Development and validation of a system based on spectral-photometry for measuring fluid dynamics of multi-infusion conditions in intensive care units

Timmerman, Annemoon, Riphagen, Brechtje, Klaessens, John, Verdaasdonk, Rudolf

Annemoon Timmerman, Brechtje Riphagen, John Klaessens, Rudolf Verdaasdonk, "Development and validation of a system based on spectral-photometry for measuring fluid dynamics of multi-infusion conditions in intensive care units," Proc. SPIE 7170, Design and Quality for Biomedical Technologies II, 71700F (23 February 2009); doi: 10.1117/12.809534

SPIE.

Event: SPIE BiOS, 2009, San Jose, California, United States

Development and validation of a system based on spectral-photometry for measuring fluid dynamics of multi-infusion conditions in Intensive Care units

Annemoon Timmerman*[a], Brechtje Riphagen[a], John Klaessens[a]; Rudolf Verdaasdonk[a],
[a]University Medical Center Utrecht, Heidelberglaan 100, Utrecht, The Netherlands;

ABSTRACT

Multi-infusion setups for medication administration in Intensive Care Units seem uncontrolled due to flow and pressure differences between syringe pumps. To investigate the dynamics and interaction of multi-infusion, a dedicated set-up was developed to measure the concentrations of fluids dynamically in multiple lines using absorption spectral-photometry. For feasibility testing and calibration, various dyes and concentrations were investigated to find the optimal settings. The developed method was validated and showed satisfactory results for determining mixtures of up to three different dyes in different ratios, with average recoveries of 105.0% (±11.01) for two dyes and 99.6% (±6.26) for three dyes. The method was applied in initial simulation experiments for measuring effects of manipulations in a multi-infusion set-up simulating a clinical situation. Results showed evidence for mutual influencing of separate infusion lines. The method developed for measuring the fluid dynamics of multi-infusion will contribute to a better insight and controlled administration of medications.

Keywords: Multi-infusion system, spectrophotometry, simultaneous analysis, fluid dynamics, method development, quality, safety

1. INTRODUCTION

The development of capable monitoring devices and accurate infusion systems has dramatically changed the amount of continuously administrated drugs in intensive care units. The philosophy behind this development must obviously be the wish to provide well-controlled and safe care, preferably tailored to the needs of the individual patient. Several attempts have already been made to set up strategies for the automatically regulation of infusion of multiple drugs, mostly in order to control hemodynamic variables [1]. However, intravenous administration of highly concentrated drugs at very low flow rates itself already constitutes substantial challenges for accurate dose control. The chemical and pharmacological compatibility of drugs is customarily tested before combining two lines in a multi-infusion system. In contrast, up till now virtually no adequate quantitative description exists of the consequences of flow rate changes at the pump on the actual drug concentration that reaches the patient's bloodstream.

A suitable measuring method is needed to investigate these characteristics. Due to differences in flow rate and compliancy factors, mutual influence of the different infusion lines is expected. Pilot studies have confirmed these expectations, but an extensive analysis of the flow characteristics of multi-infusion systems has not been performed yet. This paper presents the application of a newly developed method based on spectral-photometry, used to perform real-time analysis of dynamic flow aspects of multi-infusion systems.

2. BRIEF LITERATURE REVIEW

For single infusion systems, the effect of system characteristics and several interventions have been investigated extensively. System characteristics like syringe size, design and compliance have been studied [2, 4-7], as well as interventions like start-up and change in pump height [2-5]. Considering multi-infusion systems, the effect of system

* for correspondence: a.m.d.e.timmerman@umcutrecht.nl

Design and Quality for Biomedical Technologies II, edited by Ramesh Raghavachari, Rongguang Liang, Proc. of SPIE Vol. 7170, 71700F

characteristics and interventions are neither well recognized nor well characterized [8]. Partly due to the lack of a suitable analyzing method, the number of studies which have investigated multi-infusion systems is very limited. In The Netherlands, some studies have been carried out in investigating a multi-infusion system [9,10,11]. In these studies, infusion lines were filled with different salt-containing solutions of known concentrations. Samples were taken with an interval of 3 minutes and sample analysis took place afterwards. Absorbance spectrophotometry has not been applied to investigate infusion system characteristics. However, it is a well-established method for simultaneous estimation of analytes in a mixture without previous separation. In this study, the used spectral analysis method is based on linear regression calibration. This method is developed by López-de-Alba et al. and described by Dinç et al. (2003) and application of the method gave very good results in recovery experiments [13].

3. METHODOLOGY

To investigate the characteristics of multi-infusion systems, absorbance spectrophotometry is applied. Each infusion line is filled with a fluid containing a known concentration of absorbing dye diluted in distilled water. The specific absorptivity values of the absorbers at selected wavelengths are used to determine the concentration of each absorbing dye in mixture. The ratio between original concentration and determined concentration is dependent of the dilution factor. By using this dilution factor, the proportion of each individual fluid flow in mixture can be determined.

3.1 Linear regression calibration

The methodology used for the simultaneous determination of the specific absorbers in mixture without preliminary separation, is based on linear regression calibration. This method is described before by Dinç et al. [13] and is based on the use of linear regression calibration equations describing the linear relation between spectral absorption and absorber concentration at a specific wavelength. If Beer's law is obeyed over the whole wavelength range, the relationship between these variables, for the spectrophotometric determination of dye *A* at a selected wavelength λ and a path length of 1.0 cm is given by the following equation:

$$A_A = a_A \cdot C_A + b_A \tag{1}$$

Where A_A is the absorbance of dye A at wavelength λ_i , a_A is the slope of linear regression equation of dye A, C is the concentration of dye A (in mg/l) and b_A is the intercept value of the regression model of dye A. The intercept value (b) indicates the difference between the ideal system as described by Beer's law and the calculated system.

3.2 Concentration determination

When a mixture of more than one absorber is considered, a set of equations based on Eq. (1) can be written. For a system containing *N* absorbers, a set of *n* equations measured at *n* selected wavelengths (λ_i = 1, 2, .., n) is needed:

$$\begin{aligned}
&A_{mix_1} = a_{A_1} \cdot C_A + a_{B_1} \cdot C_B + \ldots + a_{N_1} \cdot C_N + \sum_{i=1}^{N} b_{i_1} && \text{at } \lambda_1 \\
&A_{mix_2} = a_{A_2} \cdot C_A + a_{B_2} \cdot C_B + \ldots + a_{N_2} \cdot C_N + \sum_{i=1}^{N} b_{i_2} && \text{at } \lambda_2 \\
&\ldots \\
&\ldots \\
&A_{mix_n} = a_{N_n} \cdot C_A + a_{N_n} \cdot C_B + \ldots + a_{N_n} \cdot C_N + \sum_{i=1}^{N} b_{i_n} && \text{at } \lambda_n
\end{aligned} \tag{2}$$

Where $A_{mix,i}$ represent the absorbance values of the mixture of dyes (*A,B,..,N)* at wavelengths λ_i (with *i =1,2,..,n*) and C_k represents the concentrations of dye *k* (with *k =A,B,..,N*) . The slopes of the linear regression equations at the *n* wavelengths are represented by $a_{i_1}, a_{i_2}, \ldots, a_{i_n}$ .The sum of the intercept values is given by $b_{mix_1}, b_{mix_2}, \ldots, b_{mix_n}$, with

$$b_{mix_{k,i}} = \sum_{k=i=1}^{n} b_{k_i} = b_{A_i} + b_{B_i} + \ldots + b_{N_i} .$$

This set of equations is the mathematical basis of the method used for simultaneous determination of the specific absorbing dyes in mixture. A matrix formed by the set of equations can be solved by means of the program Matlab in the computer and the concentrations of each dye in mixture can be determined.

3.3 Recovery determination

The ratio between original and found concentration was calculated and expressed as a percentage by the following formula:

$$\% \text{ Recovery} = (C_{A,\text{ mixed}} / C_{A,\text{ original}}) * D_A * 100 \quad (3)$$

Where $C_{A,\text{ mixed}}$ is the determined concentration of absorbing dye *A* after mixture has taken place and $C_{A,\text{ original}}$ is the determined concentration of absorbing dye *A* before mixture has taken place. Both determinations of dye concentration were performed by applying the spectral analysis method. As only the ratio between both dye concentrations is needed, the possible effect of inaccuracies in the sample making process is eliminated. Factor D_A in Eq. 3 is the dilution factor of dye *A*, indicating the dilution as a result of changing total volume due to mixing. Dilution factor D can be calculated by the following formula:

$$D_A = \frac{V_A}{V_A + V_B + .. + V_N} \quad (4)$$

Where V_i is the total volume of dye i (with i= A, B,..,N) when a total number of N dyes is considered. When dilution factor *D* is known, the ratio of each individual fluid flow in mixture can be determined.

4. EXPERIMENTAL SECTION

4.1 Experimental Setup

The setup shown in Fig.1 was used for flow measurements. The light source and spectrometer were coupled via two optical fibers and connected to the inline flowcell. This flowcell has an internal diameter of 1.5 mm and was connected to a 0.6 mm central infusion line. Because a larger internal diameter corresponds to a smaller resistance, contributions to increased resistance in the central line due to flowcell connection are not significant. The flowcell was covered during all measurements to prevent interference by external light sources. The fluid was pressed through the infusion lines and the interconnected flowcell by two or more infusion pumps. At the end of the central line, the out flowing fluid was collected in a cylindrical glass, standing on a 0.001 g precision balance to measure the total amount of pumped fluid gravimetrically. The cylindrical glass was closed airtight to prevent evaporation effects.

4.2 Apparatus

For the setup a DT-100 Deuterium Tungsten Halogen light source (Ocean Optics, USA) with a spectral output of 200-1100 nm was used together with a QE65000 Optic Spectrometer (Ocean Optics, USA) with a detector responsive from 200-1100 nm. Two 200 µm multi-mode optical fibers (Thorlabs, USA) were used for light energy transmission. An in-line flow cell (Ocean Optics, USA) with an optical path of 10 mm was used. For weighing measurements, a 0.001 g precision balance (PGW 450, Adam Equipment, USA) was used. SpecSuite software (Ocean Optics, USA) was used for all spectral data acquisition. For data analysis, Matlab 7.0 (Mathworks, USA) was used.

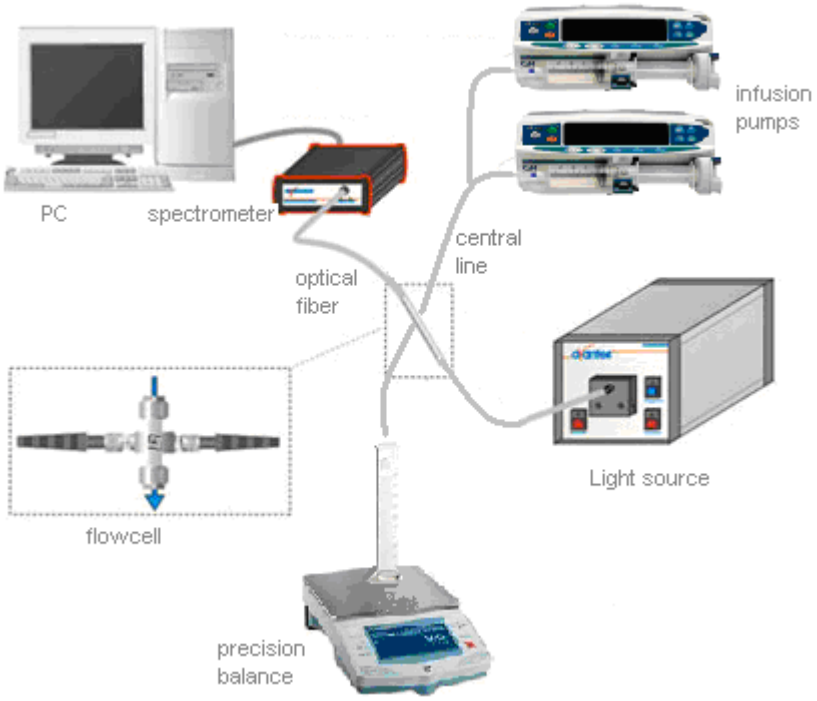

Fig.1. schematic view of experimental setup

4.3 Chemicals

From many dyes and colorants, three absorbing dyes were selected and used in the flow experiments. The dyes were selected on their absorbance properties, narrow-banded absorption peak and the ability to pass a 0.2 µm membrane filter when dissolved. The filter is a fixed element of the used infusion lines. The absorption properties were considered suitable when the absorption spectra showed a single absorption peak in the VIS spectrum and the peak was narrow-banded, set by a maximum bandwidth of 200 nm. The following absorbers with minimal overlapping spectral absorption peaks equally distributed over the spectral range of 400-800 nm, were selected:

Absorbing dye	λ_{max} *	Used abbreviation
Disodium Fluorescein	487nm	DF
Allura Red	500nm	AR
Simacid Blue	628nm	SB

Table 1: used absorbing dyes (* when dissolved in distilled water)

4.4 Standard Solutions

Stock solutions of the absorbers were prepared by dissolving 200.0 mg of dye in a 100.00 ml volumetric flask and adding distilled water to the mark. Before use, stock solutions were further diluted by pipetting 20.0 ml of stock solution in a 100.00 ml volumetric flask and filled with distilled water. The obtained standard solutions were 40.0 mg/l. According to manufacturer guidelines, the solutions would remain stable for at least two months if kept stored in a cool and dark place.

4.5 Procedures

Samples were prepared by pipetting a suitable amount of standard solution into a 100.00 ml clean and dry volumetric flask and adding distilled water to the mark. For measurements, standard solutions were transferred into the flowcell by using a clean and dry 1.0 ml syringe. To obtain the calibration data needed to set up the linear regression equations, a standard series of solutions was used. Their absorption spectra were recorded over the wavelength range 400-800 nm with respect to a blank of distilled water without any absorber. Measurements were repeated five times.

5. RESULTS

5.1 Absorbance characteristics of each dye

The absorbance characteristics of each dye were determined and analyzed. Maximal absorbance values were determined graphically. The absorbance spectra are shown in Fig. 2:

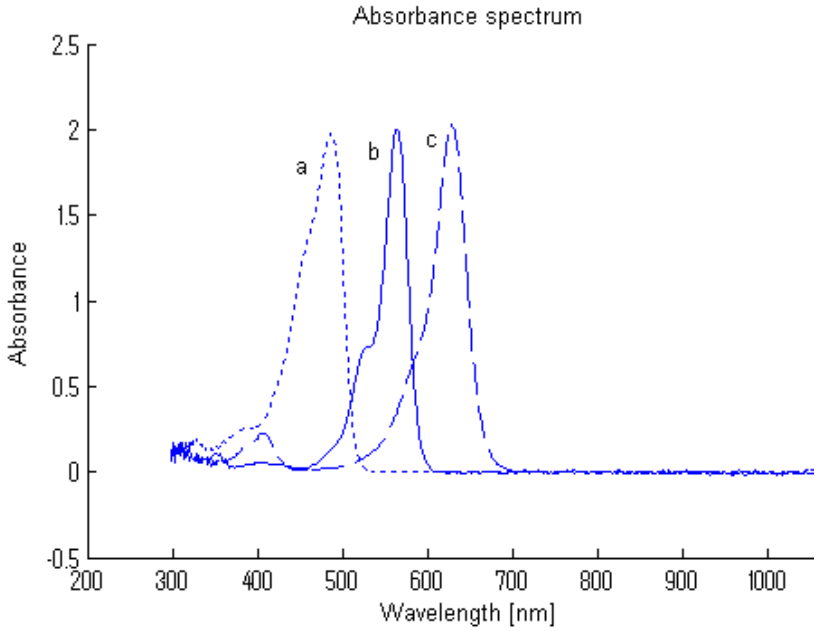

Fig.2. Absorption spectra of 13.0 mg/l of Disodium Fluorescein (DF), 15.0 mg/l Kiton Red (KR) and 13.0 mg/l Simacid Blue (SB).

5.2 Linearity characteristics of each dye

The absorptivity values at the λ_{max} value of each standard series of solutions were determined for each absorber. Linear regression calibration was performed and the results are presented in Table 2. Values obtained for the regression coefficients and linearity parameter indicated a good fit in all cases. Statistical data was obtained from five repeated calibration measurements at each standard concentration.

Table 2. Statistical data (n=5)

Absorber	λ_{max}	Correlation coefficient *r*	Linearity (%)
DF	487	0.9972	97.1632
AR	500	0.9991	98.2899
SB	628	0.9977	97.4591

Linearity (%) = $(1\text{-}S_a/a) *100$, where S_a = standard deviation of slope (a).

5.3 Mixing results

To assess the validity of the calibration model, recovery experiments were performed. Sample mixtures of the three dyes in different ratios were made. The concentration of each dye before mixing was compared with the concentration after mixing and was expressed as percentage. A recovery result of 100% corresponded to a perfect estimation of the amount of dye in mixture by applying the developed method. The average recovery was 99.6% ± 6.26. Measurements were repeated three times to emphasize validation.

5.4 Clinical simulation results

The proposed and validated method was applied to simulate a multi-infusion system. A set-up considering two parallel infusion pumps (Braun Perfusor© Space P) was used. Infusion lines and syringes from our Neonatology Intensive Care were applied, to obtain a clinical relevant set-up. The clinical relevant interventions which were simulated, included a syringe exchange in which one infusion pump was stopped for the period of three minutes while the other pump was kept constant. The other intervention was the flow rate increase and decrease of one infusion pump while the other flow rate was kept constant. These interventions are listed in Table 4 and the result of the simulation experiment is shown in Fig. 3. Pump adjustments are indicated by the dotted line.

Table 4. Manipulations in clinical simulation experiment

	Pump 1	Pump 2
T=0	4.0 ml/h	1.0 ml/h
T=1	0 ml/h (after 3 min back to original flow rate)	1.0 ml/h (after 3 min back to original flow rate)
T=2	4.0 ml/h	0 ml/h (during 3 min)
T=3	8.0 ml/h	1.0 ml/h
T=4	4.0 ml/h	1.0 ml/h

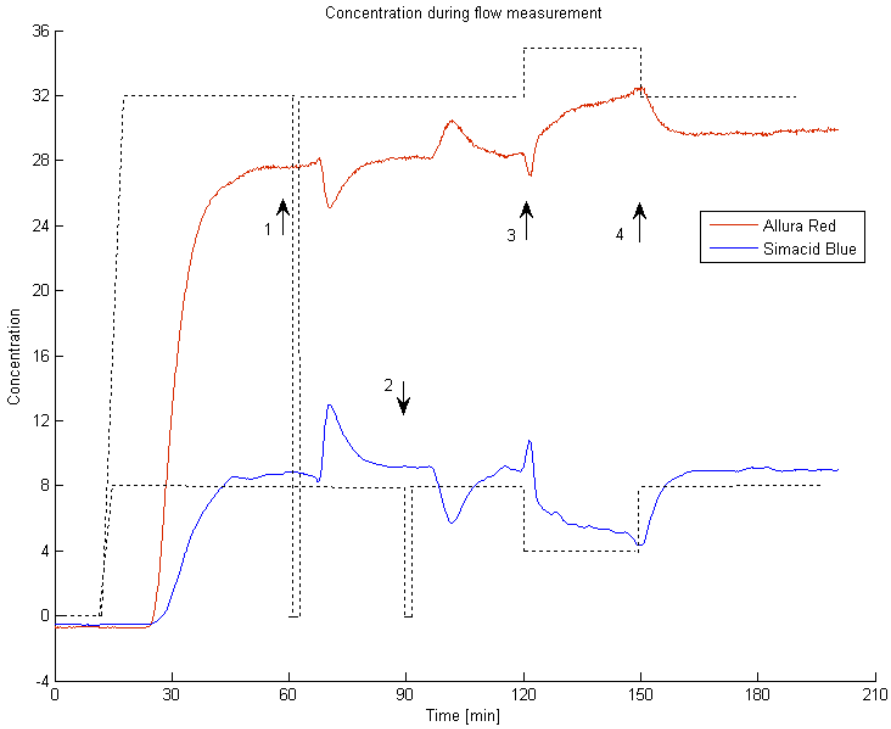

Fig.3. Absorption spectra of 40.0 mg/l Allura Red (AR) and 40.0 mg/l Simacid Blue (SB) in infusion measurement. Dotted line indicates the concentration input values.

As shown in Fig. 3. both infusion pumps show deviation from the concentration input value. The start-up time is about 25 min. and it takes up to 45 min for the slower flowing pump and up to 50 min. for the faster flowing pump to reach a stable situation. When a pump-specific manipulation is applied, both pumps show a change in concentration. When one of the pumps is stopped for 3 min. it takes about 6.5 min. before a change in concentration occurs (t=1, 2). It takes about 12 min. before the original concentration is reached again. When the flow rate of one pump is changed, both flows show an almost immediate change in concentration. When the flow rate of the fast flowing pump is doubled, the concentration first drops slightly before increasing (t=3). It takes about 20-25 min. before the new concentration is reached. The flow rate of the other pump remains unchanged but the concentration varies by first showing a slight increase before it decreases. When the flow rate of the fast flowing pump is decreased to the original concentration, it takes about 12 min. before the new concentration is reached (t=4). The other pump, which still has a constant flow rate, reaches the original level after 13 min.

6. DISCUSSION

6.1 Experimental

An essential element of the simulation method were the availability of several dyes with minimal overlapping spectral absorption peaks which are equally distributed over the spectral range of 400-800 nm. Some difficulties were encountered while searching for suitable dyes. The absorbance properties of multiple food colorants, Ecoline® inks, chemical colorants, laser dyes and chemical compounds have been assessed. From these, three dyes have been selected.

6.2 Linearity and accuracy

The most challenging in the method development process was to obtain a sufficient level of linearity and accuracy. Accuracy is influenced by the sample-preparation process. First sample measurements have been performed by using polystyrene cuvettes and when satisfactory results were obtained, the cuvette was replaced by a flowcell. Samples were prepared from previously mixed stock solutions. According to manufacturer guidelines, solutions should remain stable for at least two to three months. To assess stability, measurements were performed over three weeks. The RSD values were comparable to the previous obtained RSD values and there was no significant difference between the different weeks. Therefore, stock solutions could be considered as stable.

6.3 Mixing experiments

To validate the method, mixing experiments were performed. Different ratios were assessed. The error in determining the original concentrations of the specific dyes in mixture, is relatively high. What can be seen from the results was that the ratio of absorbers in mixture played an important role for most dyes. All dyes showed increasing errors as soon as their ratio in mixture decreased. Upcoming research will aim on lowering the recovery error by further increasing the accuracy of the method and will include quaternary mixtures.

6.4 Simulation experiments

After validation and calibration testing, the method was applied in a simulated clinical setting. The set-up was identical as used in clinical setting. The results clearly show the significance and importance of this real-time measuring method. The results shown in Fig. 3 support our hypothesis of mutual influence of individual infusion lines. The start-up time showed to be much longer than was theoretically expected. We assume that these effects are caused by pressure changes in the infusion system and by compliancy of syringes and infusion lines. In upcoming experiments, more interventions and manipulations will be simulated. Further research will also include theoretical modeling of multi-infusion systems.

7. CONCLUSION

The developed method is fast, accurate and can perform real-time measurements on multi-infusion systems. The expected fluctuations in syringe pump infusions were present in the initial simulation experiments. This result strongly encourage us to apply this method in order to identify potential risks of applying multi-infusion in clinical settings. The developed method has great promise for the performance of real-time analysis of flow aspects of multi-infusion systems. Application of the method will contribute to a better insight and controlled administration of medication, and will therefore contribute to a safer application of multi-infusion systems in clinical settings.

REFERENCES

[1] R. R. Rao, Control of a Non square Infusion System – A Simulation Study. Biotechnology Process 15, 556-564 (2008).

[2] K. R. Dunster and P. B. Colditz, Flow Continuity of Infusion Systems at Low-Flow Rates. Anaesthesia and Intensive Care 23, 605-609 (1995).

[3] M. A. Lovich, M. E. Kinnealley, N. M. Sims and R. A. Peterfreund, The delivery of drugs to patients by continuous intravenous infusion: Modeling predicts potential dose fluctuations depending on flow rates and infusion system dead volume. Anesthesia and Analgesia 102, 1147-1153 (2006).

[4] S. B. Neff, T. A. Neff, S. Gerber and M. M. Weiss, Flow rate, syringe size and architecture are critical to start-up performance of syringe pumps. European Journal of Anaesthesiology 24, 602-608 (2007).

[5] M. Weiss, M. I. Hug, T. Neff and J. Fischer, Syringe size and flow rate affect drug delivery from syringe pumps. Canadian Journal of Anaesthesia-Journal Canadien D Anesthesie 47, 1031-1035 (2000).

[6] D. W. Kim and D. J. Steward, The effect of syringe size on the performance of infusion pump. Paediatric Anaesthesia 9, 335-337 (1999).

[7] M. Weiss, J. Fischer, T. Neff and O. Baenziger, The effects of syringe plunger design on drug delivery during vertical displacement of syringe pumps. Anaesthesia 55, 1094-1098 (2000).

[8] C. Clark. A study to determine the extent and impact of problems associated with poor mixing of fluids in medical infusions into the vascular system (2004).

[9] S. v. Thoor. Multi-infusie: het effect van manipulatie. University Hospital Maastricht, The Netherlands (2003).

[10] N. Laheij. Multiple infusions: problems, risks, safety and solutions. Proceedings: FBMT. Annual congress, Würzburg, Germany 2-5 June (2002).

[11] M. Franken, S. R. Vaartjes, Multi-infusie: Meer dan een pomp alleen. FMT Gezondheidszorg 20 – 24 (2008)

[12] Y. N. Ni and X. F. Gong, Simultaneous spectrophotometric determination of mixtures of food colorants. Analytica Chimica Acta 354, 163-171 (1997).

[13] E. Dinc, Linear regression analysis and its application to the multivariate spectral calibrations for the multiresolution of a ternary mixture of caffeine, paracetamol and metamizol in tablets. Journal of Pharmaceutical and Biomedical Analysis 33, 605-615 (2003).

[14] M. De Luca, G. Ioele, A. Risoli and G. Ragno, Improvement of multivariate calibration techniques applied to 1-to-N component mixtures through an optimized experimental design. Microchemical Journal 83, 24-34 (2006).