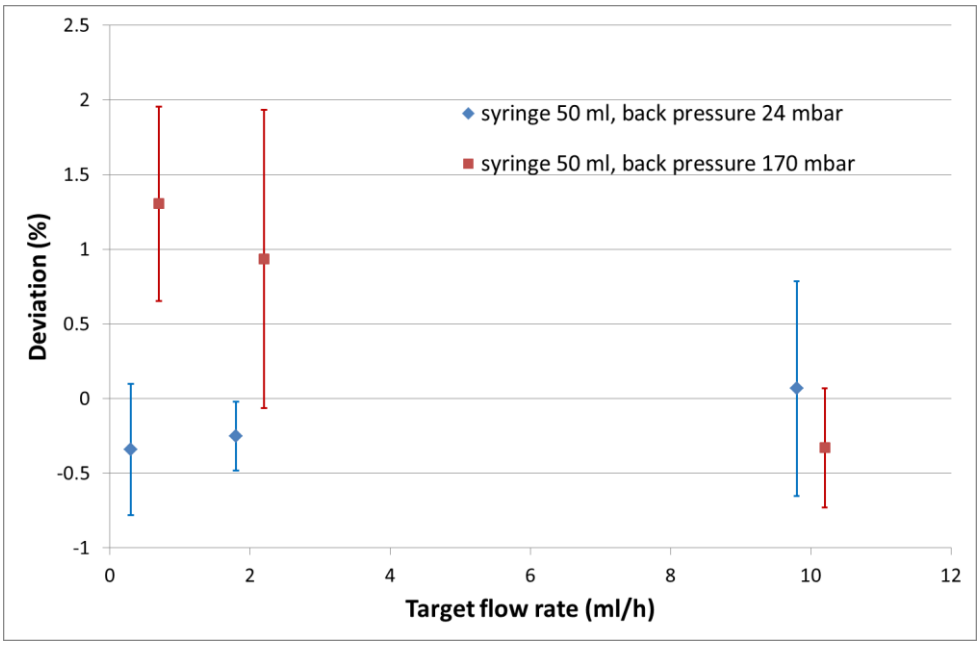

Figure 12 Relative flow rate deviation as function of the target flow rate and the applied back pressure at the outlet of the syringe of 50 ml.

In the case of the 10 ml syringe, the measured deviations show no dependence of the applied back pressure and are within the stated accuracy of ± 2 % of the manufacturer.

In the case of the 50 ml syringe, the measured deviations show no dependence of the applied back pressure for the flow rate of 10 ml/h. At lower flow rates (0.5 ml/h and 2 ml/h) the results are not consistent anymore for different back pressure. However, the discrepancy is still within the stated accuracy of ± 2 % of the manufacturer. Therefore, the results obtained for different back pressures are not significantly differing from what we can expect to measure.

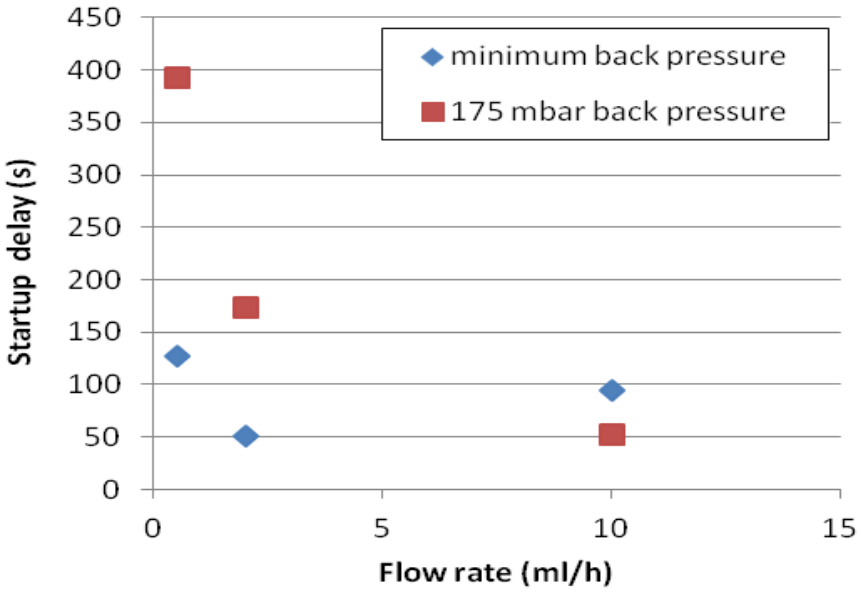

Figure 13 Start up delay as function of the back pressure.

7 Impact of temperature

7.1 Motivation and goal

The goal of these series of tests is to determine the impact of the temperature on the compliance, flow rate and flow rate stability.

7.2 Equipment and scenarios

The following equipment has been used:

- One syringe pump, two syringes: 10 mL (Omnifix) and 50 mL (OPS)
- 1 peristaltic pump.

The combination "pump alone and connected to the default connections of the micro flow set up" have been used.

This scenario has been tested using 3 different temperatures: 10, 20 and 30 degrees Celsius (water and ambient temperature) and various flow rates: 0.5 mL/h, 2 mL/h and 10 mL/h for the syringe pump and 2 mL/h, 10 mL/h and 50 ml/h for the peristaltic pump. Each measurement has been repeated 2 times.

7.3 Results and discussion

The results are shown in the following figures.

From the results the following can be observed:

- Compliance: The Compliance has been calculated as the ratio of volume increase to the measured increase in pressure after closing a downstream valve placed right after the device. The results show that Compliance globally increase with the temperature for all the tested configurations, even if it is less sensible for the syringe pump with the smallest syringe volume.
- Time to reach 50 % and 95 % of the final flow rate (start-up delay): from the results, we can say that the start-up delay is globally not affected by the temperature, despite some differences at the lowest tested flow rates.
- Stability: as expected, the stability decrease with the flow rate for all configurations, and with the temperature for the syringe pump with Omnifix 10 ml syringe and with the peristaltic pump.
- Relative error: globally, the relative error between reference and actual flow rates increases when the flow rate decreases, and increases when the temperature shift away from 20°C. This last point is most sensible for the Perfusor syringe pump.

Table 2. Compliance at 10 °C, 20 °C and 30 °C for various scenarios

Scenario	**10 °C**	**20 °C**	**30 °C**
Perfusor syringe pump with Omnifix 10 ml syringe	0.94	0.95	1.00
Perfusor syringe pump with OPS 50 ml syringe	2.08	2.05	2.84

Infusomat peristaltic pump with Infusomat Space line	0.92	0.96	1.13

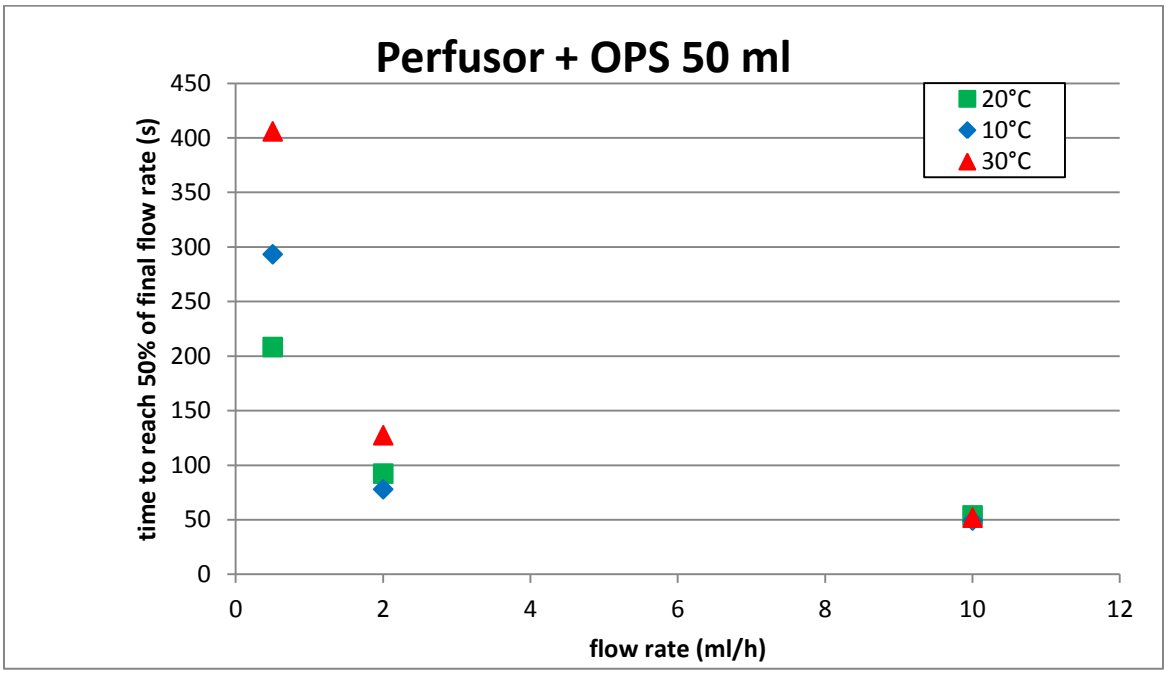

Figure 11: Time to reach 50% of final flow rate for the Perfusor syringe pump with the OPS 50 ml syringe

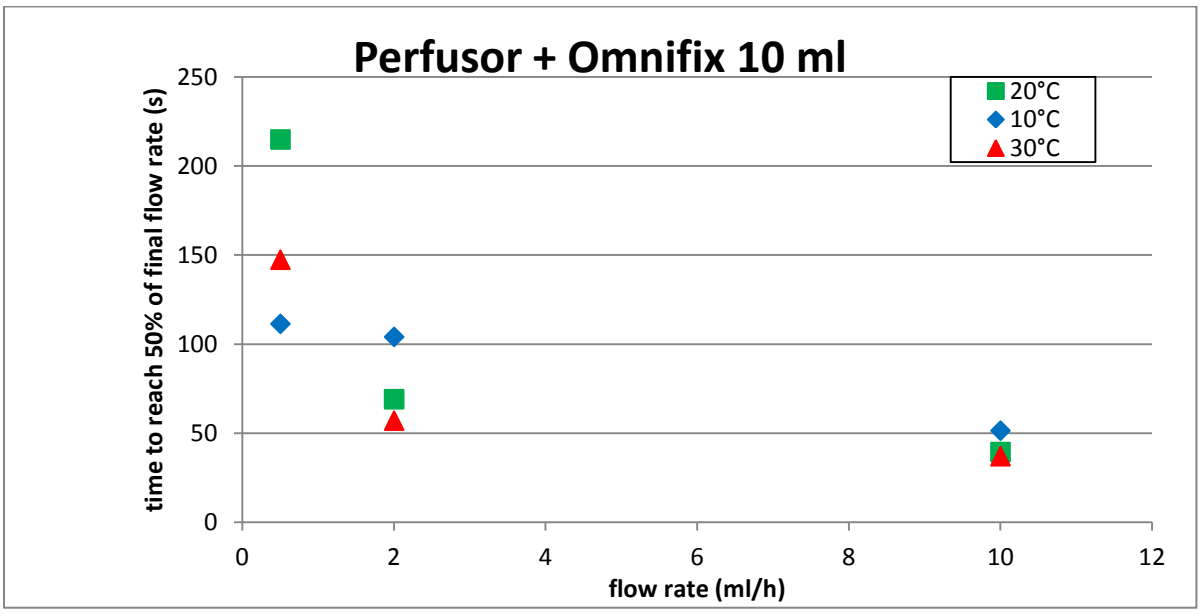

Figure 12: Time to reach 50% of final flow rate for the Perfusor syringe pump with the Omnifix 10 ml syringe

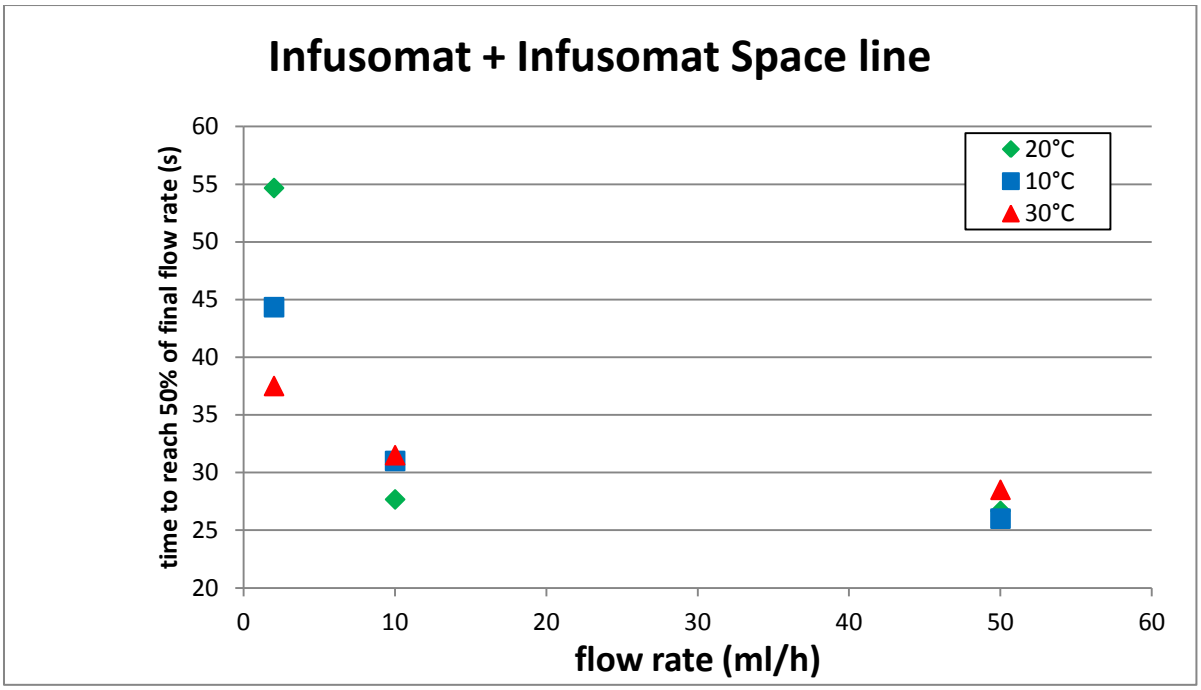

Figure 13: Time to reach 50% of final flow rate for the infusomat peristaltic pump with the Infusomat Space Line

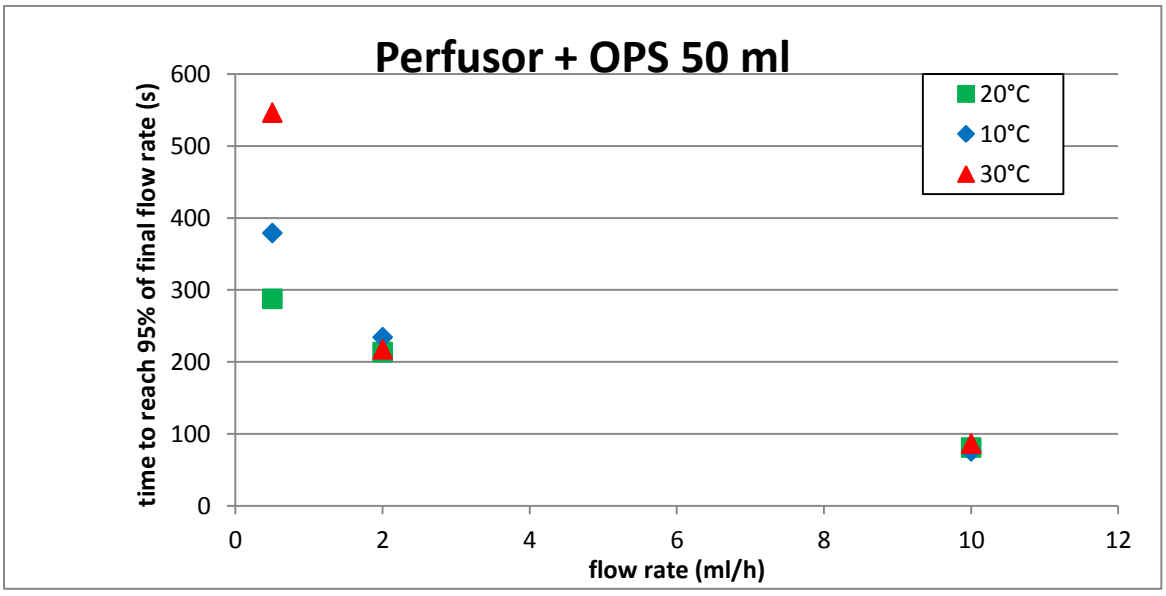

Figure 14: Time to reach 95% of final flow rate for the Perfusor syringe pump with the OPS 50 ml syringe

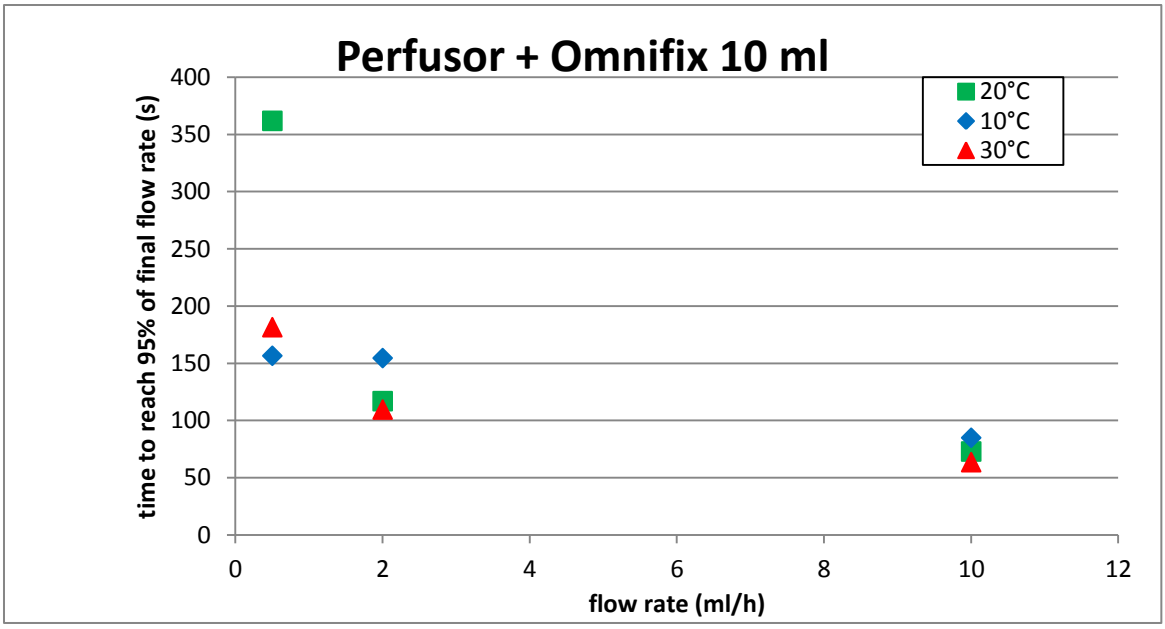

Figure 15: Time to reach 95% of final flow rate for the Perfusor syringe pump with the Omnifix 10 ml syringe

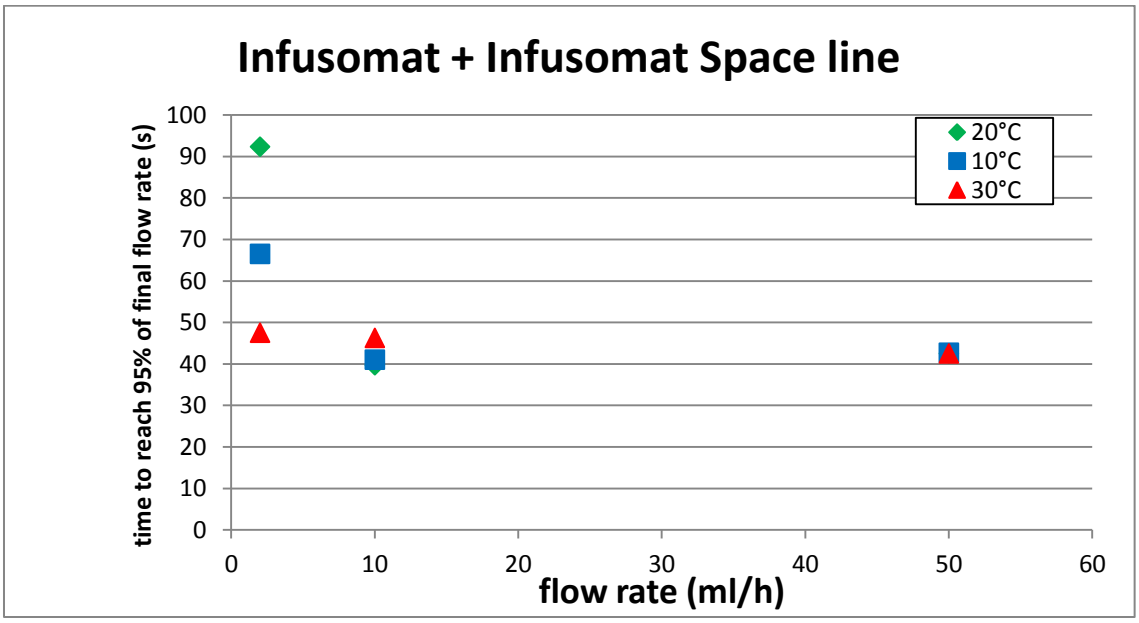

Figure 16: Time to reach 95% of final flow rate for the Infusomat peristaltic pump with the Infusomat Space Line

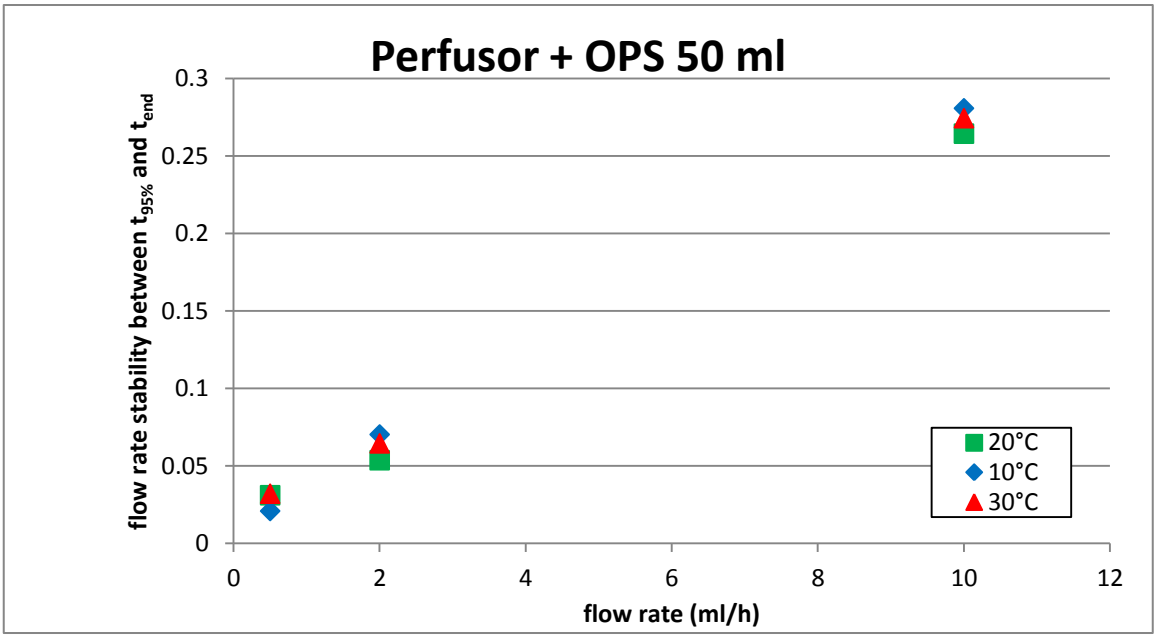

Figure 20: flow rate stability between $t_{95\%}$ and t_{end} for the Perfusor syringe pump with the OPS 50 ml syringe

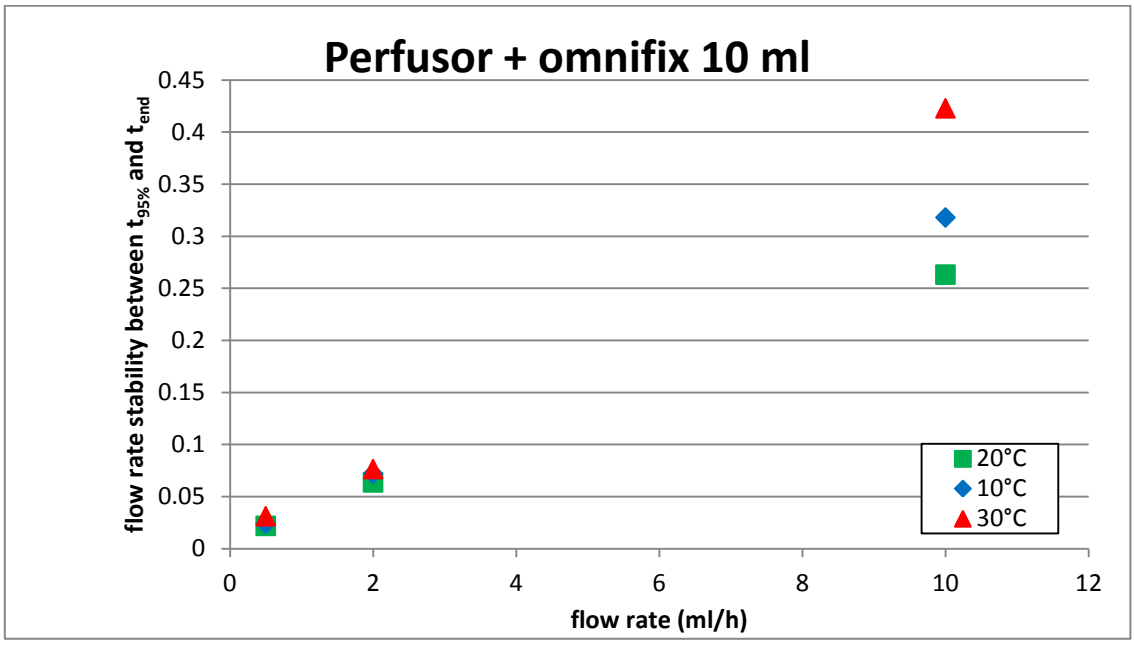

Figure 7: flow rate stability between $t_{95\%}$ and t_{end} for the Perfusor syringe pump with the Omnifix 10ml syringe

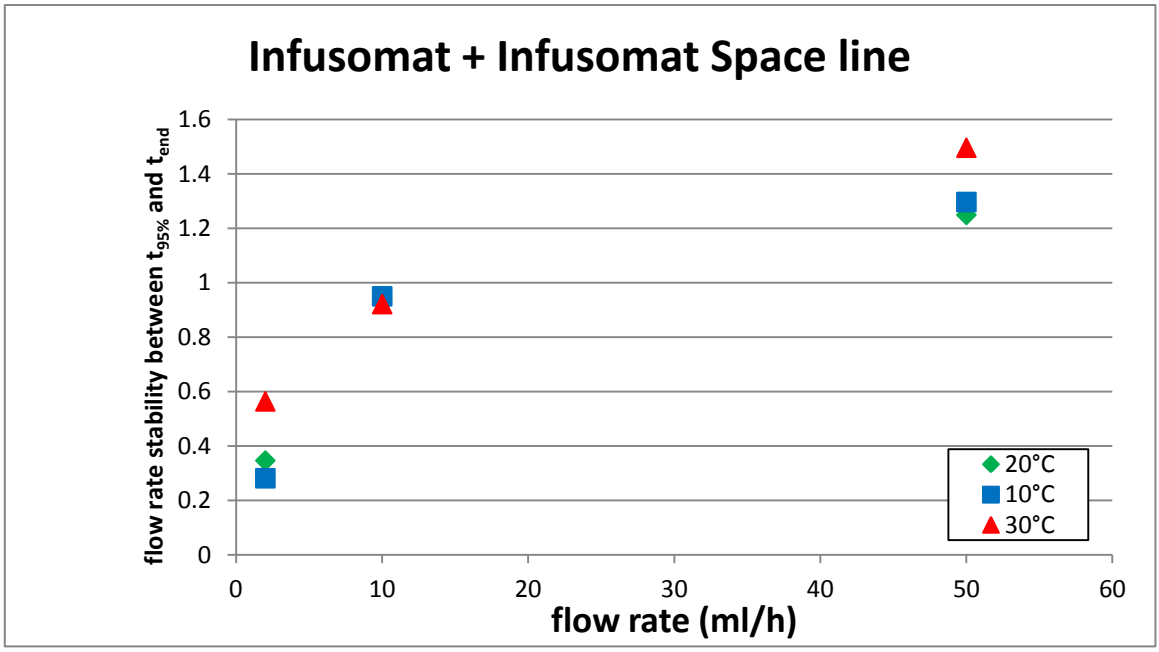

Figure 8: flow rate stability between t95% and tend for the Infusomat peristaltic pump with the Infusomat Space Line

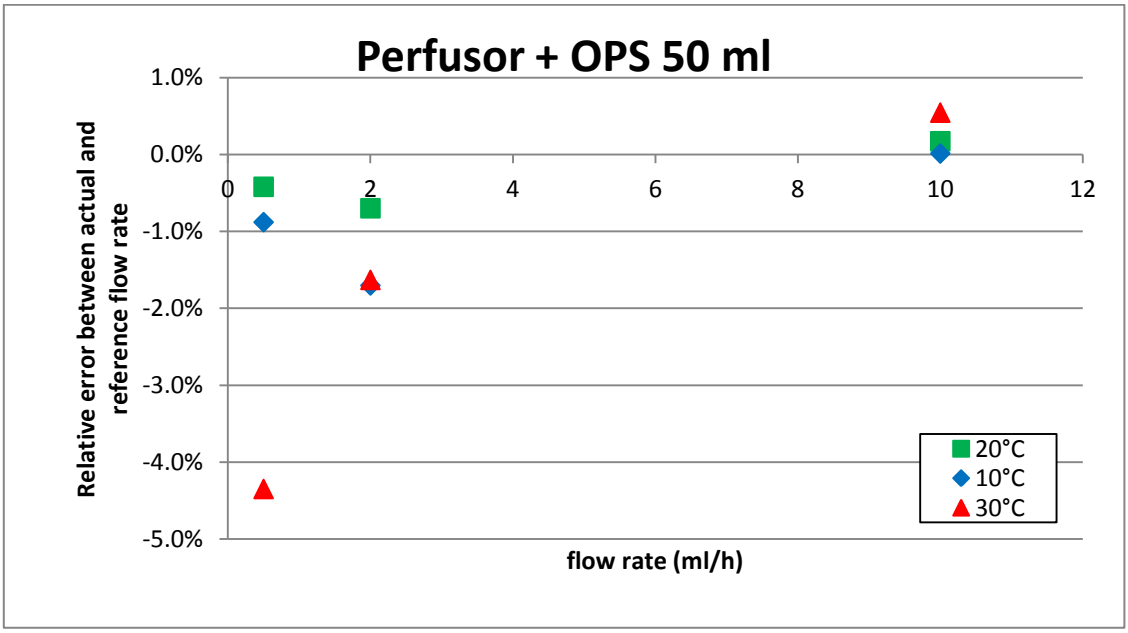

Figure 9: Relative error between actual and reference flow rate for the Perfusor syringe pump with the OPS 50 ml syringe

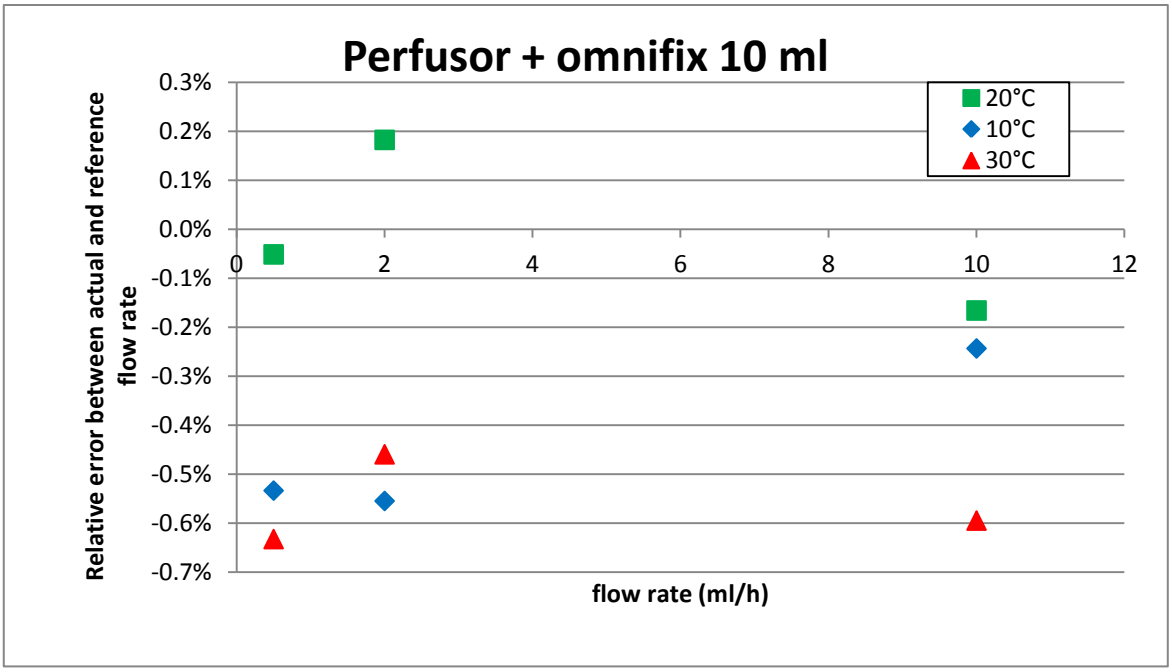

Figure 10: Relative error between actual and reference flow rate for the Perfusor syringe pump with the Omnifix 10 ml syringe

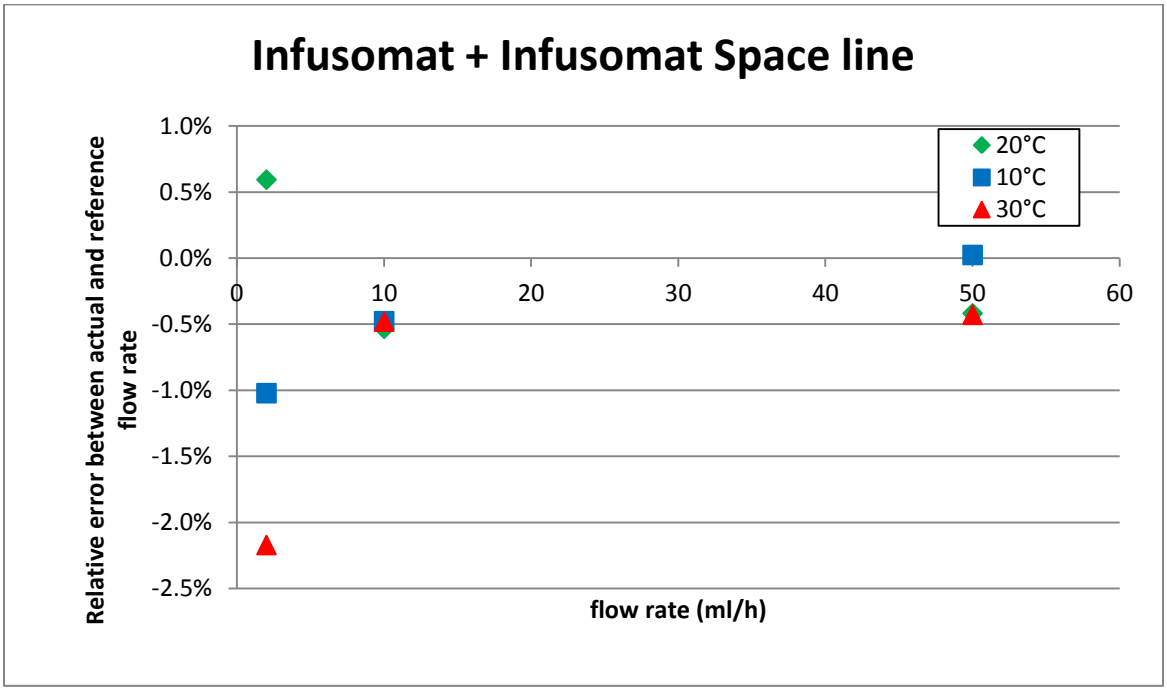

Figure 11: Relative error between actual and reference flow rate for the Infusomat peristaltic pump with the Infusomat Space Line

8 Impact of make, model and procedure (reproducibility)

8.1 Motivation and goal

To determine the reproducibility of drug delivery devices. Here, reproducibility should be interpreted in a wider sense than typically used in metrology, i.e. more like how the flow rate will reproduce for different brands, makes, etc. for the 'replaceable' elements of syringe and peristaltic pumps. The reproducibility will analyzed base on three main different study:

- "Flow Rate Reproducibility Dependency on Different Syringes"
- "Flow Rate Dependency on the Syringe Plunger Level or Position l"
- "Flow Rate Dependency on the Administration Set Length"

8.2 Equipment and scenarios

The following equipment is used for the assessment of the drug delivery devices reproducibility:

- Syringe Pump (Braun /Perfusor Space)
- Syringes:
  - 10 mL (Braun- Omnifix) (LOT:1k10048)-(BD-Plastipak) (LOT:4203728)
  - 50 ml (Braun-OPS) (LOT:10M1082022)- (Terumo) (LOT:1301011)
- Needles Gauge IDEX (ID:762µm-Length:250mm/ID:180µm-Length:250mm)
- Peristaltic Pump (Braun /Infusomat Space)
- Administrations Set (Braun /Infusomat Space Line)(300/200cm)-(250/145cm)
- BBraun (Water Bi-distillated)(Lot:14024413)(only for peristaltic pump)
- Flow Meter: Sensirion [SLI_0430(up to 4.8 mL/h)- SLI_1000(up to 60mL/h)

The following test set up will be investigated:

1 - Syringe Pump with standard syringe (OPS /Omnifix/Terumo/BD Plastipak) and connected to the default connections of the micro flow set up. That is, from the pump via rigid tubing via a dispensing needle into the measurement beaker. (Every test is performed with a new syringe) Working flow rate: 0.5 mL/h and 10 mL/h) (scenario 2)

2 - Syringe Pump with syringe standard (OPS(50mL) /Omnifix(10mL)) and connected to a flow meter via rigid tubing ending in the dispensing needle. Working flow rate: 0.5 mL/h and 10 mL/h

3 - Peristaltic Pump connected to a typical infusion line (1.5 m) and then via a dispensing needle into the measurement beaker. Working flow rate: 2 mL/h and 10 mL/h.

4 - Pump connected to a typical infusion line (2 m) and then via the default micro flow set up into the measurement beaker. Working flow rate: 2 mL/h and 10 mL/h. (scenario 3)

Figure 26 Setup of Reproducibility Dependency on Different Syringes

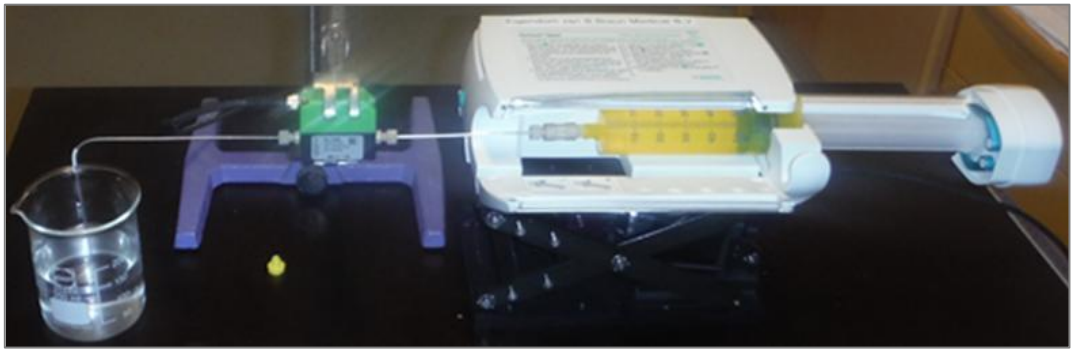

Figure 27 Setup of Flow Rate Dependency on the Syringe Plunger Level

Figure 128 Setup of Flow Rate Dependency on the Administration Set Length

8.3 Results

8.3.1 Syringe Pump Study: "Flow Rate Reproducibility Dependency on Different Syringes"

Table 3. Flow Rate Reproducibility Dependency on Different Syringes

Mean Flow and % Standard Deviation								
Target Flow Rate Value (mL/hr)								
0.5	Braun(50mL)		Terumo (50mL)		Braun(10mL)		BD Plastipak(10mL)	
	Mean Value	%Std Dev	Mean Value	%Std Dev	Mean Value	%Std Dev	Mean Value	%Std Dev
	0.477	2.74%	0.518	3.69%	0.495	3.20%	0.453	3.33%
	0.468	2.67%	0.488	2.82%	0.490	6.27%	0.443	3.55%
	0.487	7.48%	0.478	3.72%	0.502	5.02%	0.459	7.34%
10	Braun(50mL)		Terumo (50mL)		Braun(10mL)		BD Plastipak(10mL)	
	Mean Value	%Std Dev	Mean Value	%Std Dev	Mean Value	%Std Dev	Mean Value	%Std Dev
	10.032	2.57%	9.968	2.18%	10.038	1.08%	9.185	1.43%
	10.006	1.59%	10.120	1.31%	10.105	1.18%	9.182	2.49%
	9.885	1.32%	9.899	2.25%	10.102	1.48%	9.009	1.40%

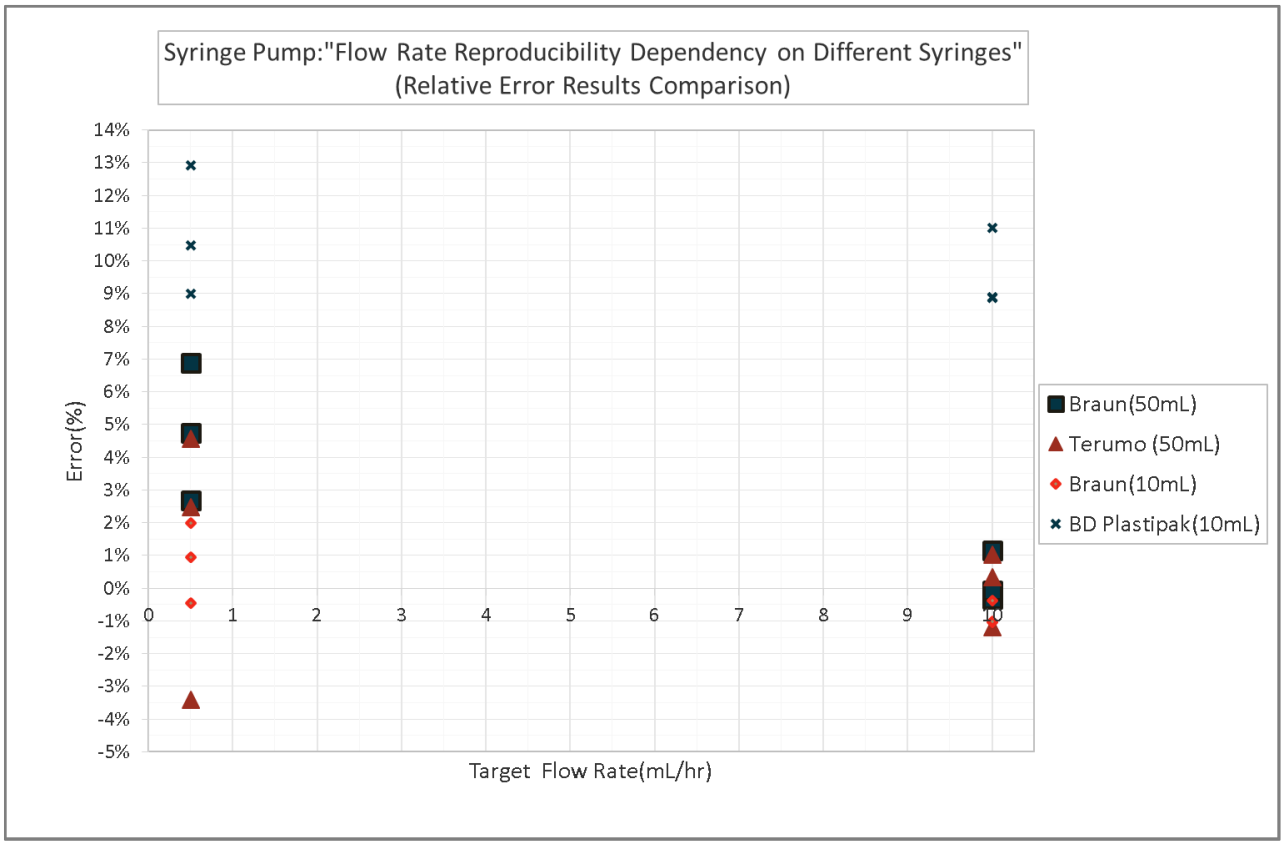

Figure 29 Relative Error of Different Syringes

8.3.2 Syringe Pump: "Flow Rate Dependency on the Syringe Plunger Level"

8.3.2.1 Syringe Braun (50mL) at 0.5 mL/h

Table 4 - Syringe Braun (50 mL-10 mL) at 0.5 mL/h

Mean Flow /Std.Deviation/%Error						
Target Flow (mL/hr)	Braun(50mL)			Braun(10mL)		
	Mean	%Std Dev	%Error	Mean	%Std Dev	%Error
0.5	0.495	2.09%	1.10%	0.505	3.89%	-0.92%

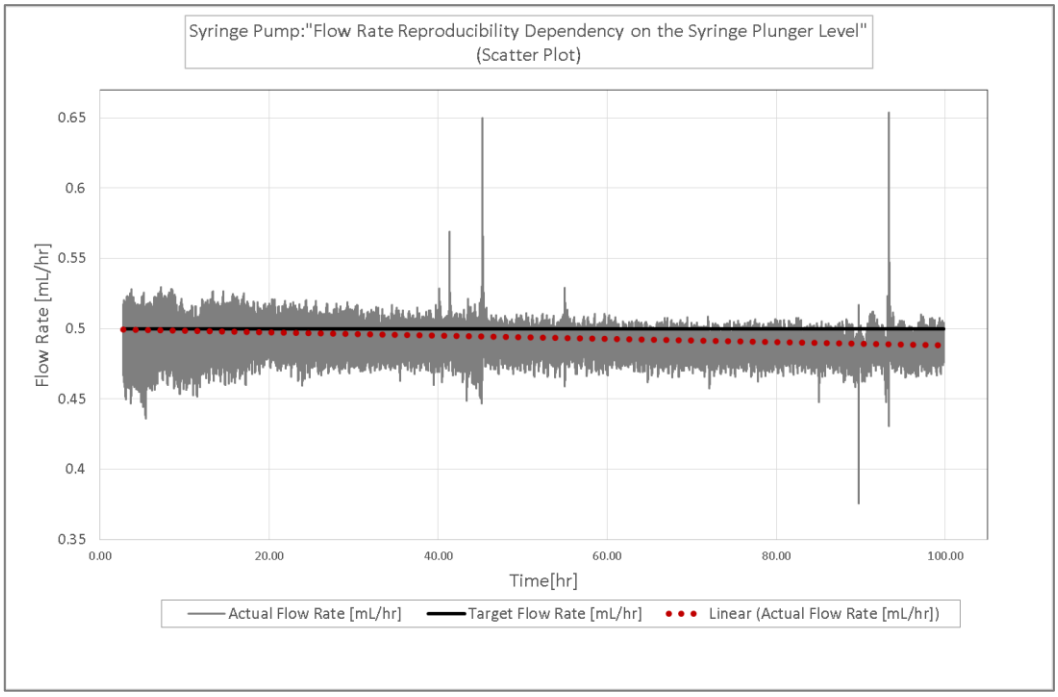

Figure 30 Syringe Braun (50mL) at 0.5 mL/h (Complete Test)

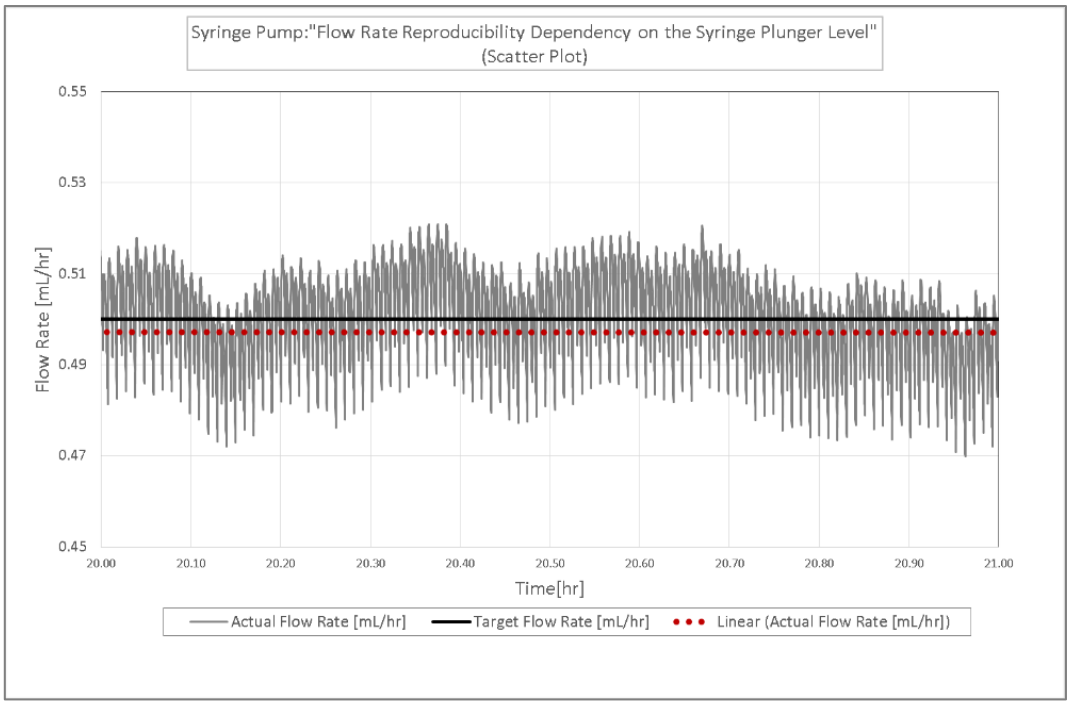

Figure 31 Syringe Braun (50mL) at 0.5 mL/hr (1 Hour Interval)

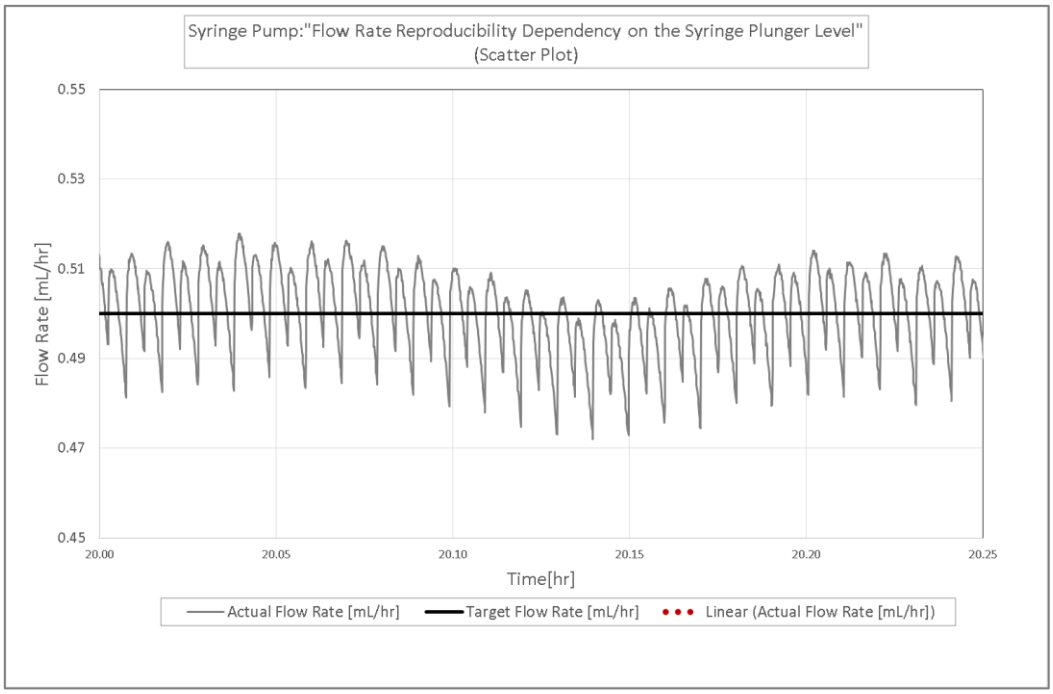

Figure 32 Syringe Braun (50mL) at 0.5 mL/h (15min Interval)

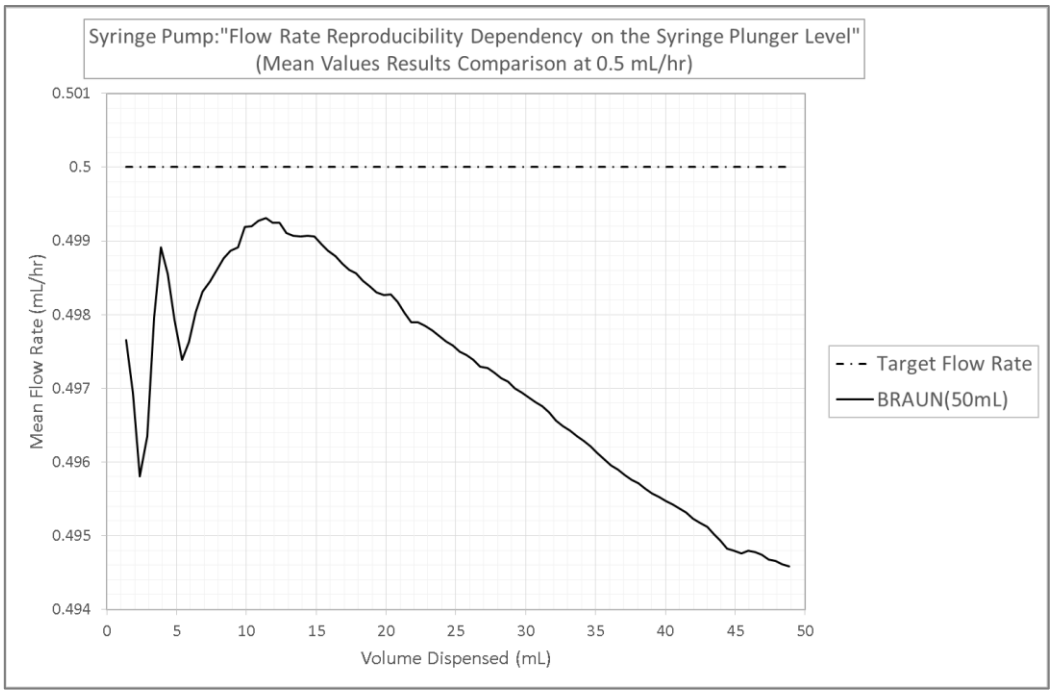

Figure 33 Syringe Braun (50mL) at 0.5 mL/h (Mean Flow/Volume Dispensed)

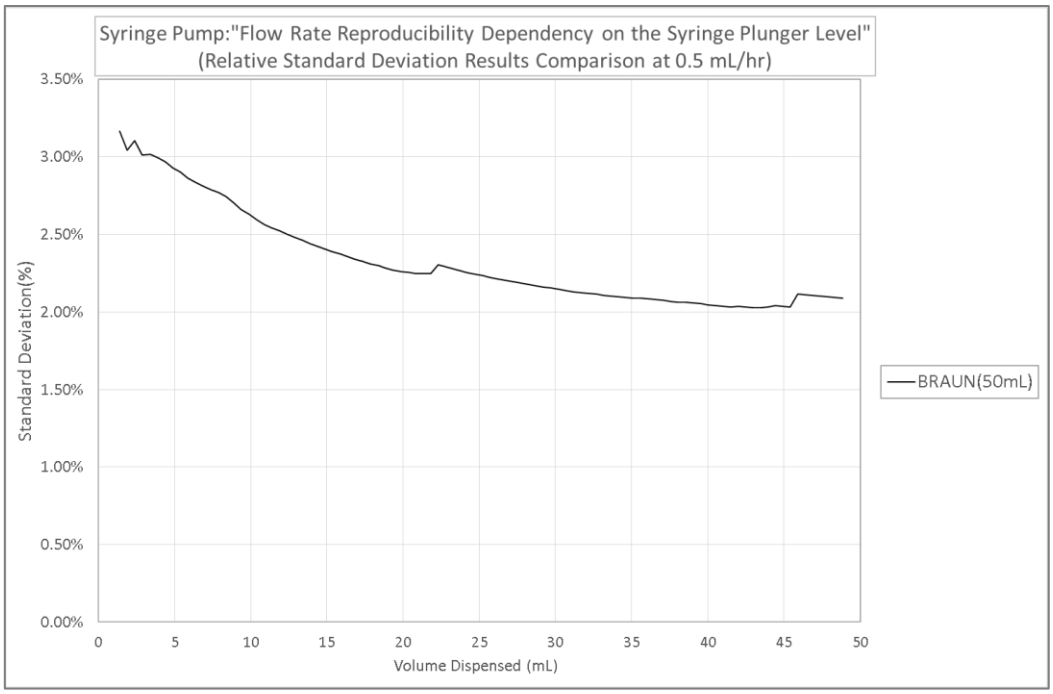

Figure 34 Syringe Braun (50mL) at 0.5 mL/h (Standard /Volume Dispensed)

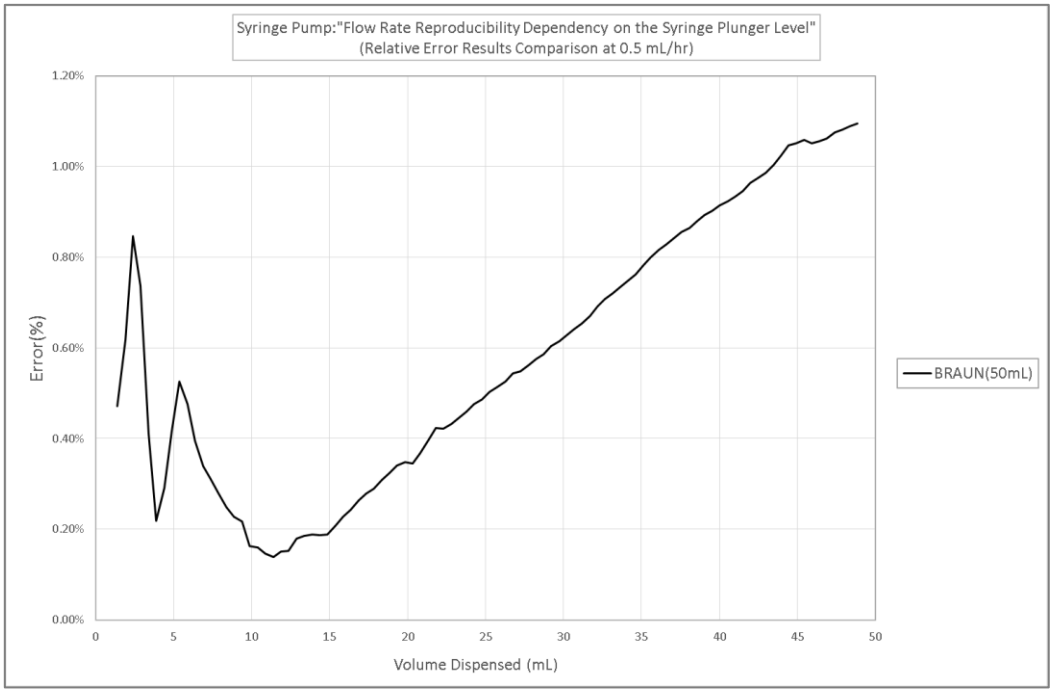

Figure 35 Syringe Braun (50mL) at 0.5 mL/h (%Error/Volume Dispensed)

8.3.2.2 Syringe Braun (10mL) at 0.5 mL/hr

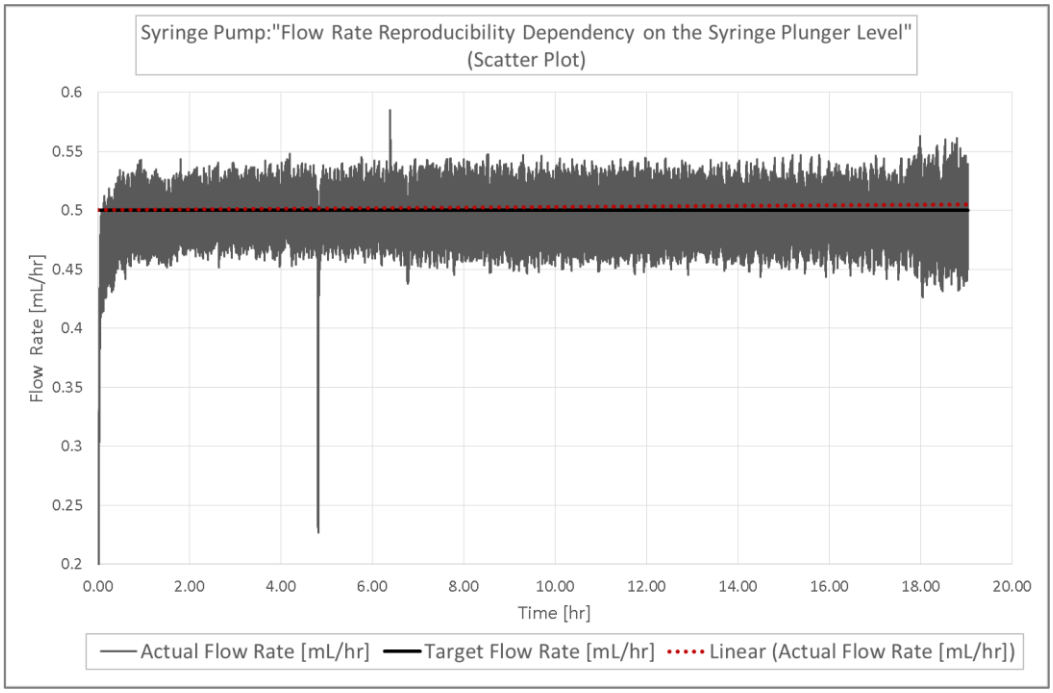

Figure 36 Syringe Braun (10mL) at 0.5 mL/h (Complete Test)

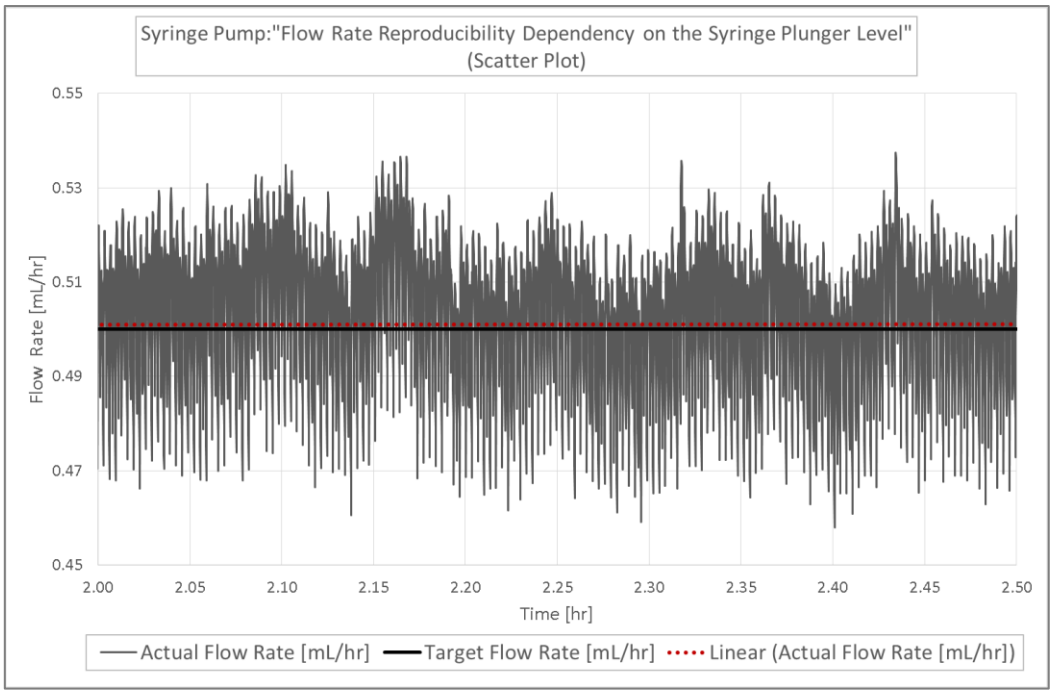

Figure 37 Syringe Braun (10mL) at 0.5 mL/h (Half hour Interval)

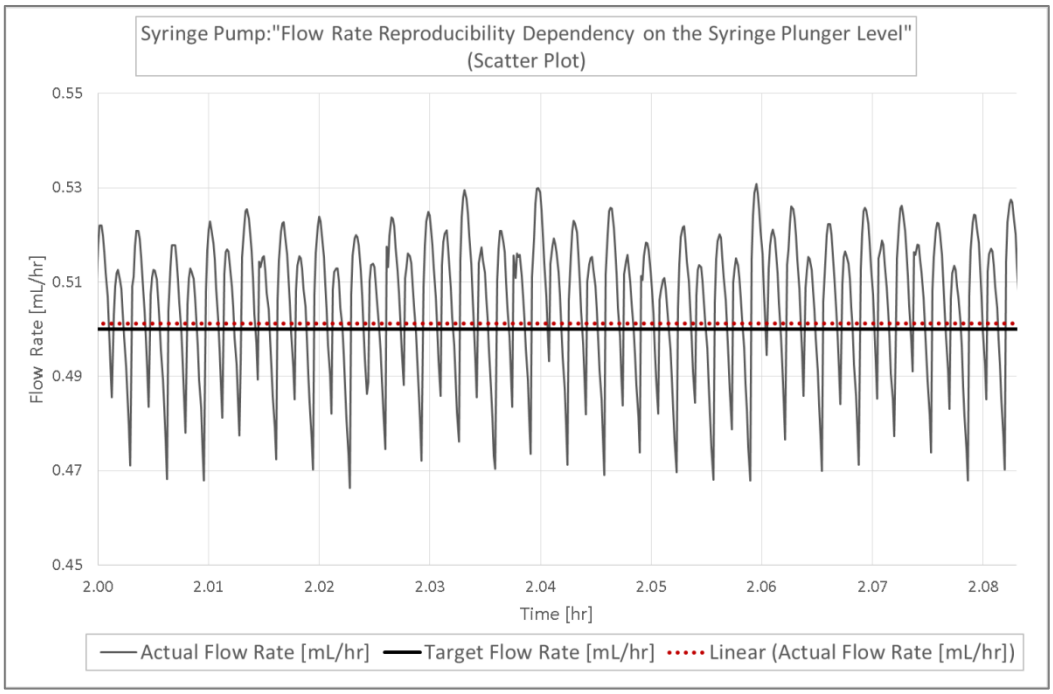

Figure 38 Syringe Braun (10mL) at 0.5 mL/h (5min Interval)

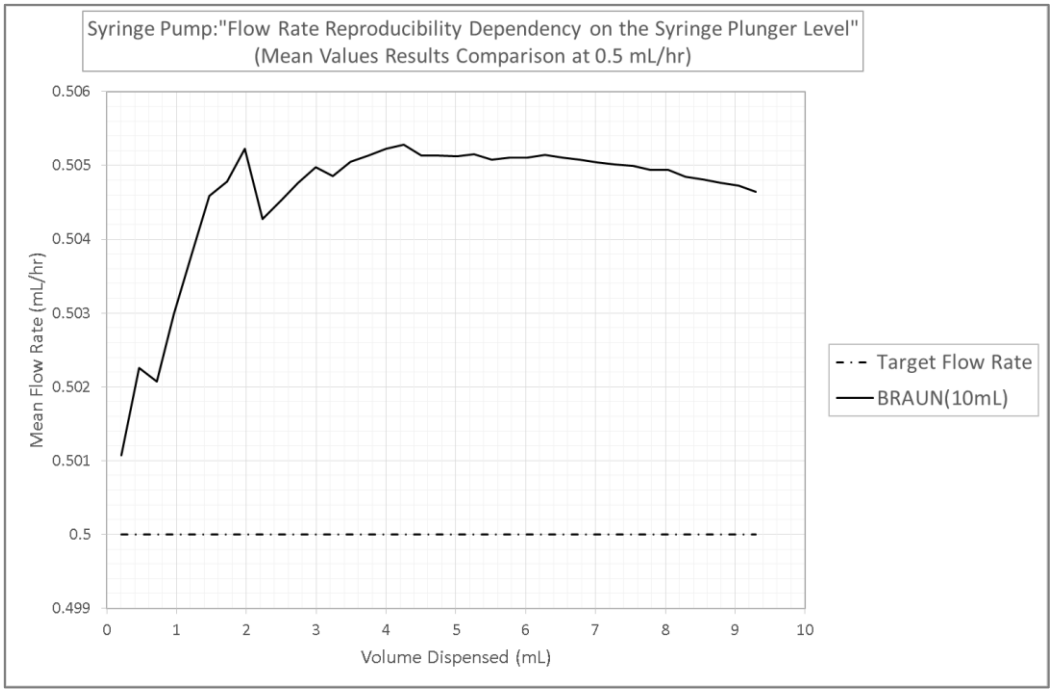

Figure 39 Syringe Braun (10mL) at 0.5 mL/h (Mean Flow/Volume Dispensed)

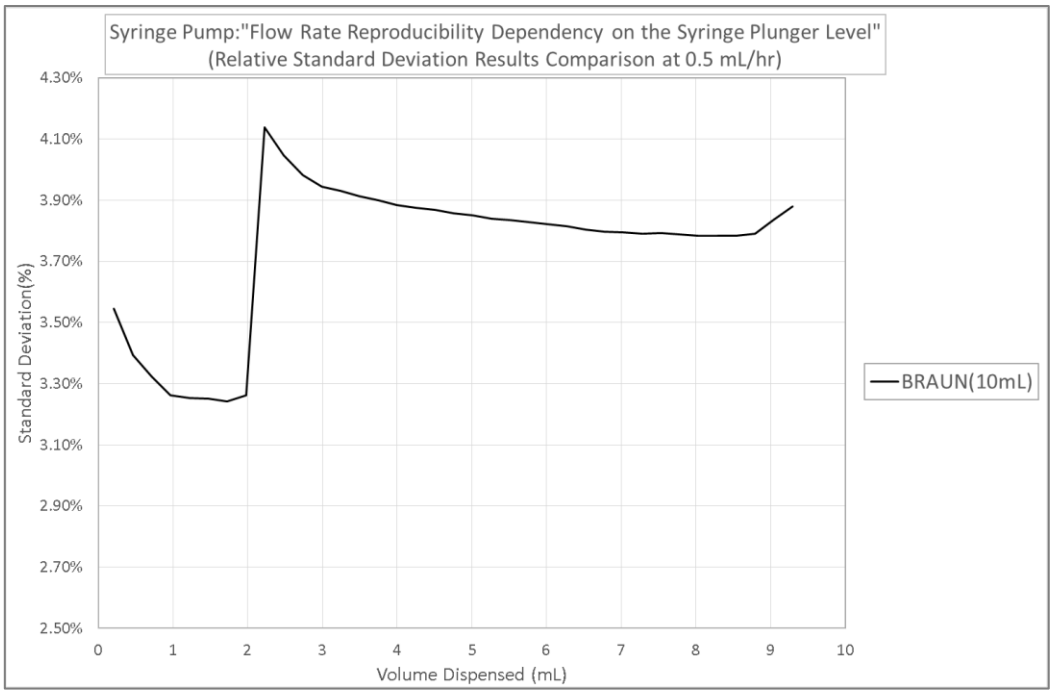

Figure 40 Syringe Braun (10mL) at 0.5 mL/h (Standard /Volume Dispensed)

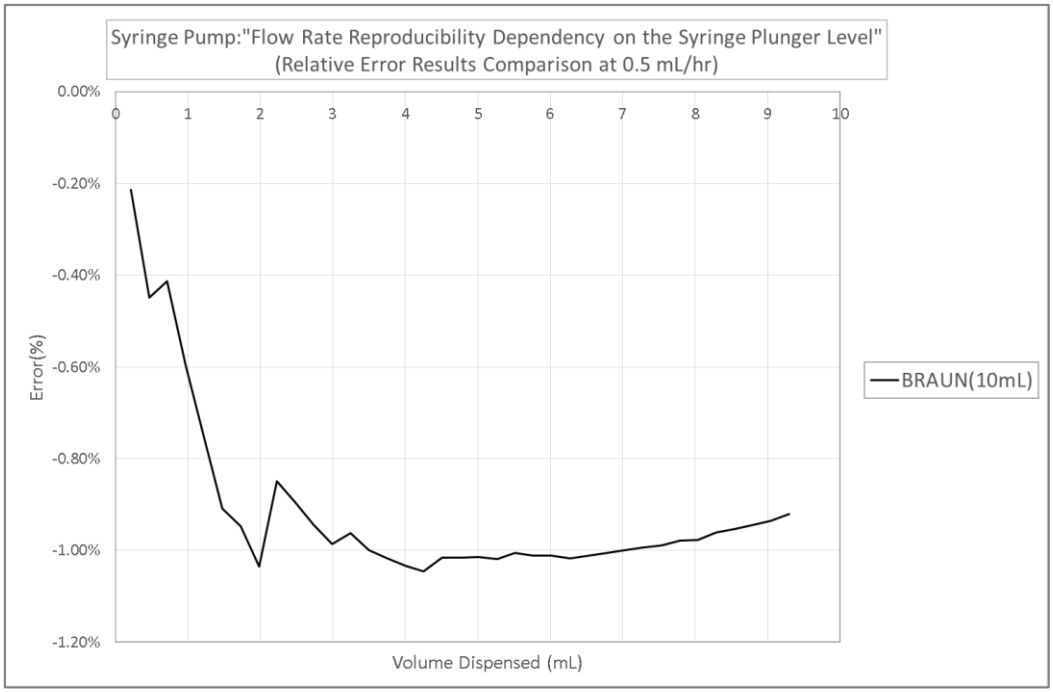

Figure 41 Syringe Braun (10mL) at 0.5 mL/h (%Error/Volume Dispensed)

8.3.2.3 Syringe Braun (50mL) at 10 mL/h

Mean Flow /Std.Deviation/%Error						
Target Flow (mL/hr)	Braun(50mL)			Braun(10mL)		
	Mean	%Std Dev	%Error	Mean	%Std Dev	%Error
10	9.832	0.89%	1.71%	9.883	1.28%	1.18%

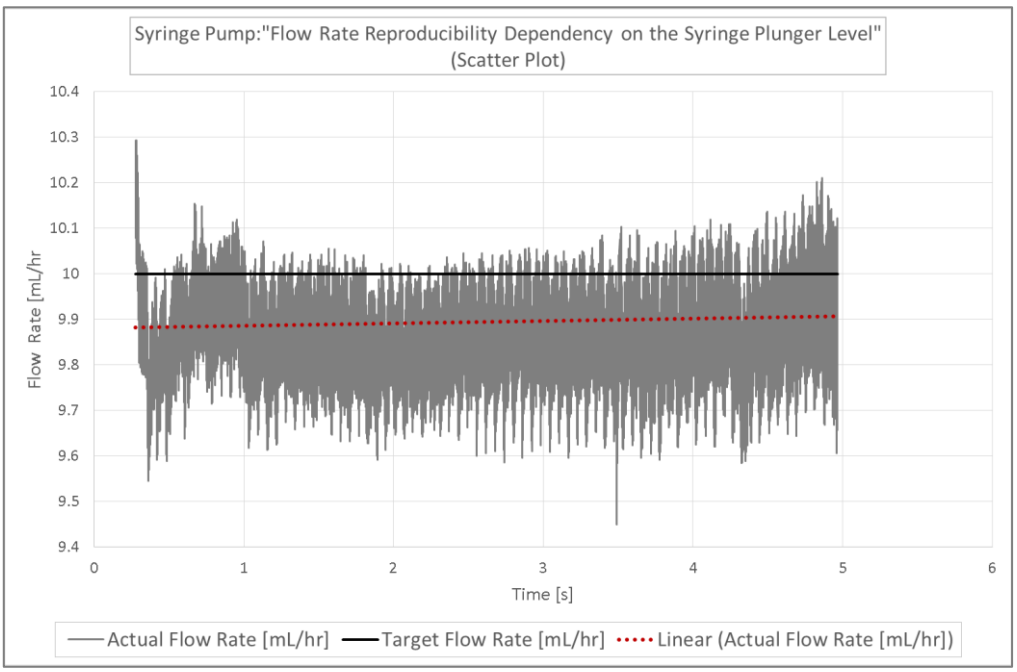

Figure 43 Syringe Braun (50mL) at 10 mL/h (Complete Test)

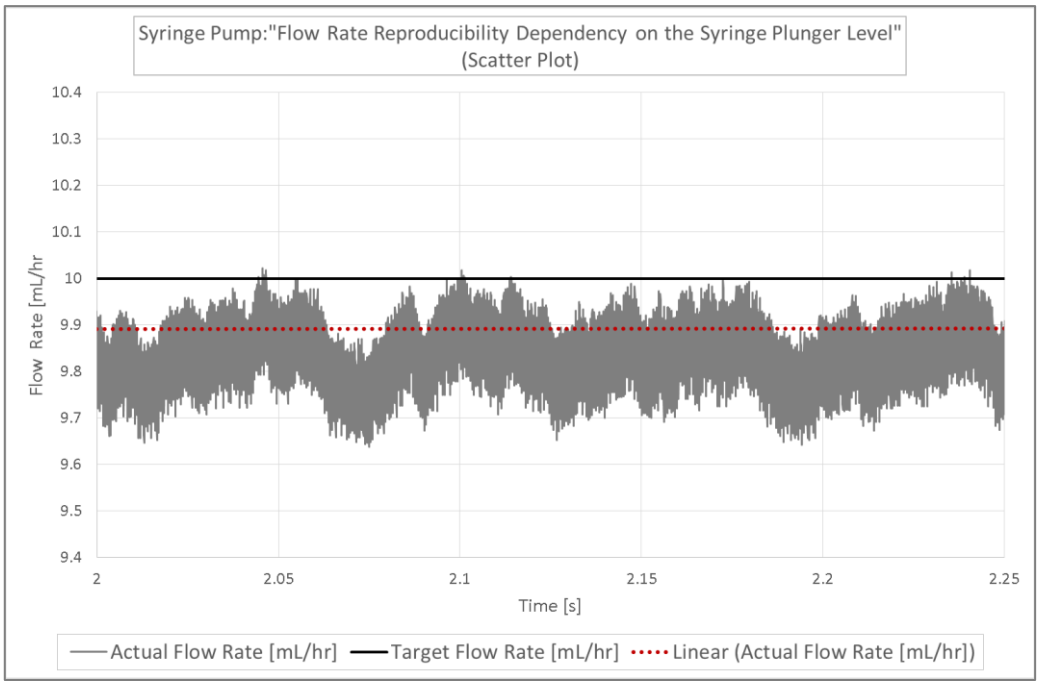

Figure 44 Syringe Braun (50mL) at 10mL/h (15min Interval)

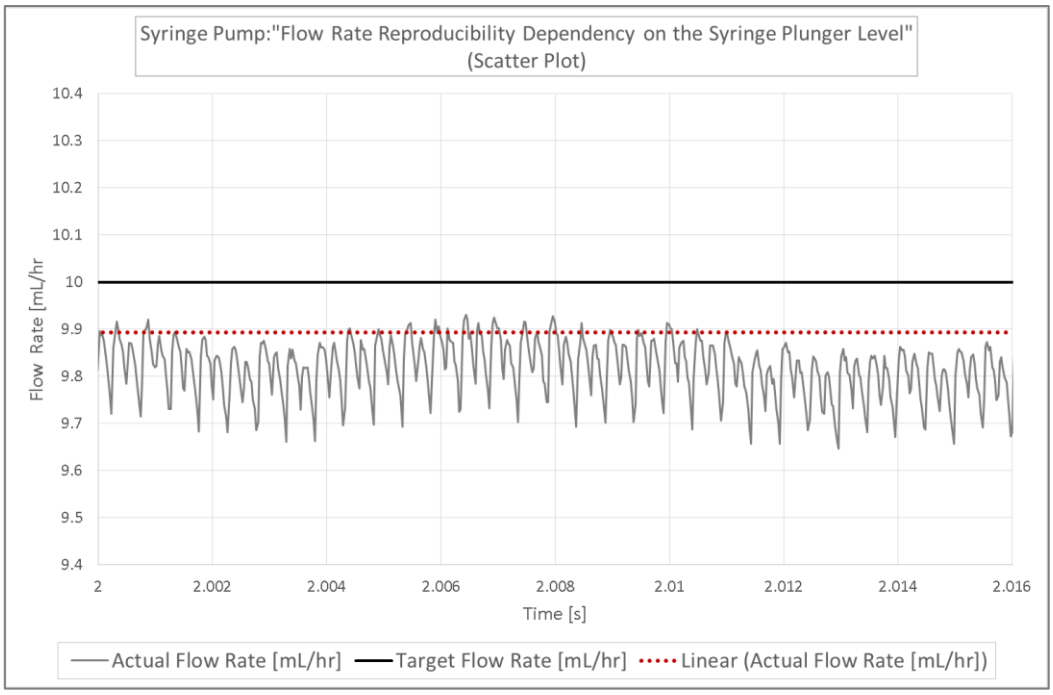

Figure 45 Syringe Braun (50mL) at 10mL/h (1min Interval)

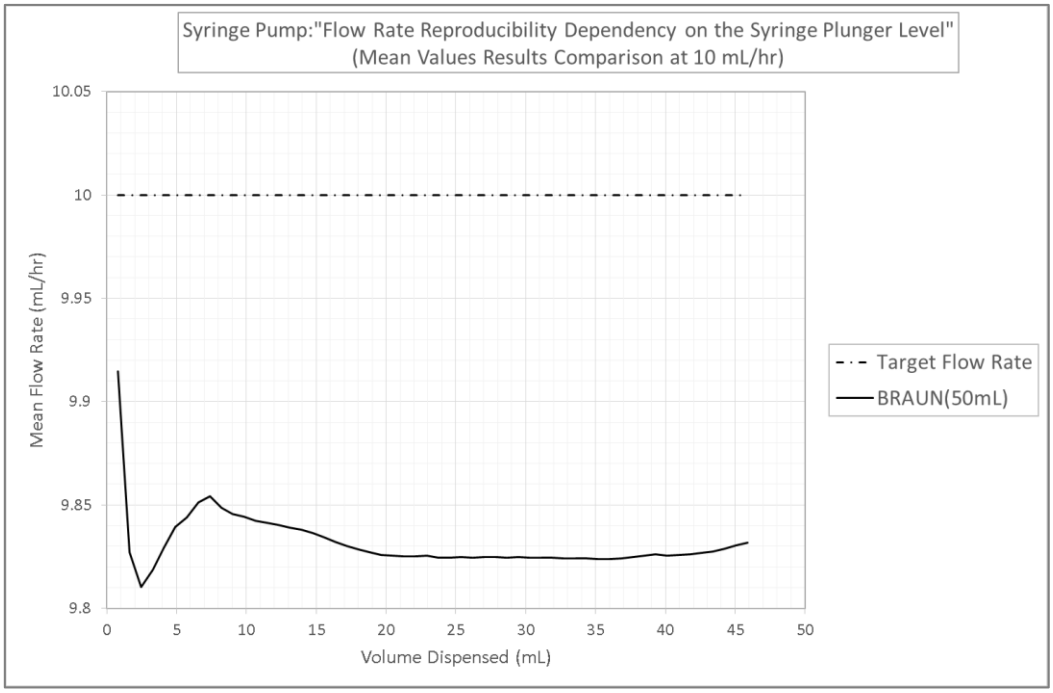

Figure 46 Syringe Braun (50mL) at 10 mL/h (Mean Flow/Volume Dispensed)

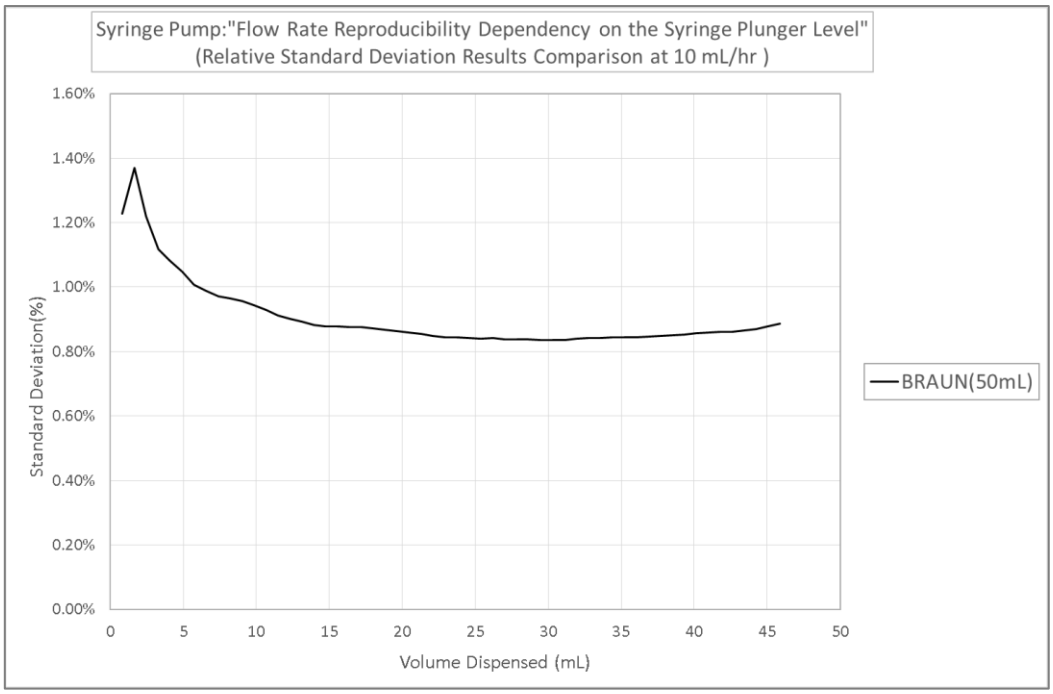

Figure 47 Syringe Braun (50mL) at 10 mL/h (Standard Dev. /Volume Dispensed)

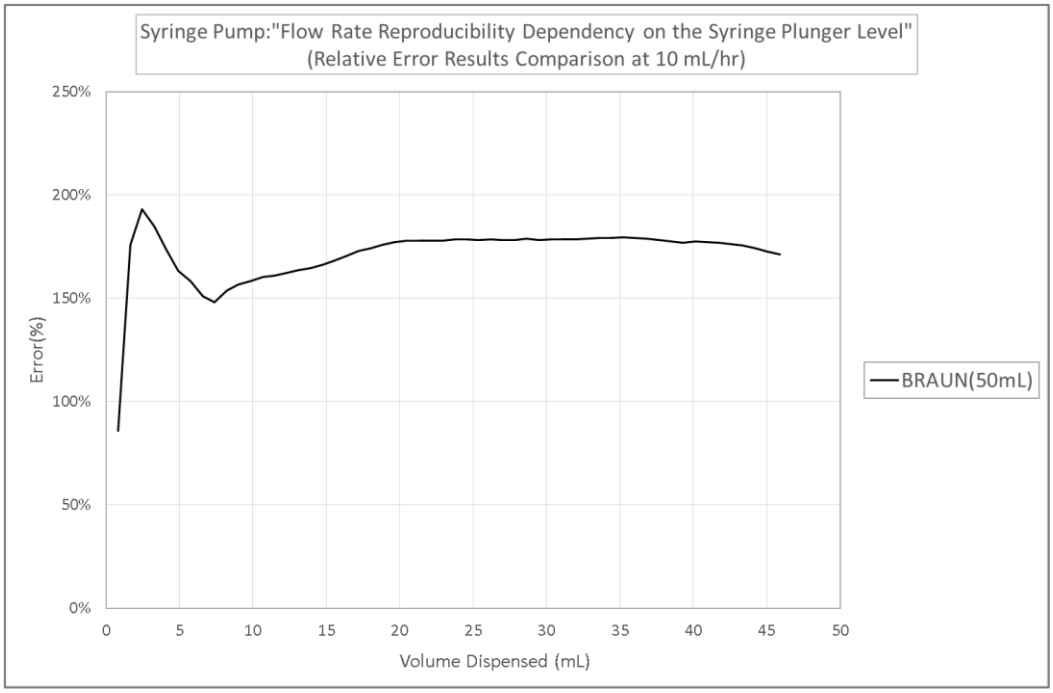

Figure 48 Syringe Braun (50mL) at 10 mL/h (%Error/Volume Dispensed)

8.3.2.4 Syringe Braun (10mL) at 10 mL/h

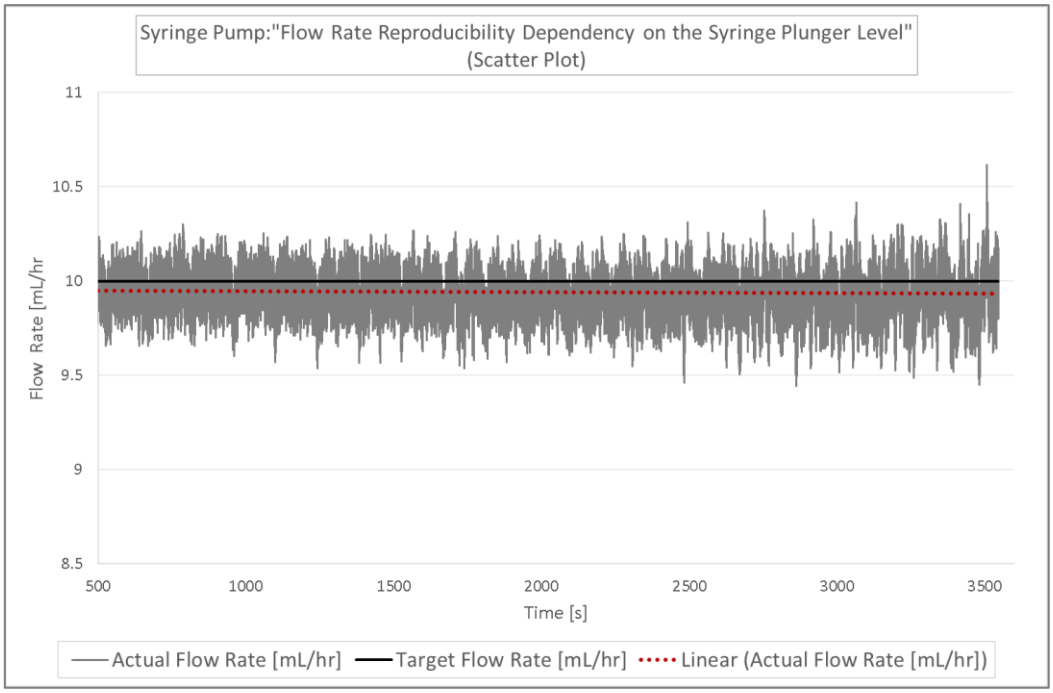

Figure 49 Syringe Braun (10mL) at 10 mL/h (Complete Test)

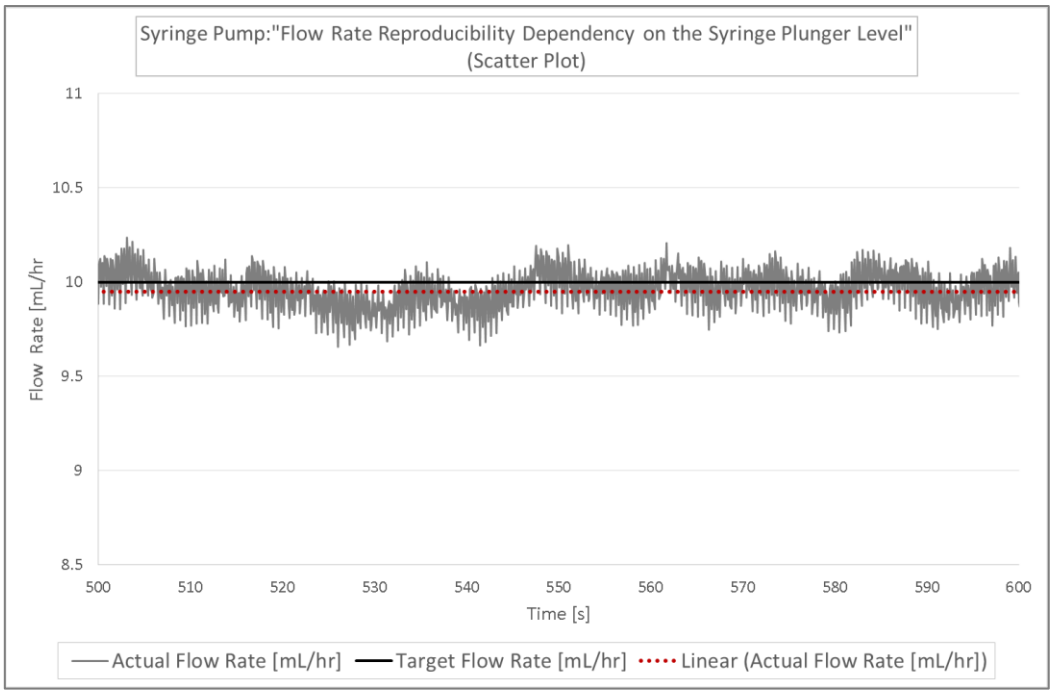

Figure 50 Syringe Braun (10mL) at 10 mL/h (100s Interval)

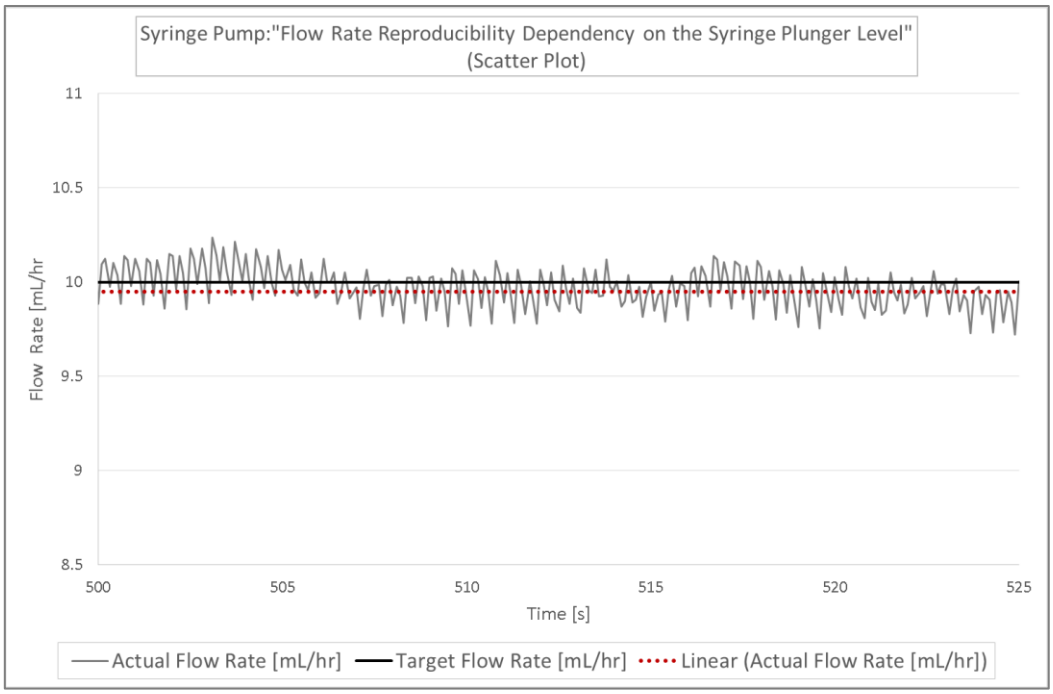

Figure 51 Syringe Braun (10mL) at 10mL/h (25s Interval)

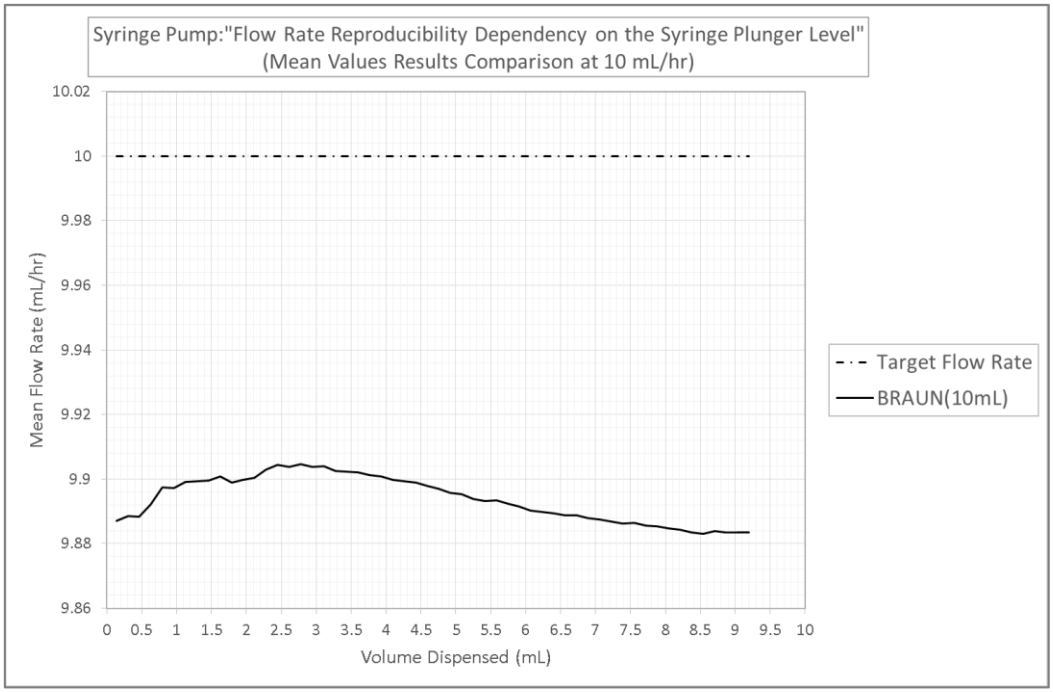

Figure 52 Syringe Braun (10mL) at 10 mL/h (Mean Flow/Volume Dispensed)

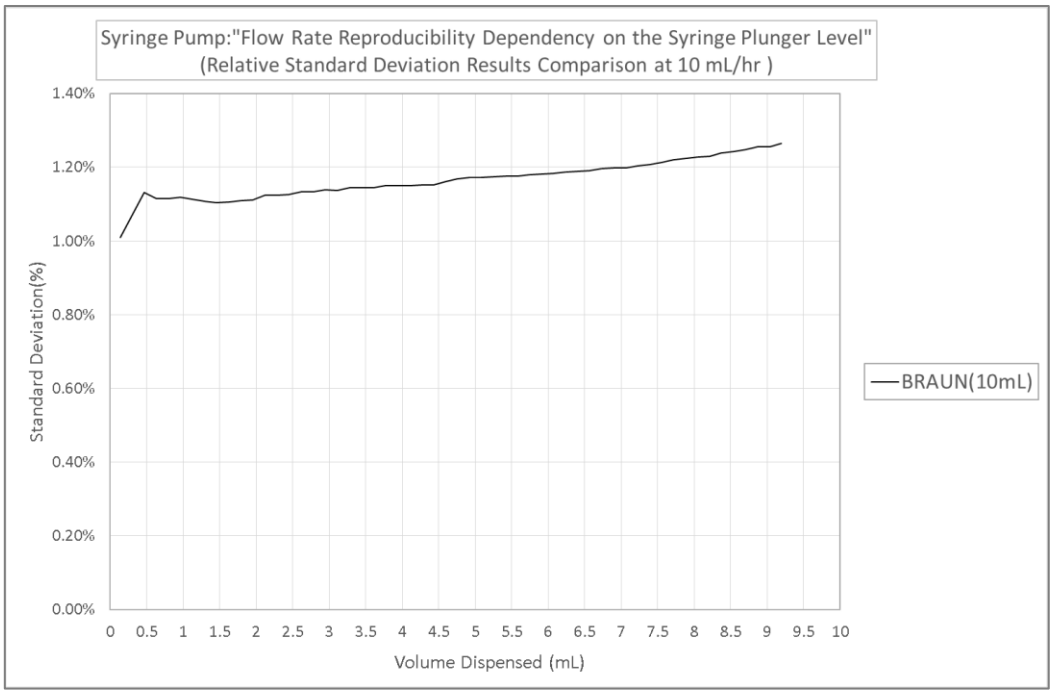

Figure 53 Syringe Braun (10mL) at 10 mL/h (Standard /Volume Dispensed)

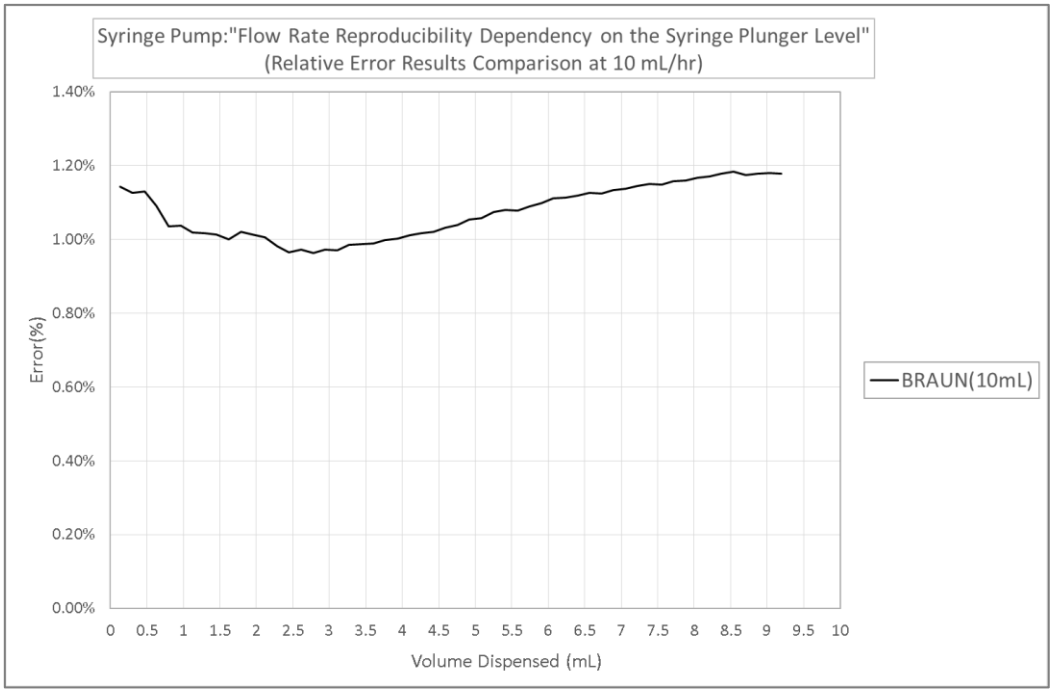

Figure 54 Syringe Braun (10mL) at 0.5 mL/hr (%Error/Volume Dispensed)

8.3.3 Peristaltic Pump: "Flow Rate Dependency on the Administration Set Length"

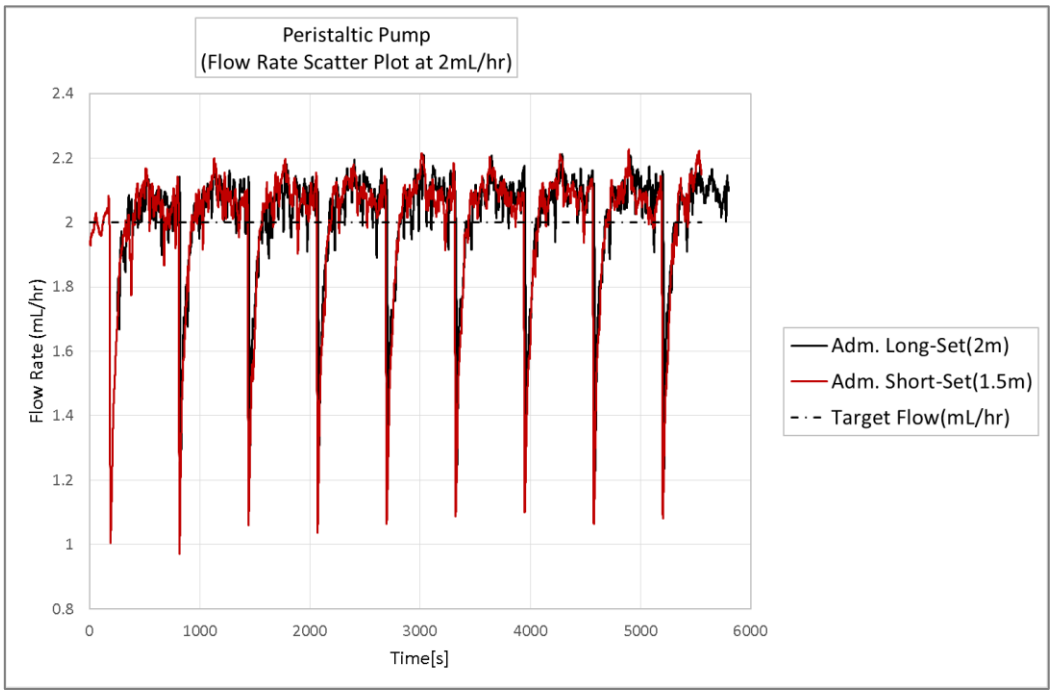

Figure 55 Administration Set at 2mL/h

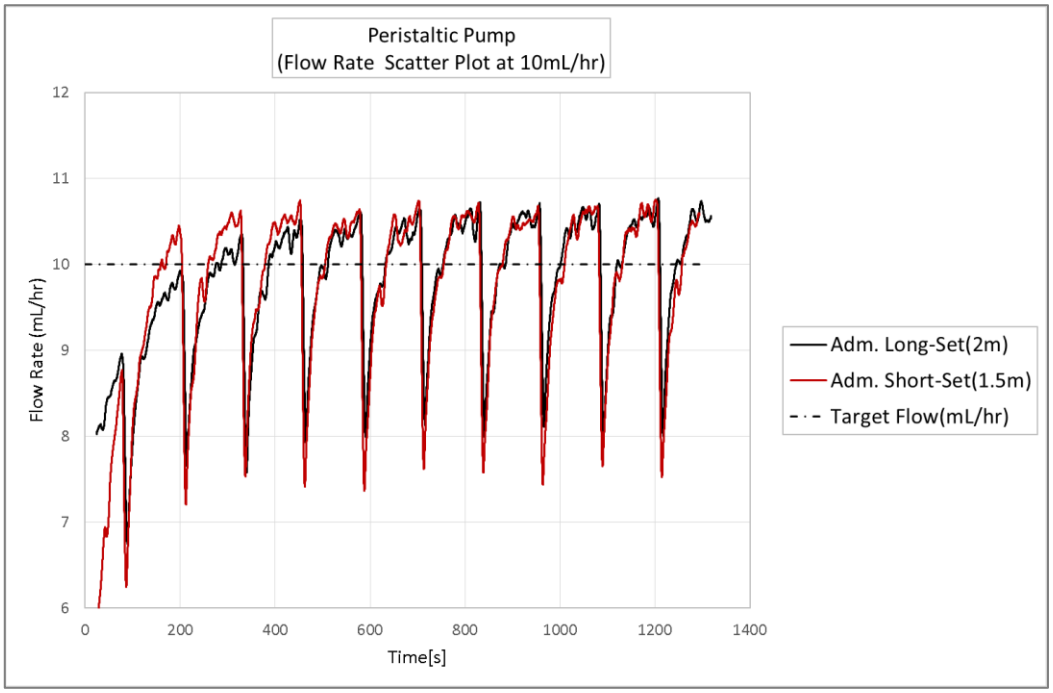

Figure 56 Administration Set at 10 mL/h

Table 5. Mean Values and % Std. Dev at 2-10 mL/h

Mean Flow and % Standard Deviation				
Target Flow Rate Value (mL/hr)	Adm. Long-Set(2m)		Adm. Short-Set(1.5m)	
	Mean Value	% STD Dev	Mean Value	%STD Dev
2	2.017	7.35%	1.979	11.89%
	2.024	7.43%	1.991	10.69%
	2.009	7.56%	1.976	10.83%
10	9.934	8.57%	9.916	8.27%
	9.989	6.46%	9.936	9.24%
	9.969	6.87%	10.060	10.06%

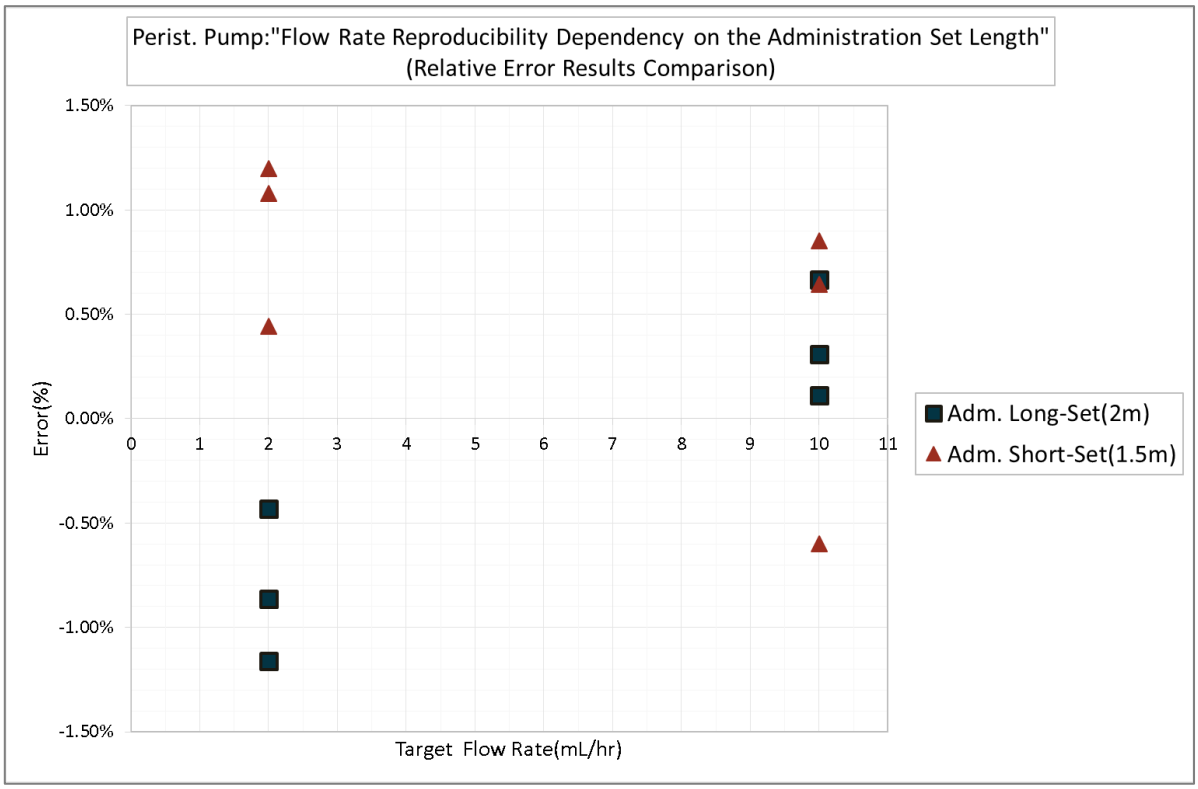

Figure 57 % Error at 2-10 mL/h

8.4 Discussion

8.4.1 Syringe Pump

- Study: "Flow Rate Reproducibility Dependency on Different Syringes"
  - The mean flow rate reported are corrected for the buoyancy, needle immersion and for differences in inner diameter in the case of the syringe that are different than Braun syringe. This is because the syringe did not display in the settings all the different brands.

8.4.2 Peristaltic Pump

- Study: "Flow Rate Dependency on the Administration Set Length"
  - The relative error (table 5) with respect to the different administration set is in accordance with the claimed 5% of accuracy by the manufacturer (Accuracy of set delivery rate ± 5 % according to IEC/EN 60601-2-24)
  - It is observed that the relative standard deviation (figure 57) with respect to the administration set at both flow rate of 2 mL/h and 10 mL/h has a tendency to be higher for the short administration set (250/145 cm) compared to long administration set (300/200 cm).This probable caused by difference in length between sets that makes the short one more rigid.
  - The large standard deviation observed is due to the internal mechanism of the peristaltic pump. It's a cyclic behavior due to an internal aspiration of fluid by the pump upon the final passage in the last finger (dead volume effect, see picture below)

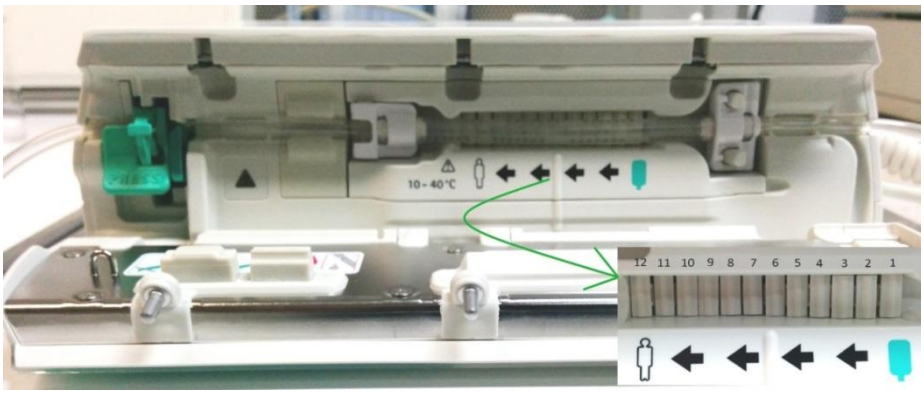

Figure 58 % Error at 2-10 mL/h

9 Flow rate stability and responds time to a step change in flow rate

9.1 Motivation and goal

The main purpose of this test series is to investigate the responds time when the flow rate is changed during drug administration.

9.2 Equipment and scenarios

The following equipment will be used:

- One syringe pump, two syringes: 10 mL (Omnifix) and 50 mL (OPS)
- 1 peristaltic pump.

The following combinations for the two pumps and accessories will be made:

1. Pump alone and connected to the default connections of the micro flow set up.
2. Pump connected to the default infusion line and then via a typical catheter into the measurement beaker. (different catheter and lines will be studied)

The tests in both pumps will be performed at various flow rates: 0.5 mL/h, 2 mL/h and 10 mL/h. The flow rate will be increased with a factor of 2 (F2) and in a factor of 4 (F4) (IPQ), or decreased with the same factors (UME). In case of sufficient time, the pump measurements can be repeated also using a filter or check valve.

9.3 Results and discussion

From figure 59 and 60 some conclusion can be taken:

- The smaller the flow the longer is the delay time to reach a steady flow rate after doubling or even quadrupled the flow.
- The larger syringe takes more time to reach steady flow that the smaller syringe
- The type of setup used only has some influence in the smaller flowrate.

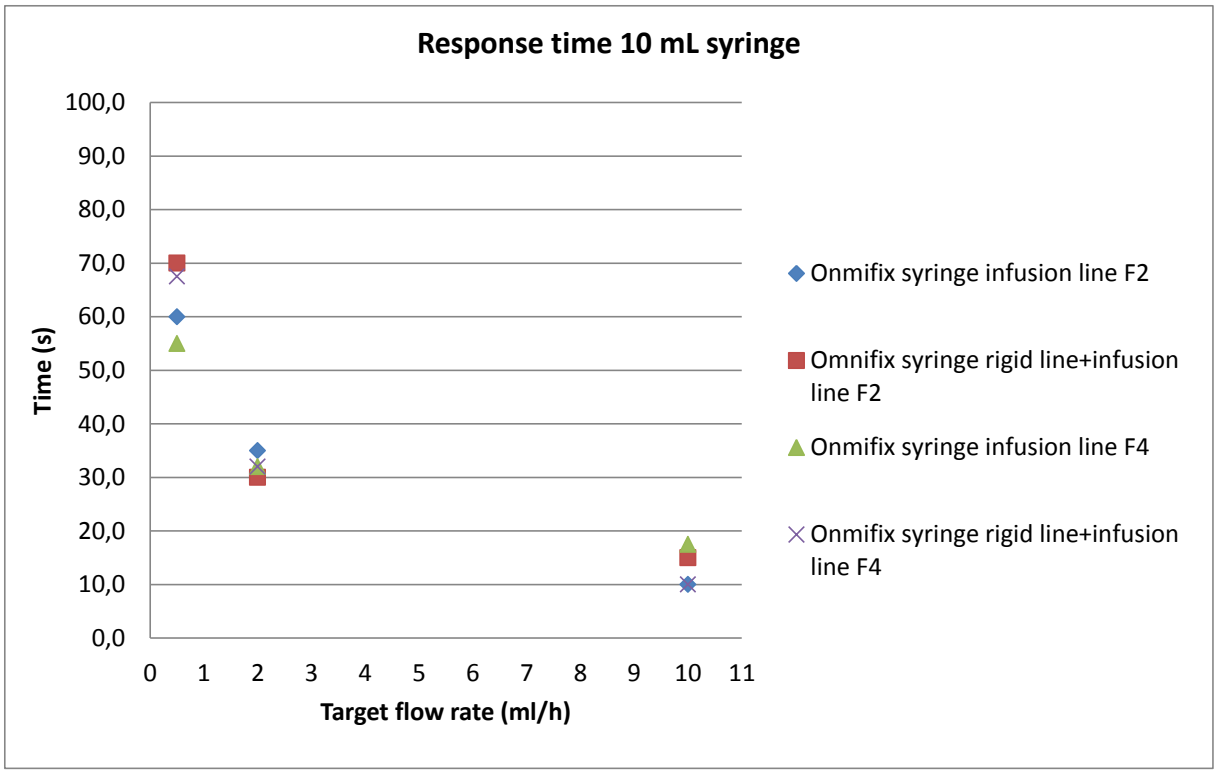

Figure 59 Response time (time to reach 95% of the final flow rate) as function of the target flow rate (F2 – double flow rate, F 4 quadrupled flow rate) for the syringe pump with a 10 mL syringe).

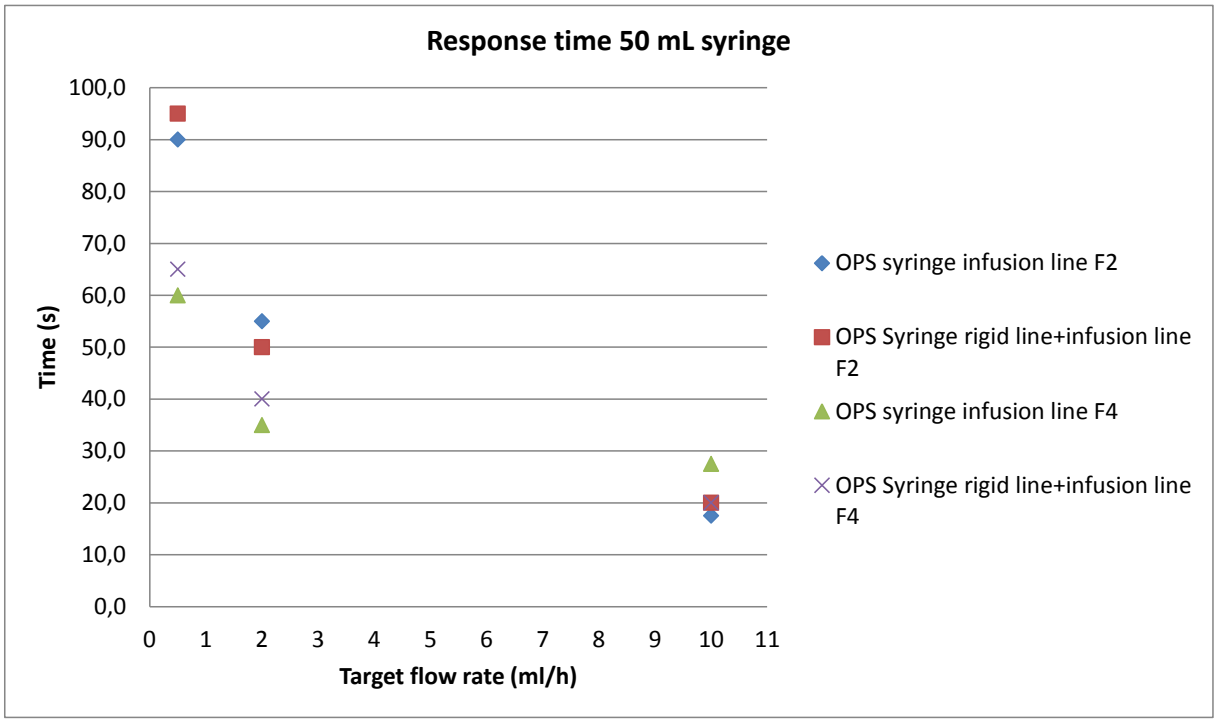

Figure 60 Response time (time to reach 95% of the final flow rate) as function of the target flow rate (F2 – double flow rate, F 4 quadrupled flow rate) for the syringe pump with a 50 mL syringe).

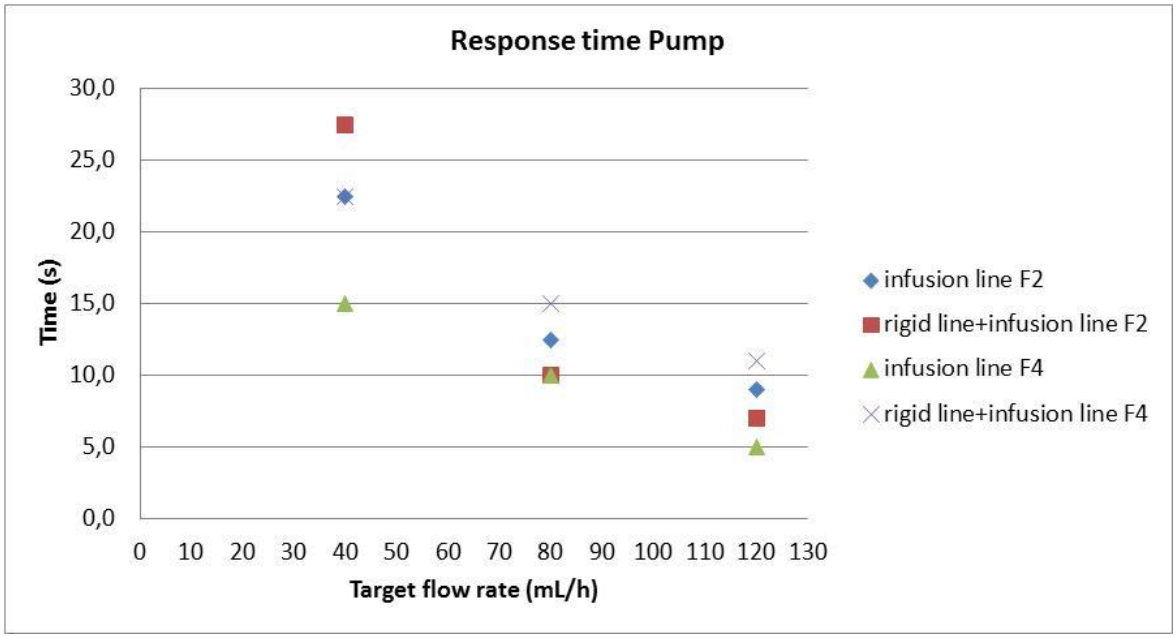

Figure 61 Response time (time to reach 95% of the final flow rate) as function of the target flow rate (F2 – double flow rate, F 4 quadrupled flow rate) for the peristaltic pump

10 Recommendations on priming and filling accessories

In this Section some advice is given on how the syringes and accessories can be filled. For the fluid, demineralized water is recommended.

10.1 Priming and filling syringes

At all times, keep the luer connection of the syringe at the top (vertical). One can extract water from a evacuated storage vessel, however this makes it difficult to fill the syringe. Furthermore, degassing the water prior to filling a syringe does not seem to make it easier to fill the syringe without bubbles.

1. Fill the syringe a little(10-20%) while leaving the initial air in the syringe
2. Knock the air bubbles to the top (use your finger or the soft handle of a screwdriver). With any luck, the bubbles will merge with the remaining air at the top.
3. Slowly empty the syringe until all air is out, and most of the water is out.
4. Very slowly fill the entire syringe. If you see any bubbles being created, you're going too fast.
5. Overfill the syringe a little, but not as much as the syringe allows, i.e. until the plunger hits the end
6. Knock on the syringe to remove any remaining air bubbles. If they get stuck in the top corners, allow a little air in the syringe and gently move and rotate the syringe to get the bubbles to merge. A larger bubble is easier to remove.

10.2 Priming and filling syringes mimicking hospital usage

Simply extract water from your storage (e.g. measurement beaker) by quickly retracting the plunger. Hit the syringe a few times with your finger to merge the largest bubbles. Hold the syringe vertically and empty the syringe just until the air bubble sitting at the top is removed. You typically end up with a syringe that contains some air in the corners of the syringe.

10.3 Priming and filling filters

Connect the filter to a primed syringe

1. Hold the filter with the arrow pointing up
2. Slowly push on the syringe until water starts entering the syringe. Go slowly, and watch the edge of the water moving around the filter.
3. When the water reaches the arrow, hold the filter horizontal with the text facing up. While slowly filling the filter, pay close attention to the water edge. It should first wet the filter housing before going through the hole
4. Fill until the length of tubing is mostly filled, and let the filter rest for a couple of minutes, text facing down.
5. After a couple of minutes, the air from the filter will have released. Flush the air out at a high flowrate (text still facing down).

10.4 Priming and filling basic Neutrapur peristaltic lines

These are very easy to prime

1. Insert the line into the pump. Follow the pumps instructions regarding the opening of the roller clamp
2. Connect to a water bag. Attach the drop counter
3. Use the pumps “BOL” button to prime the line. This should result in an air-free line

10.5 Priming and filling Piggyback Neutrapur peristaltic lines

1. Prime as a basic Neutrapur peristaltic line
2. Connect an empty Luer-lock syringe to the upstream Piggyback connection.
3. Fill the syringe until all air is removed from the piggyback connection.
4. Remove the syringe
5. Repeat steps 2 through 4 for the downstream connection. It may be necessary to perform this during a priming action form the pump to prevent air getting in from the end of the line.

11 Results for the Alaris pump

A pump of a different brand was tested for flow error using different syringes and accessories, start-up delay, response time and viscosity.

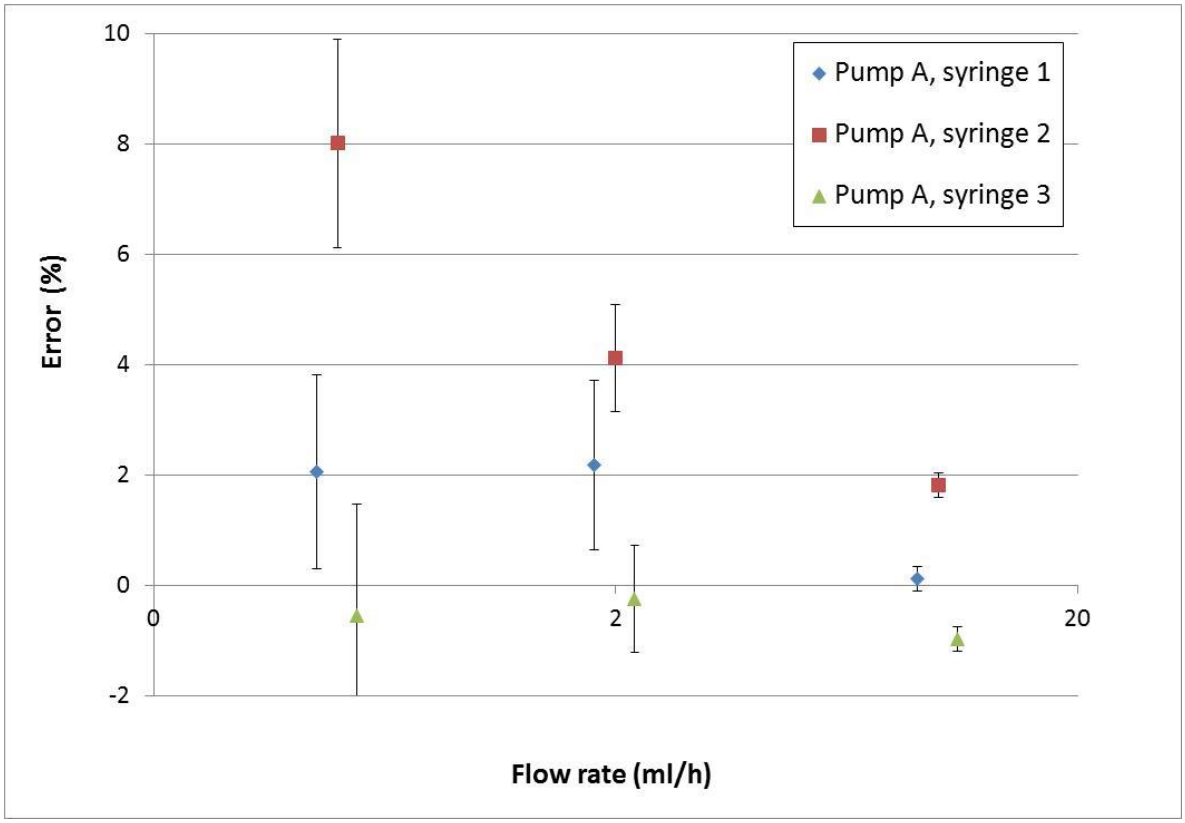

Figure 62 Relative flow rate error as function of the target flow rate for 3 types of syringes using the Alaris Pump

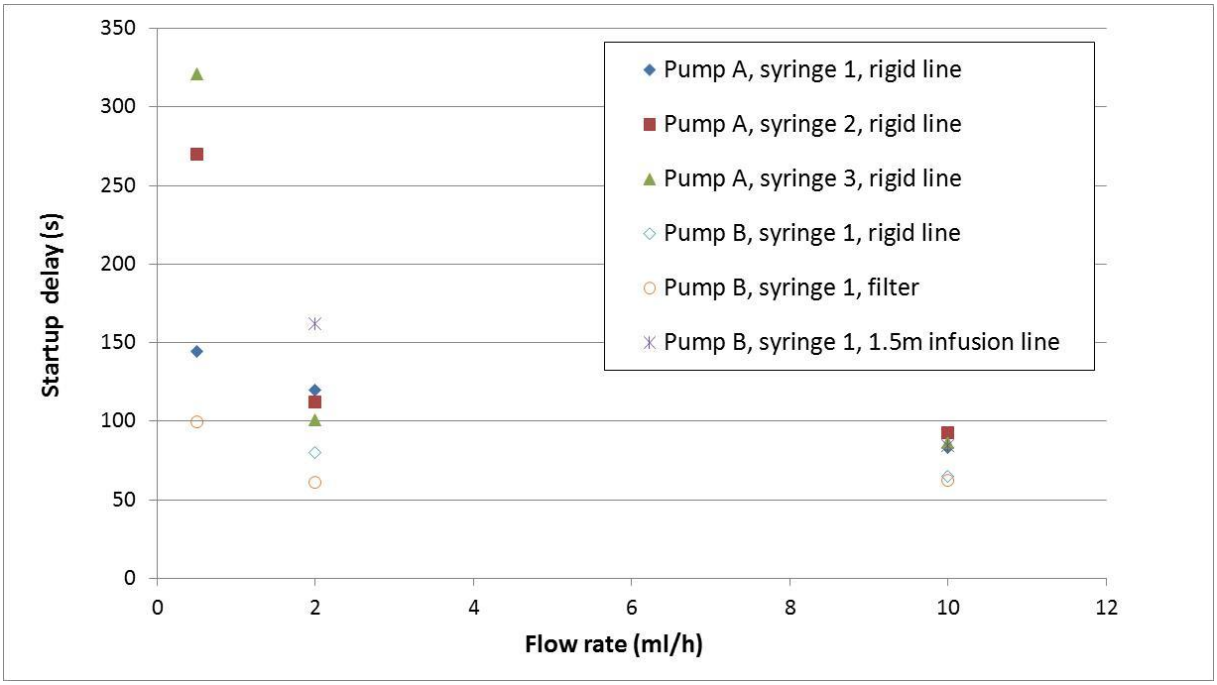

Figure 63 Start-up delay (SUD) as function of the target flow rate and various accessories for the Alaris syringe pump with different syringe

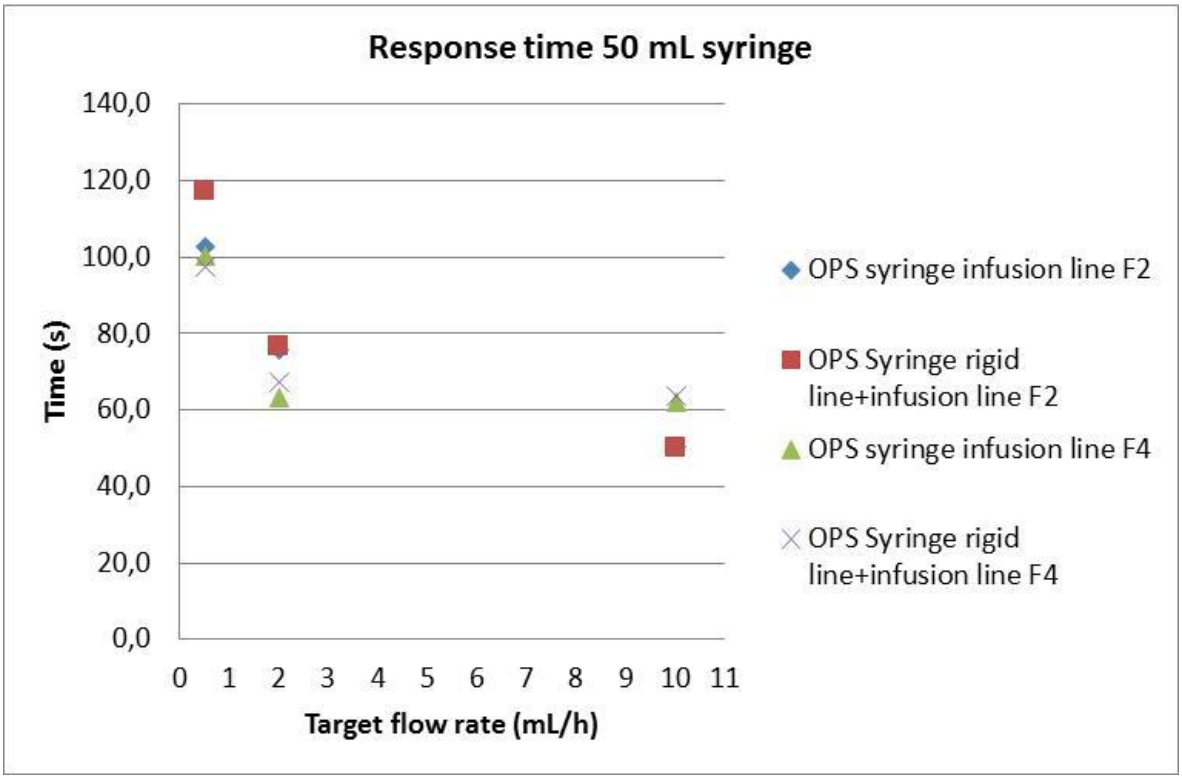

Figure 64 Response time (time to reach 95% of the final flow rate) as function of the target flow rate (F2 – double flow rate, F 4 quadrupled flow rate) for the Alaris pump).

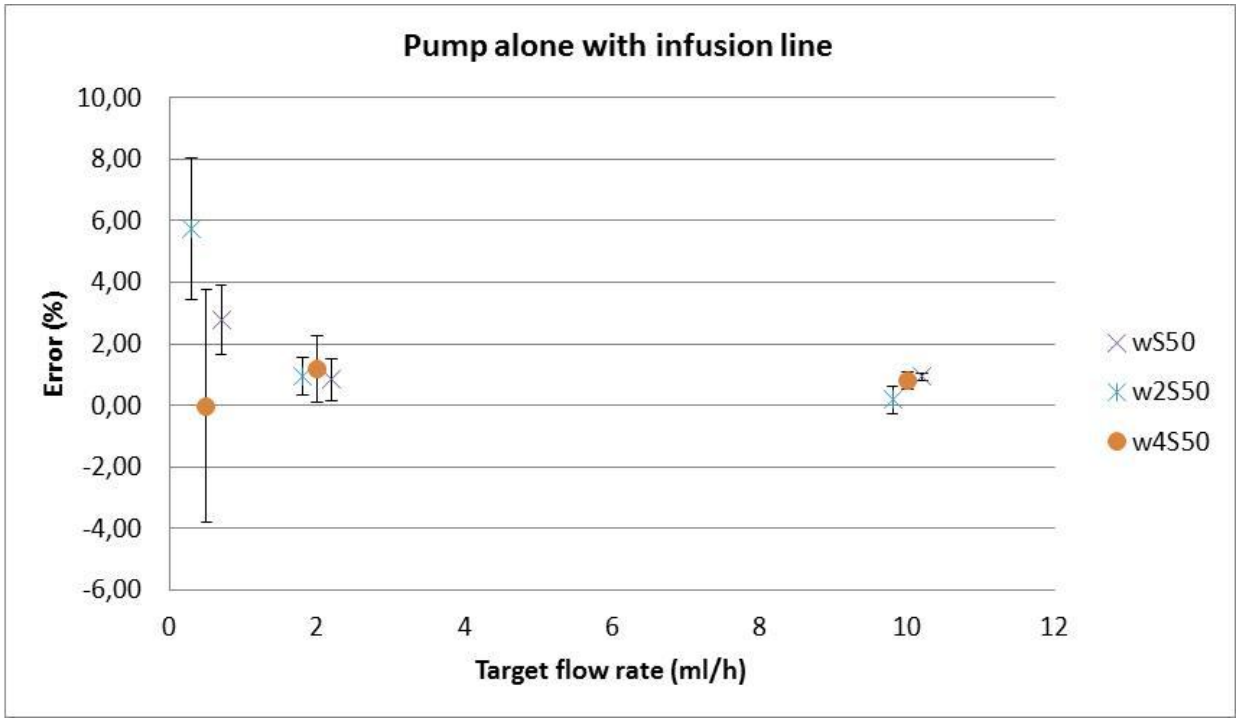

Figure 65 Relative flow rate error as function of the target flow rate and viscosity of the used liquid using only the Alaris syringe pump with the infusion line and syringe 1.

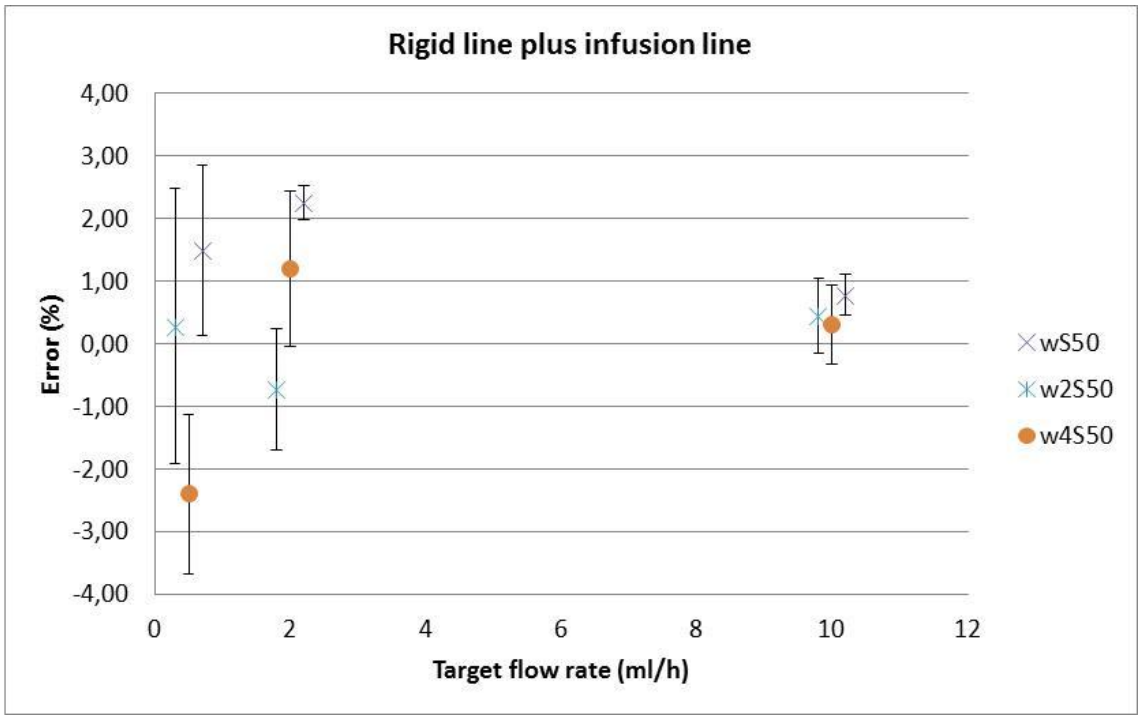

Figure 66 Relative flow rate error as function of the target flow rate and viscosity of the used liquid the Alaris pump connected to an infusion line and to the microflow setup using syringe 1.

The results with syringe 2 are different because the pump had a different internal diameter programed and therefore the error is larger.

For the response time, viscosity and start up delay the results are similar than for the BBraun syringe pump. The lower the flow the larger the dispersion of results.

References

[1] Schmidt, N., Saez, C., Seri and I., Maturana, A., Impact of syringe size on the performance of infusion pumps at low flow rates, Pediatric Critical Care Medicine, Vol. 11(2), p.p. 282-286, 2010

[2] Snijder, R.A., Radermacher, J.H., Konings, M.K. and Timmerman, A.M.D.E., A theoretical model for catheter outflow concentrations, technical report available at www.drugmetrology.com (Project page, REG3)

[3] Lucas, P. *et al.*, MeDD – Metrology for drug delivery, EMRP project 2012-2015, website at www.drugmetrology.com

[4] Technical data Infusomat®, Volumetric pump and Perfusor® Space, available online at: http://www.space.bbraun.com/documents/Space_System_Technical_Data_I.pdf