Measurement methods in multi-infusion: a review of possible methods in biomedical literature

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1 Introduction

1.1 Background

New soluble, very potent therapeutic agents with well-defined half-lives and knowledge about human physiology[1]have enabled physicians and pharmacists to develop infusion treatments in which very slow and accurate flow rates as low as 0.1ml/h 5 ml/h are required[2].Highly accurate motorized syringe pumps are used to meet this increasing demand for advanced and precise medication schedules.

Infusion constitutes a burden to patients by piercing through their skin. Especially in vulnerable patients, most notably neonates, the number of access points should be reduced to a minimum. As such, medication from multiple pumps is combined into a single catheter before entering the patient's bloodstream[3].

It has been shown that multi-infusion causes a mutual influence between the different infusion lines. Consequently, several interruptions and alterations such as height differences between pumps, the use of check valves and occlusions cause complex behaviour in the flow rates. Ultimately these phenomena were shown to alter the total volume delivered to the patient. These effects become more prominent with IV therapy in neonates who require very low flow rates[4]. Physicians need new and refined measurement methods In order to achieve optimal dosage control for their patients.

Although single infusion has been thoroughly investigated and it has already been established that infusion systems using accurate syringe pumps may still deviate from the set flow rates in some cases [5][6][7], there are only a few groups that have developed measurement methods for multi-infusion. The UMC Utrecht has developed an *in-vitro* measurement method to measure concentrations in infusion lines of multi-infusion while simulating several manual disturbances in one or more pumps [8].The aim of this report is to provide an overview of other studies describing similar multi-infusion concentration measurement and flowmetry methods in order to obtain new concepts for the improvement, modification or replacement of our current method.

2 Methods

2.1 Search strategy

Before searching for literature the goal of the measurement method was defined. Subsequently, the properties that make such a method suitable for multi-infusion measurement were assessed. Many methods to measure either concentration or flow from elementary chemistry and physics are known. From these, we chose to investigate studies in the area of multi-infusion for this report. In order to indicate the suitability of the measurements for our purpose we reviewed the articles for the following parameters:

- Precision
  This is defined as the statistical variation between equal measurements. Precise measurements are desirable.
- Accuracy
  This is defined as proximity of the measurement to the actual physical quantity.
  In order to determine the accuracy of a certain measurement device, one should compare it with a measurement device traceable to international accepted standards.
- Selectivity
  Ability of the method to detect an analyte without interference of other chemicals.
- Sensitivity
  Measure of uncertainties between input and output. (in binary terms a measure of true positives)
- Acquisition time.
  As infusion is a continuous process, a real time acquisition method is desirable.
- Recovery
  How well the measured concentration agrees to the actual concentration.

In flowmetry common parameters are:

- Error = $Q_{Indicated} - Q_{ref}$
- Relative Error = $(Q_{indictated} - Q_{ref}) / Q_{ref}$
- Accuracy

Where Qref is the flow rate according to a flow meter traceable to international standards.

Another important property to explore was the analytical method used to process the measured data. The analytical method typically involves some applied mathematical methodology or algorithm to differentiate between the multitude of solutions that were measured. Usually multiple methods can be used and some improvement might be achieved by using a more sophisticated methodology.

A consistent error can be eliminated or reduced by calibration. Calibration can be defined as: *set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument and the corresponding values realized by standards or references of established uncertainty.*

2.2 Systematic search strategy

From several key publications keywords were extracted and used to search PubMed.

- General infusion keywords:

  infusion, drug delivery systems, drug therapy, pharmaceutical, flow rate, infusion pumps, infusions, parenteral, instrumentation, multi-access infusion, fluid dynamics

- Keywords in the context of analytical method:

  Partial least square, linear regression, simultaneous determination, multivariate analysis

- Keywords in the context of measurement:

  Spectrophotometry (or spectral-photometry), photometry, high-performance liquid chromatography (or HPLC), real-time, flowmetry

It was recognized that keywords like chemistry, chemical analysis, measurement were too general and should be discarded. Most of the keywords are common and known in the medical literature database. The databases therefore automatically provided synonyms for the words or abbreviations. Finally the keywords were combined into the following search string:

> ((Infusion OR drug delivery systems OR multi infusion OR real-time) AND (pharmaceutical OR drug OR dye) AND (flow rate OR concentration) AND (HPLC OR Spectrophotometry OR fluorescence OR voltammetry OR drop counter OR flowmetry OR measurement method]) AND (Partial least square OR linear regression OR simultaneous determination OR multivariate analysis))

The screening methodology is explained in Figure 1.It was attempted to review the abstract on new methods and discard similar methods for different applications as much as possible. It should be noted that methods used in single infusion measurement are not necessarily sufficient to measure multiple chemical compounds in a solution simultaneously.

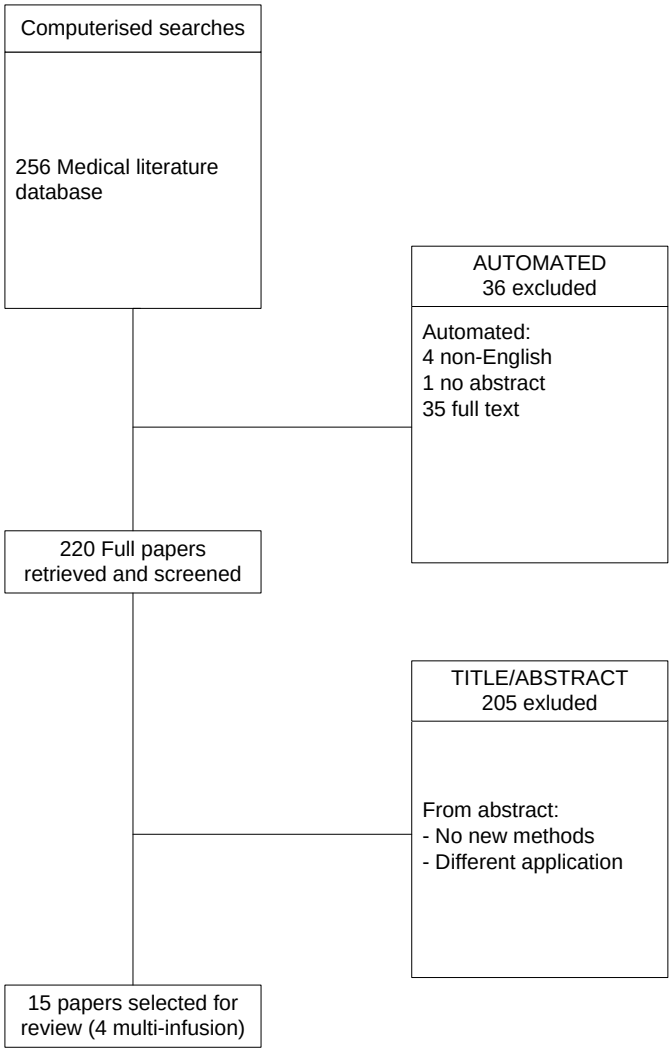

Figure 1. Flowchart study selection

After the analysis some additional literature sources like dissertations and technical reports were also analyzed.

2.3 The UMC method

In this report, we use the UMC measurement method[8] as a starting point to investigate similarities and differences in measurement methodologies. The UMC method can be described as absorbance spectral-photometry. Throughout literature spectrophotometry was described in many applications, for example, to determine the amount of colorants in food[9], [10]. However, spectral-photometry studies for in vitro infusion flow measurements were scarce. The mathematical analysis method that was chosen is based on linear regression. More specifically, we used linear regression calibration, developed by López-de-Alba et al. (1997), described by Dinç*et. al*. [11].

The photo-spectrometric method developed by the UMC was based on the simultaneous spectral photometric measurement of multiple water solved laser dyes. The schematic representation of this process is shown in Figure 2.First a light source(DT-100, Ocean Optics, USA) emits light in the visible spectrum. Subsequently, the light is guided through 200 µmoptical fibers into a flow cell(FIA-Z-SMA, Ocean Optics, USA), shown in the middle of the schematics of Figure 2. The flow cell was similarly connected to a 140 cm long central line (1.5 mm in diameter) where the solvents from each syringe pump are joined.Consequently, light emitted from the source and guided through fibers has the opportunity to pass through the solution, allowing the solvent to absorb part of the light spectrum. The spectrum is finally analysed by a spectrometer (QE65000, Ocean Optics, USA). After the measurement the solvent is was guided through a line of 50 cm (1.0 mm in diameter) and released into an Erlenmeyer flask. A precision (+/- 0.0001 g) balance (PGW 450, Adam Equipment, USA) was used to verify the total mass measurements. The Erlenmeyer flask was filled with some water to simulate the counter pressure of the human cardiovascular system. For data analysis, MATLAB 7.5.0 (Mathworks, USA) was used.

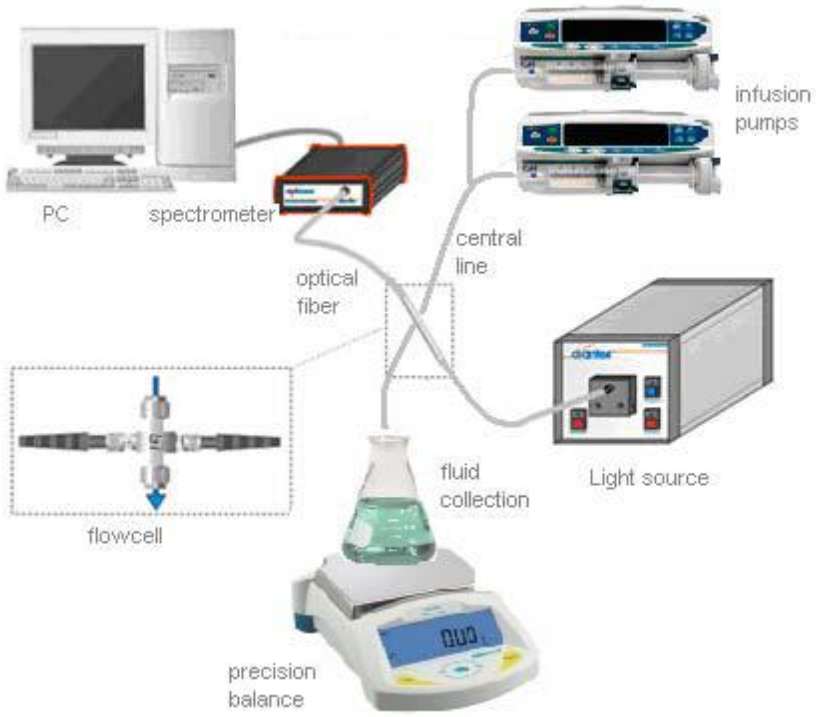

Figure 2. Schematic view of the UMC experimental spectral-photometry setup.

Each syringe pumps contains a specific laser dye (colorant) solved into distilled water (40 mg/L), all of these laser dyes absorb light at specific light spectra. The laser dyes were selected based on physical and chemical properties[8]. To minimize optical overlap narrow-band absorption spectra were preferred, a maximum bandwidth of 200 nm was experimentally obtained from range limit experiments.Furthermore, viscosity and thickness of the solvent was required to pass the 0.2 µm membrane filter under normal pressure applied in clinical practice. Table 1 shows the chosen laser dyes.

Table 1. laser dyes used in the UMC spectra-photometric method.

Absorbing dye	λ_{max}[a]	Used abbreviation
Tartrazine	431nm	TT
DisodiumFluorescein	487nm	DF
Allura Red	500nm	AR
Kiton Red	565nm	KR
Indigo Carmine	610nm	IC
Simacid Blue	628 nm	SB

[a]Wavelength of maximum absorption of laser dye solved in distilled water.

Linear regression calibration

In the single infusion case, the law of Lambert-Beer could simply be used to find a correlation between concentrationsand the ratio decrease of the output signal intensity and the input signal intensity. However, in the multi-infusion case multiple dyes had to be distinguished in order to identify the interference of a specific syringe pump. This results in an unavoidable overlap in the absorption spectra of the used dyes. In order to recover the concentration of a specific dye without preliminary separation linear regression calibration is used, this method will be explained. Consider the following first-orderlinear equation:

$$A_n = a_n \cdot C_n + b_n$$

Where A is the absorbance of dye n at a specific wavelength, a is the slope of the linear regression of dye n and C is the concentration (mg l^{-1}) to be obtained, b is the intercept or offset between the ideal and the measured situation. In the single dye situation, the equation simply answers to the Beer-Lambert law $A = -log\frac{Io}{I}$, where I_0 is the incident intensity (power or counts) and I is the transmitted intensity. In the multi-infusion and therefore multi-absorbents case the equation can be written as a series of equations resulting in a first-order polynomial. Consider the following polynomial, let i be the number of wavelengths $\lambda_{max}$for each dye.

$$A_{n,i} = a_{1,i}C_1 + a_{2,i}C_2 + \ldots + a_{n,i}C_n + b_{sum} \quad \text{at } \lambda_i$$

Where A_n represents the absorbance values of the mixtures of dyes at wavelength λ_i. $b_{sum} = \quad b_i$ is the sum of each intercept for dye n as described by Dinc et al. [12]. We assume that arrhythmic mean is a more accurate description of b than the sum used by Dinc et al. In the current situation the number of dyes alone is a variable for determining b, which is incorrect. This correction has not been applied yet.

This method has not been applied yet but we will use this in future measurement analysis.

Proceeding in matrix notation:

$$A = K_{n \times i} C_{1 \times n} + b_{sum}$$

Where the K matrix contains the slope $a_{i,n}$. In the measurements i = n was used, so the K matrix is a square matrix.A series of calibration measurements was used to obtain the offset b and the slope a in matrix K.

To obtain the concentration of dye 1, the matrix needs to be solved for C_1. Several elimination methods can be used such as Gaussian elimination, pivoting etc. In this case an inverse matrixwas used (in simplified form):

$$C_{1 \times n} = K^{-1\ *} * A - b_{sum}$$

Other methods, for example singular value decomposition, can be investigated for their possible improvement of the signal to noise ratio in data analysis.

2 Results

Table 2shows an overview of the studies found in peer-reviewed literature describing a measurement method applied in a multi-infusion setup. The table (a) shows the analytes used to distinguish a separate (mass) flow rate and the analytical method/algorithm. The table (b) is continued with the acquisition time and metrological/analytical parameters: recovery, precision, accuracy, sensitivity and selectivity if published.

Table 2. Summary of peer-reviewed literature findings (a)

Year	Author	Method	Analytes	Analytical Method
2012	Tsao	Quantitativespectrophotometry (430 nm, 630nm)	erioglaucine, tartrazine	-
2012	Van der Eijk	Flowmetry	H_2O	-
2009	Moss	Photospectometry / volume measurement	flow / total volume	Linearinterpolation
2009	Seqh et al.&Decaudin et al.	Simultaneous UV spectrophotometric determination (spectrum 220 – 300nm)	isosorbidedinitrate, midazolam, noradrenaline	partial least square (PLS) regression
	UMC method	Spectral-photometry (spectrum vis. light ~400- 700 nm)	misc. laser dyes	linear regression calibration
	Bronkhorst (µ-flow)*	Liquid mass flow meter, thermal thru-flow measuring principle.	H_2O / heat gradient (calometry)	-
Proposed	Bronkhorst (mini cori-flow)*	Coriolis liquid mass flow meter.	H_2O / Vibrations	-

*Name of manufacturer

Table 2. Summary of peer-reviewed literature findings (b)

Year	Author	Recovery	Time†	Sensitivity	Selectivity	Precision and/or Accuracy
2012	Tsao	-	RT	-	-	-
2012	Van der Eijk	-	0.01 s / RT	-	-	-
2009	Moss	-	-	-	-	-
2009	Seqh et al. &Decaudin et al.	99.5% - 101%	RT, 30s interval	1.93, 1,278, 0,302	0,075, 0,189, 0,018	-
	UMC method	100.8% (±2.0%) and 101.8% (±6.5)	RT	-	-	2.0% and 6.5% (precision)
	Bronkhorst (μ-flow)*	-	-	-	-	± 2% (accuracy)
Proposed	Bronkhorst (mini cori-flow)*	-	RT, Sensor response 50 – 100 ms	-	-	± 0.2% of rate (accuracy)

*Name of manufacturer

†RT = real-time

256 initial studies were found. In the systematic search, only full-text English papers with abstracts were considered, which excluded 36 papers immediately. 76 articles were published in the last 5 years,16 articles were older than 20 years. No *locus classicus* was found. 5 articles describing a multi-infusion(mass) flow rate measuring method werefound. Figure shows a flow chart of the search and inclusion criteria.

Three categories were found:

- Photospectrometric methods
- Flowmetry
- Chemical analysis

In the next section these methods will be discussed in more detail.

3.2 Spectrophotometric methods

3.2.1 The UMC method (absorbance spectral-photometry)

The UMC method was explained in detail in the method section.

The average recovery ranges found were 100.8% (±2.0%) and 101.8% (±6.5).Table 3Table 3 shows the statistical data from the recovery experiments. For each dye the standard series of solutions were determined. The statistical data was obtained from five repeated calibration measurement.The method was validated for linearity, precision and accuracy. Table 4Table 4shows linear regression calibration results for every laser dye, based on literature guidelines[13]. The validation process involved a series of experiments in order to empirically obtain the optimal parameters, dyes and concentrations.

The recovery was calculated as

$$\text{Recovery } \% = \frac{C_{1,\text{measured}}}{C_{1,\text{measured}}} D_1 \cdot 100$$

Where $C_{1,measured}$ and $C_{1,refrence}$ are the measured and actual concentration of dye 1 respectively. As the dyes are mixed the total volume increases, therefore a correcting dilution factor D_1 had to be applied as

$$D_1 = \frac{V_1 + V_2 + \cdots + V_N}{V_1}$$

Where $V_n$is the volume of each solution.

Table 3. Statistical quantities

Absorber	λ_{max}	Linearity Range (mg l^{-1})	Correlation coefficient*r*	Linearity (%)	RSD
Tartrazine (TT)	431	4.0–20.0	0.9987	97.4	1.12
DisodiumFluorescein (DF)	487	2.0–16.0	0.9972	97.2	1.79
Allura Red (AR)	500	4.0–40.0	0.9991	98.3	0.63
Kiton Red (KR)	565	2.0–20.0	0.9994	98.7	1.73
Indigo Carmine (IC)	610	2.0–40.0	0.9995	98.8	1.16
Simacid Blue (SB)	628	2.0–20.0	0.9977	97.5	1.77

A = absorbance value; C = absorber concentration.
RSD (%) = relative standard deviation.
*Linearity (%) = (1-S_a/a) *100, where S_a = standard deviation of slope (a).*

Table 4. Results of initial calibration measurement

Absorber	Dye 1	Dye 2	Dye 3	Dye 4	Average recovery (%)[a]
1	Allura Red	Indigo Carmine			100.8 ± 2.0
2	Allura Red	Indigo Carmine	Tartrazine		101.8 ± 6.5
3	Allura Red	Indigo Carmine	Tartrazine	Kiton Red	108.5 ± 5.2

[a]*results based on three repeated measurements of two different mixing ratios*

3.2.2 Other absorbance spectral-photometry studies

Another recent study by Tsau et al. [14] investigated flow rates in multi-infusion using absorption quantitative spectrophotometry*in vitro*. This method shows many similarities to the UMC method. Two water-soluble dyes were used: tartrazine yellow (0.1 mg ml^{-1}) and erioglaucineblue (0.4 mg ml^{-1}) and analyzed at the absorbance peaks of 430 nm and 630 nm respectively. The method proved successful in measuring mass flow rates. Unfortunately very little details were shared with respect to the measurement method such as recovery power or sensitivity.

3.2.3 UV Spectrophotometry

A French group from Lille[i]conducted some experiments to assess the flow rates in a multi-infusion setup. Seqh*et al.*[1] have successfully applied simultaneous UV spectrophotometric (220-300nm) determination using partial least square (PLS) regressionin order to analyze three common anesthetic drugs: dinitrate, midazolam and noradrenaline, infused using a multi-infusion device.Mixture ranges were: 6.67-30 µgml^{-1}, 0.83-7.5 µgml^{-1} and 1.67-23.33 µgml^{-1} for isosorbidedinitrate, midazolam and noradrenaline respectively, in ternary mixtures. Recovery range was 99.5% – 101%. The limits of detection were found to be similar to specific HPLC. The multivariate method of PLS is typically used in full-spectra analysis methods[15].Seqh et al. claimed that such a full-spectrum method is more powerful than a single-wavelength methodology. The rationale given for this claim explains that the intensity of multiple wavelengths can improve the precision and applicability of the analysis of mixtures. No substantial proof or quantification was provided.However, many studies showed successful analysis of complex mixtures including mixtures of pharmaceuticals[1], [16], [17],[18]. The choice of optimal spectral zone and influence of pH were determined in a series of preliminary experiments. Décaudin*et al.*[19]used the method of Seqh*et al*. to study the effect of multi-infusion. The mass flow rate (µgmin^{-1}), mass flow rate plateau, change of flow rate and some other detailed assessments were successfully studied. The method was real-time

with a temporal acquisition interval of 30s between analysis at the catheter egress. Sensitivity was given by

$$Sensitivity = \frac{1}{|\ b\ |} = |\ NAS\ |$$

Where b is the norm of the regression vector containing the response vector. The method is based on the netanalyte signal calculations.

$$Selectivity = \frac{|\ NAS\ |}{|\ x\ |}$$

Where x is the analyte of interest.

Sensitivity and selectivity are shown in Table 5.

Table 5. Sensitivity and selectivity Seqh et al.

	Isosorbidedinitrate	Midazolam	Noradrenaline
Sensitivity	1.930	1278	0.0302
Selectivity	0.075	0.189	0.018

The specific PLS algorithm used was PLS-2. PLS is based on factor analysis for building regression models based on *latent variable decomposition* relating a block of independent variables (spectra) to a block of dependent variables (concentrations) [15]. Similar to the UMC method, calibration measurements were conducted. The predicted concentration was compared to the measuredone for each calibration sample. From this the predicted error of sum squares was calculated, this quantity is given by

$$PRESS = \quad {}^{n}_{j=1}(Cpj - CJ)^2$$

Wherenis the total number of calibration samples; Cj, the reference concentration for ith sample and Cpjrepresents the estimated concentration of Cji(where i represents the observation[11].

The statistical factor determining the quality of the prediction was the root mean square error (RMSE). However, also a Q^2cum index was calculated which measures the global contributions of each component to the predictive quality of the model. The maximum Q^2cum index is equal to the most stable model. Exact formulas were not given. Finally the variable importance for projection (VIP) was calculated. The VIP summarizes the contribution of each variable to the model. Secq et al. considered a VIPj> 0.8 as relevant to explain the non-contribution of other variables. Table 6Table 6Table 6shows the statistical values of each analyte with every wavelength and only those with a VIP > 0.8 showing good very good correlations with optimized errors. Figure 3 shows the results of absorption spectra.

Table 6. Statistical quantities Seqh et al.

Spectral zone	Product	R^2	RMSE
All λ	Isosorbidedinitrate	0.9998	0.2495
	Midazolam	0.9996	0.5231
Only VIP > 0.8	Noradrenaline	0.9999	0.0655
	Isosorbidedinitrate	0.9999	0.2170
	Midazolam	0.9997	0.4566
	Noradrenaline	0.9999	0.0631

VIP variable importance for projection R^2 correlation coefficient, RMSE root means square error.

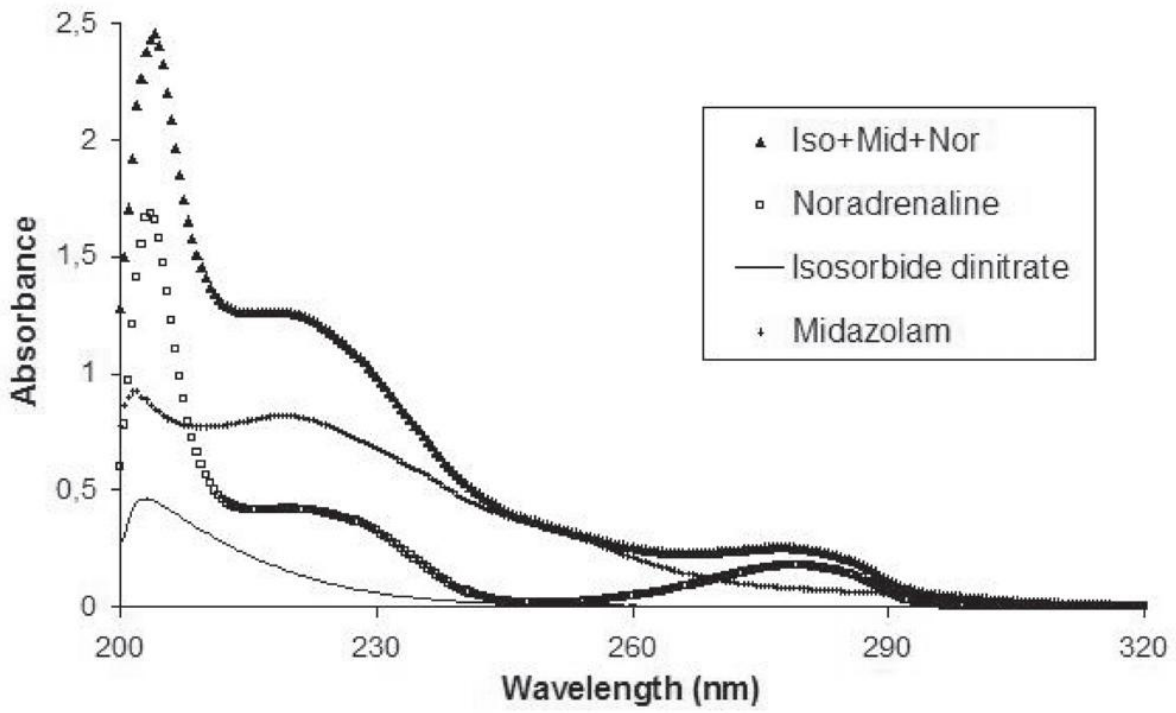

Figure 3. *UV absorption spectra of the three drugs, separately and combined [11].*

3.2.4 Fluorescence spectrometric method

The university medical centerof Maastricht[20] conducted a fluorescence spectrometric measurement study with two syringe pumps. A Krotonfluorescence device was used. The principle of fluorescence spectrometry relies simply on reflective properties of the analyte at specific wavelengths. With the right setup the light intensity is proportional to the concentration of the analyte. The method was not validated. However, the measurement results were in agreement with a theoretical flow model.

3.3Flowmetry

There are many techniques to measure flow. The easiest method is probably to measure the accumulative volume or mass using a balance.A second intuitive method is a positive displacement meter. Positive displacement meters are mechanical solutions to flowmetry, which involves some moving cavity as a result of flow. The rate of movement is transduced to a sensor resulting in the measurement of volumetric flow.

3.3.1 Microfluidics

Microfluidics can be defined as the research discipline dealing with transport phenomena and fluid based devices at microscopic length scales[21]. A number of microfluidic techniques may be suitable to measure flow rates in a multi-infusion setup.

Direct velocity movement

Micro particle velocimetry (PIV) uses a flow seeded with fluorescing particles to measure and image flow characteristics. The fluorescing properties are excited by a double-pulsed lasers technique. The particles are typically in the order of several hundreds of nanometers. Besides flow velocity it is also possible to obtain turbulence intensity and higher order flow statistics. Due to the small size of the particles, Brownian motion may occur (related to Reynolds number). The limits of measurement are defined by the particle size and optical resolution. Wereley et al. [22] reviewed some state of the art PIV techniques and concluded that a resolution of 1 µm can be obtained. Micro particle velocimetry aims at very precise measurement of flow characteristics, usually in very small tubes. The disadvantages of this method are the complexity and cost which makes it beyond the scope of the multi-infusion REG 1 project at this time.

Electrokinetic methods are usually used to create flow applying charged particles in microfluidics [23]. Osmosis is probably the best known example of the electrokinetic phenomenon. However, measurement methods measuring several complex properties such as electrostatics, electrodynamic molecular and particle transport were also reported [24]. These methods are too laborious to use in the current project, but may be part of future investigations.

3.3.2 Microfluidic flowmeters

In microfluidics a variety of micro-flow sensors can be identified. These sensors include[21]:

- Thermal (Transfer of thermal energy is related to velocity and flow rate)
- Static pressure (Pressure difference correlated to flow rate)
- Mechanical (mechanical forces)
- Coriolis force
    - E.g. Coriolis sensors
- Direct velocity movement (E.g. particles (uPIV), Doppler)

Boththermal flow sensors and Coriolis sensors can be used to measure very low flow rates of non-aggressive liquids such as water or aqueous solutions. The following points are characteristic for thermal sensors

- *Requires heaters and thermometer*
- *Must be thermally insulated*
- *Suitable for micro fabrication*
- *For measurements of minute flow* rates[ii]

A heater is used to dissipate heat to the moving liquid. Micro-calorimetry, time-of-flight of the thermal signal or a combination can be used to measure flow rates and velocity.

Recent developments in Coriolis mass flow sensors were found to show less uncertainty and were faster than the thermal sensors.Moreover, manufacturers claim good performance even in changing operating conditions such as pressure, temperature, density, conductivity and viscosity.[iii]

The following points were characteristics for Coriolis mass flow sensors

- *Liquid flow in tube structure*
- *Superimposed twisting of structure*
- *Measured twisting due to Coriolis pseudo force proportional to liquid mass flow.*

The Coriolis mass flow measuring apparatus contains a vibrating tube in which the flow causes changes in frequency, phase or amplitude. The curvature of the tube results in a mechanical Coriolis force to which the vibrating liquid is superimposed. The changes in the wave mechanics of the fluid are directly proportional to flow rate, whereas the thermal mass flow meters are dependent on several other physical properties of the fluid.

In summary, the Coriolis method is expected to yield the best results in the multi-infusion situation.

3.3.3Flowmetry in a multi-infusion setup

Van der Eijk et al. evaluated the effect of three different types check valves in a multi-infusion setting. An in vitro experimental IV setup with in-line flow-meters was used to measure the flow rates while simulating a clinical situation. Two pumps were programmed with flow rates of 2.5 mL H^{-1} and 0.1 mL H^{-1} for pump 1 and pump 2 respectively. Two different Bronkhorst flow meters were used, pump 1 was measured with a mini cori-flow and pump 2 with a µ-flow flow meter.Moss et al. [25] conducted a multi-infusion study using the model drug methylene blue (peak at 668 nm). The goal was to assess the difference of different ports on the manifold or micro infusion line, which is where the drugs are combined. Volumes were simply calculated from the flow rate and analyzed using quantitative spectrophotometric analysis at specific times.

3.4 Chemical analysis

Analytic chemistry describes a wide variety of analytical method to separate and analyze chemicals. We added the methods that are relevant to the scope of this report.

3.4.1 HPLC

Many studies were found that described an application of the analytical method of High-performance liquid chromatography (HPLC). HPLC can beused to analyze and separate a wide variety of different analytes including many pharmaceuticals. Therefore HPLC can be of interest in future multi-infusion measurements.

HPLC is based on a stationary and mobile phase. A sample (the mobile phase) is injected through a column (the stationary phase) under high pressure. The stationary phase is polar and the mobile phase is non-polar in normal HPLC, whereas the polarity is reversed in reversed-phase HPLC. As every chemical has a different polarity each chemical has a different affinity to the mobile or stationary phase, which is the basis of chromatographic separation. Therefore, if the stationary phase is polar, the more polar chemicals in the mobile phase tend to move more quickly through the stationary phase than the less polar chemicals. The time it takes for a chemical to move through the column is called its retention time, which can be used to identify an unknown chemical. Finally the separated chemicals can be further quantified with severalanalytical methods. Most commonly an optical method is used. In literature UPLC (ultra-performance liquid chromatography UPLC was often found. This method is similar to HPLC but applies an even higher pressure.

It was found that HPLC is often used to study concentrations of pharmaceuticals *in vivo* to understand the pharmacokinetics of specific drugs. Commonly HPLC was combined with some mass spectrometric modality known as HPLC-MS, LC-MS or HPLC-MS/MS. A number of recent studies that describe the analysis of pharmaceuticals are summarized below

- Sumatriptan (SUM) and naproxen (NAP)[26]
- Methocarbamol (MET) and aspirin (ASP)[27]
- Gestodene, dienogest, drospirenone, etonogestrel, cyproteroneacetate and levonorgestrel[28]
- Sufentanil (opioid)[29]

3.4.1 Chemical analysis in multi-infusion

Franken et al. [30] conducted an experiment with a multi-infusion setup. Two setups were compared, setup 1 consisted of 4 pumps (Fresenius Vial, Module DPS) with 50 mL syringes of which 2 were in relay configuration. In this function an empty pump is automatically replacedwith a new one. One of the pumps was a volumetric pump.The pumps were combined using a multi-lumen catheter. The second setup was similar, but a manifold instead of multi-lumen was used and no relay function was applied.Three salts were used as analytes: Magnesium (6 mmol l^{-1}), Calcium (4.64 mmol l^{-1}), and Potassium (10.19 $mmoll^{-1}$). After the simulation of several clinical interventions (interruption every 30 minutes) a mixture of the analytes was collected and analyzed. In addition the pump pressures were registered. The mixtures were analyzed using a concentration-analyzer. This was possible because of the selection of analytes (salts). The results were finally compared with a theoretical model.This method was not real-time and in-line a similar experiment with two rumps. No additional statistical or technical information about the method was provided by the authors.De Wilde et al. [31]conducted an experiment with 5 parallel BBraun pumps containing:Glucose (50 cc, $10mlh^{-1}$), NaCl(50 cc,$1mlh^{-1}$), KCl(10 cc, $0,5mlh^{-1}$), $CaCl_2$ (50 cc, $2mlh^{-1}$) and $MgCl_2$ (10 cc, $0,3mlh^{-1}$). The experiments were performed in an incubator to control the environmental physical variables. A number of clinical interventions were simulated, including: start-up characteristics, flow-rate adjustment and changing the syringe and situation after occlusion.The salt concentrations in the samples were measured by a chemical clinical lab.

4 Discussion and conclusion

Besides the UMC method one other absorbance spectrophotometric methodhas been found[14].The absorbance spectrophotometric UMCmethod was capable of achieving good results using laser dyes.Good correlation and recovery was achieved, the RSD was between 063 and 1.12, good linearity was also achieved between ~2.0 – 40.0 mg l^{-1}. The analytical method applied was linear regression calibration and is open to improvement.

The method used by Décaudin et al. [19] was found to be agood option for improvement of the UMC method. The use of actual pharmaceuticals may prove to be an advantage as it is not entirely known how the physical properties of laser dyes relate to the physical properties of pharmaceuticals. The advantage of using laser dyes as opposed to actual pharmaceuticals or fluorescence spectroscopy are the narrow photo (absorption) peaks. Simple analytical methods can therefore be used as a result of little spectral overlap. In the area of spectrometry one otherfluorescence method was found but not validated;however, results were in agreement with a predictive model.The use of absorbance is more established than fluorescence in biomedical experiments.

Several flowmetry possibilities were investigated, including microfluidics. Electrokinetic and Micro particle velocimetry were found to be theoretically possible in a multi-infusion setup but too laborious at this point. Two microfluidic flowmeters were considered, both providing very promising accuracy for very low flow rates. The µ-flow was found to offer an accuracy of 2% and the mini Cori-flow showed an accuracy of 0.2%. Both flow meters were successfully applied by van der Eijk et al [4] in a multi-infusion setup.The method applied by Moss et al. [25]is suitable to study the influence of the manifold used in multi-infusion by simple volume measurement. The conclusion of Moss, that the port of the manifold is factor in drug delivery in multi-infusion is therefore only a fragment of the entire story. Dynamic real-time changes in flow or mass-flow cannot be assessed with volume measurement. In any case, the method used is not suitable for the assessment of flow rates in a complex multi-infusion setup.

Chemical analysis has been successfully applied by Franken et al. [30] andde Wilde et al.[31] in a multi-infusion setup. However, the method was not real time and in-line with the multi-infusion setup. Moreover, the analysis of the salts is complex and costly.Chemical analysis was found to be a broad subject, where HPLC takes a very prominent position among pharmaceutical analysis [27], [28], [29], [32]. The statistical parameters: recovery (around 100%), sensitivity, precision (around 1%), accuracy (around 100%) and selectivity were generally very good. However, the method is not real-time, analysis takes several minutes and the samples have to be prepared.

It is recommended to try and improve the current method with a different analytical technique, perhaps the PLS method used by Décaudin et al. There is also room for the improvement of the current analytical method using SVD or try to implement a higher derivative method in order to improve differentiation between the absorption spectra.Taking into account the advantages and drawbacks of the techniques found in literature, we consider a combination of methods the best option to improve the measurement method for multi-infusion research.A combination of flowmetry and mass spectrophotometry in which the results of measurements can be validated is recommended.

5 Outlook

Improvement of the measurement method can contribute to a reduction of risks for medical errors. Insufficient knowledge on the actual dose by multi-infusion poses a risk as a result of alteration and mutual influence of flow rates between the numerous pumps[3], [33]. Moreover, it is hard to predict the influence of the flow rate change in one pump and the time it takes to reach steady state after the disruption. Despite the fact that medical errors in infusion technology are well documented, less is known about these multi-infusion risks.It is therefore essential to find an accurate, reliable and validated measurement method.

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