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DEVELOPMENT OF A MICRO OPTO-FLUIDIC SENSOR FOR CONTINUOUS SELECTIVE IN-LINE MONITORING OF ELECTROLYTES

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ABSTRACT

The aim of this work is to investigate a fluorescent micro opto-fluidic sensor based on the principle of photo-induced electron transfer (PET). As a first proof-of-principle, a lab setup has been developed using a low crosstalk 1×2 splitter and a glass tube of 3.2 mm diameter. The laser intensity peak and the emission spectrum of Rhodamine B have been recorded using a spectrometer at 530 nm and 580 nm respectively. As a next step, a micro opto-fluidic device with integrated optical fiber with a core diameter of 50 µm is fabricated using soft lithography technique. Two different designs have been investigated for their optical performances. The influence of flow rate on the sensitivity of the device is measured by varying the flow rate from 0 to 10000 µl/min and plotting it against ratio of the peak intensity of laser and Rhodamine B emission spectrum. It is noticed that, changing the flow rate from still to a flow rate of 300 µL/min the intensity reduces exponentially (~ 84%) and from 300 µL/min till 600 µL/min it reduces gradually (~ 40%) and becomes stable after 600 µL/min onwards.

1. INTRODUCTION

Patients with end-stage renal disease (ESRD) are dependent on dialysis for the maintenance of fluid and electrolyte balance. The physical principle of hemodialysis is based on convection and diffusion. The dialyzer in hemodialysis machine allows the solutes to diffuse between blood and dialysate such that, during the course of treatment the plasma composition is re-established to the normal values. The dialysate is prepared in most outpatient centers with a fixed concentration of electrolyte. But pre-dialytic serum concentrations of the major electrolytes (Na⁺, K⁺ and Ca²⁺) differ widely between individual patients. This “one-size fits all approach” leads to the occurrence of acute and chronic cardiovascular complications in dialysis patients. As the age and additional disorders of dialysis patients increase in number, a patient specific dialysate is preferable [1][2]. In some dialysis modules, on-line measurement of dialysate conductivity at in- and outlet are applied which has resulted into the availability of on-line clearance monitors on various contemporary dialysis monitors (Diascan® Hospal-gambro; OCM; Fresenius). This is primarily the assessment of urea clearance [3], given the strong relation between diffusive sodium and urea transport [4]. Conductivity measurements are unspecific for ion type distinction and moreover, this method enables the calculation of ionic mass balance as a surrogate of sodium balance and plasma conductivity as a surrogate of plasma sodium [5][6]. However, due to the effect of other ions such as bicarbonate on conductivity measurements and despite the strong interrelation, neither dialysate nor plasma conductivity can be considered a full substitute for equivalent sodium concentrations. In addition to sodium, potassium balance is also of great importance in dialysis patients. Insufficient removal of potassium during dialysis

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could result in hyperkalemia with a zenith before next dialysis procedure whereas excessive removal might result in hypokalemia with a nadir just after the dialysis procedure. Both post-dialytic hypokalemia and pre-dialytic hyperkalemia are related to mortality [7][8]. In contrast, calcium, mass balance is complicated as next to removal by convection, also depending on the pre-dialytic plasma calcium concentration during dialysis either diffusive gain or loss can occur [9]. The dialysis calcium concentration is a two-edged sword as both positive as well as negative calcium balance can be good or lead to complications [10][11]. Therefore, there is a clinical need for the ion-selective on-line measurements of vital electrolytes such as sodium, potassium, and calcium during hemodialysis.

Although, electrochemical methods are routinely used for the assessment of ion concentrations in watery solutions, they need frequent calibration and are prone to fouling. Optical sensors offer intrinsic electrical safety (no galvanic contact), good miniaturization perspective, improved biocompatibility, less fouling and simultaneous real-time measurement of multiple ions [12][13][14]. One of the most sensitive optical sensor platform for biomedical application is based on molecular fluorescence. Apart from its sensitivity, other advantages include (a) possibility of single molecule detection, (b) limited or no damage to the host system, (c) non-invasive sensing technique can be envisaged by the use of infrared regime, (d) both fluorescence intensity as well as decay times can be utilized for increased sensitivity and (e) time resolved fluorescence for in-vivo sensing [15]. Recent developments in the field of MEMS-based optical sensors have increased the interest of miniaturized biochemical sensors with additional system functionalities. A Microfluidic device with integrated optics, also known as micro opto-fluidic, is an emerging technology in the field of bio-sensing. Polymer fabrication techniques [16][17] of integrating optical elements into microfluidic devices have several advantages in terms of simplicity and cost reduction [18]. Therefore, in this work a polymer based approach is used to fabricate microfluidic channels in poly (dimethylsiloxane) (PDMS) with SU8 as a patterning layer. Optical fibers are integrated into the channel for coupling-in and – out of light and to demonstrate the performance of the device under various flow regimes. The final aim of this work is to integrate PET molecules into the optofluidic device for the in-line monitoring of electrolytes. The PET principle exploits selective quenching of fluorescence. The sensor consists of a fluorophore, spacer and ion-specific receptor for Na⁺, K⁺ and Ca²⁺. The intensity ratio between fluorescence and absorption indicates specific ion concentration [19] [20]. In this work Rhodamine B is used as a fluorescent dye to test the proof-of-principle. For this purpose, an experimental set up has been developed and two different designs with integrated optical fibers are under investigation and the dependence of fluorescence intensity on flow rate has also been examined.

2. EXPERIMENTAL SET-UP

For showing the proof of principle, two experimental setups have been developed. Firstly a mini-scale set-up is developed for testing the optical sensor principle. Then, this set-up is further miniaturized to a micro-scale opto-fluidic device.

2.1 Proof-of-principle set-up

Firstly, a laboratory set-up is built to verify and observe the working principle of the optical sensor. The schematic of the experimental set-up is shown in Fig. 1.

![Figure 1: Schematic of the PET proof-of-principle set up](image)
A diode pumped solid state green laser source (Roithner LaserTechnik GmbH) operating at a wavelength of 532 nm with a maximum power of 10 mW is used as excitation source. Rhodamine B dissolved in water serves as fluorescent sample for the experiment. A syringe pump (Harvard, PHD2000) is used to precisely control the flow rate of the sample in a glass tube of 3.2 mm diameter (made at TU/e EPC workshop). A low cross talk 1×2 splitter (DieMount GmbH) is used for the light coupling into the solution and a spectrometer (Ocean Optics USB 4000) is used to record the fluorescence signal. A photograph of the experimental set up is shown in Fig. 2.

![Figure 2: Photo of laboratory set-up for PET proof-of-principle](image)

2.2 Micro opto-fluidic set up

The idea of the previous set-up is now miniaturized into an micro-optofluidic device.

2.2.1 Device Fabrication

The device has been fabricated using soft lithography technology, it is an inexpensive and convenient technique to make high quality patterns [21]. The device is fabricated on a standard 4-inch silicon (Si) substrate. The steps for the fabrication procedure are illustrated in Fig. 3.

![Figure 3: Cross sectional view of the fabrication steps of an enclosed microfluidic channel with fiber coupler grooves](image)
The fabrication of the device can be divided into, (i) SU-8 patterning, (ii) optical fiber alignment into the channel and (iii) sealing the channel with a thin layer of PDMS or a microscopic glass slide.

SU8 is an epoxy based negative photoresist used extensively as a patterning layer for the fabrication of microfluidic devices [22][23]. In this work, SU8-2100 (MicroChem) is spin coated on a Si wafer with a rotational speed of 500 rpm for 10 s and 1900 rpm for 30 s respectively to achieve a thickness of 150 µm. Afterwards, the wafer is soft-baked on a hot plate at 65 °C for 5 min, cooled down to room temperature and then again baked at 95 °C for 30 min. The UV lamp used for exposure operates at a wavelength of 365 nm with a maximum intensity of 11.4 mW/cm². The exposure is executed for 45 s illumination to get a total dose of 513 mJ/cm². Afterwards, a post exposure baking step is followed at 65 °C for 5 min and 95 ºC for 10 min respectively. Development is carried out in mr-Dev 600 (micro resist technology GmbH) solution for 12 min. The patterned layer is rinsed with extra developer and then with isopropanol, blow dried with pressurized nitrogen and hard baked at 150 ºC for 20 min for further crosslinking. This resulted in a master mold for the microfluidic channels and fiber coupler groove.

PDMS (Sylgard 184, Dow Corning) prepolymer is mixed thoroughly with curing agent in the ratio of 10:1; the mixture is placed in a desiccator connected to a vacuum pump to allow the removal of the trapped air bubbles that arose from the mixing process. After degassing, the PDMS mixture is poured onto the master mold and allowed to cure in an oven at 75 ºC for 2 h. Also, the PDMS mixture is poured into a petri-dish and baked in oven at 75 ºC for 2 h to obtain a thin layer of PDMS to enclose the microfluidic channel. After curing, the PDMS layer is soft and flexible and hence it is peeled off from the mold master. This way the SU-8 pattern is transferred to the PDMS layer. The inlet and outlet ports for fluid flow are fabricated using a circular metal punch with 1.2 mm diameter. In the next step, a multimode optical fiber (50 µm core and 125 µm diameter with cladding) stripped off of its polymeric coating is inserted into the fiber coupler groove. It is then treated with a corona discharge ozone generator for surface activation. The channel is sealed irreversibly with the thin layer (3mm) of PDMS treated also with corona discharge. Instead of a PDMS layer even microscopic glass slide can also be used for sealing. The ensemble (Fig. 4) is then soft baked in an oven for 2 h at 75 ºC to ensure better sealing. Soft baking in the oven does not affect the performance of the glass fibers.

![Photograph of the microchip with integrated optical fibers.](image)

**Figure 4:** Photograph of the microchip with integrated optical fibers. The

### 2.2.2 Design

The mask has been designed using the AutoCAD program and consists of microfluidic channel with inlet, outlet and fiber coupler grooves for accommodating the optical fiber. The optical fiber coupler grooves are designed to fit the commercially available silica clad glass fibers (Thorlabs) of 50 µm core diameter with a cladding of 105 µm (after stripping off the outer jacket). Two different configurations (Fig. 5) have been investigated for their optical performances.
The absorbance of a solvent with an optical path length \( l \) can be calculated from Beer’s Law:

\[
A_s = \varepsilon_s c_s l
\]

where \( \varepsilon_s \) is the molar absorptivity of the solute and \( c_s \) is the molar concentration. The direct proportionality between \( A_s \) and \( l \) gives a tool to find an optimal path length which ultimately determines the signal-to-noise (SNR) ratio [16]. The optofluidic device in this work is designed with two different path lengths in order to study their optical performances. In Fig. 5(a) the optical path length of the device is limited by the width of the channel (500 µm) while in Fig. 5(b) the a ‘U’ shape channel is designed to increase the optical path length (to 4 mm).

3. RESULTS AND DISCUSSION

3.1 Proof-of-principle result

The laboratory set-up shown in Fig. 2 is used for the measurement of emission spectra of Rhodamine B dissolved in water. The laser intensity and emission spectra as shown in Fig. 6 are measured at 532 nm and 585 nm respectively. Since the final device will be used for measuring the fluorescence signal in a flow medium, it is important to study the effect of flow rate on the fluorescence signal detection. Initially the spectrum is measured for still (no flow) medium and then the flow rate is precisely changed in steps. Firstly the flow rate is changed from 0 µL/min to 1000 µL/min in steps of 100 µL/min and then from 1000 µL/min to 10000 µL/min in steps of 1000 µL/min. The emission peak and laser intensity peak has been recorded at each flow rate and the ratio of is plotted against the flow rate in Fig. 7.

![Figure 6: Laser intensity and emission spectra of Rhodamine B solution in water.](image)
The ratio of absorption intensity and emission spectrum denotes the sensitivity of the device. The typical result from a single experiment is shown in Fig. 7. It can be noted that the intensity is not constant over the entire measurement range. The highest value is observed when the sample fluid is not flowing and it decreases exponentially (~ 85%) with increasing flow rate up to 300 µL/min and then decreases gradually (~40%) between 300 µL/min and 600 µL/min. But, interestingly it stabilizes above 600 µL/min onwards. For clarity, in Fig. 7 the measurements from 1000 to 10000 µL/min respectively are not shown, but their mean value is 0.47 with a standard deviation of 0.05. One of the reasons for this trend with increasing flow rate could be, the dye molecules in solution are excited to higher energy states upon laser irradiation and starts fluorescing, these fluorescing dye molecules have a lifetime of less than 10 ns and depend highly on the competitive non-radiative decay process [24]. At higher flow rates, the fluorescing dye molecules move away from the detector region without interacting with the detector and hence an exponential decline is observed. The stability at higher flow rates can be due to the increase in number of dye molecules per unit area close to the detector region. This process is still under investigation.

3.2 Micro Opto-fluidic device

The micro opto-fluidic chip with dimensions of 10 mm × 500 µm × 150 µm (Length × Width × Height) and 500 µm × 150 µm (Length × Height) as shown in Fig. 5(a) and Fig. 5(b) with integrated optical fibers of 50 and 105 µm core diameters are used to measure the fluorescence of Rhodamine B solution in water. The experimental setup is as shown in Fig. 8.
In Fig. 9, the absorption and emission spectra of Rhodamine B dissolved in water is presented for the device configuration shown in Fig. 5(a). It is evident from the graph that the excitation light source is coupled very well and the emitted fluorescence signal is collected efficiently by the optical fiber in this design. As expected the results are very similar to the glass tube experiment (Fig. 6). Other device design configuration is still under investigation.

![Absorption and emission spectra of Rhodamine B dissolved in water.](image)

**Figure 9:** Absorption and emission spectra of Rhodamine B dissolved in water. The micro opto-fluidic device used for this measurement is shown in Fig. 5(a).

![Ratio of laser intensity (λ_ab) and Rhodamine B emission (λ_ex) spectrum as a function of flow rate in the micro opto-fluidic device with 10 mm × 500 μm × 150 μm dimension.](image)

**Figure 10:** Ratio of laser intensity (λ_ab) and Rhodamine B emission (λ_ex) spectrum as a function of flow rate in the micro opto-fluidic device with 10 mm × 500 μm × 150 μm dimension.

The next step is to evaluate the sensitivity with respect to flow rate. In order to do a quick test the flow rate in this case is varied from 0 μL/min to 500 μL/min and the ratio of the absorption (λ_ab) and and emission (λ_ex) spectra is plotted against the flow rate as shown in Fig. 10. It can be observed that the sensitivity decreases with increasing flow rate. This is also similar to the behavior as observed in the glass tube (Fig. 7). This clearly indicates that the principle of optical sensing can be successfully miniaturized. The performance of
the other device is still under evaluation. The results will be used to further optimize the opto-fluidic micro-device.

5. CONCLUSIONS

A proof-of-principle setup for the measurement of absorption and emission spectrum of Rhodamine B is presented and the sensitivity is measure by plotting the ratio of absorption and emission spectrum against flow rate. A micro opto-fluidic device in SU-8 and PDMS with integrated optical fiber is fabricated using standard soft lithography fabrication process. Two different designs have been fabricated and their optical performances have been evaluated. The sensitivity in case of both the proof-of-principle experiment and micro opto-fluidic device decreases with increasing flow rate.

The fabricated and developed new micro-optofluidic sensor show very promising characteristics and can sustain wide range of flow rates for the measurement. The results obtained now will be used to further optimize the device.

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REFERENCES AND CITATIONS


