American Journal of Electronics & Communication

Avik Sett et al, American Journal of Electronics & Communication, Vol. V (1), 73-76

Fabrication of pH and oxygen sensors for monitoring myocardial ischaemia during open heart surgery

Avik Sett*, Robbert Friendwijk*, Alireza Tajeddin, Massimo Mastrangeli, Paddy French*

Department of Microelectronics, Delft University of Technology, Mekelweg 4

2628 CD Delft, Netherlands

Email-p.j.french@tudelft.nl

***Abstract*— Open heart surgery encounters Cardioplegia induced cardiac arrest where the cardioplegia is administered to avoid heart tissue damage. However, in some cases, cardioplegia do not reach all cells and lead to permanent heart damage through myocardial ischaemia. Detection of oxygen, pH, lactate and carbon dioxide can allow to monitor the heart during surgery and help to eliminate such complications. In this article, hydrogel based pH and oxygen sensor is demonstrated which can detect changes in pH and oxygen levels efficiently. HPTS loaded microbeads are immobilized within hydrogel matrix to form the pH sensor whereas ruthenium particles are embedded in hydrogel to form the oxygen sensor. Future optimization and integration of the two sensors would improve the monitoring of myocardial ischaemia during open heart surgeries and even benefit organ health monitoring during organ transplant surgeries.**

Keywords*— *Ischaemia, Open heart surgery, pH detection, Oxygen sensing, Hydrogels.

I. INTRODUCTION

Open heart surgery involves administration of cardioplegia by arresting the heart temporarily. Cardioplegia is a pharmacological solution which stops the heart muscle cells from functioning, leading to Cardioplegia Induced Cardiac Arrest. In this scenario, the heart-lung machine takes over the function of the heart and lung. The heart does not recieve oxygenated blood during cardiopulmonary bypass, resulting in altered metabolism of heart muscle cells [1]. During initial phase of cardioplegia administration [2], the heart muscle cells may become fully damaged if all cells do not recieve cardioplegia [3]. Post heart surgery, myocardial damage (ischaemia) is one of the leading cause for mortality and morbidity [4]. Myocardial ischaemia is observed in 29% of patients undergoing aortic valve replacement [5] and 2-10% of the patients undergoing coronary artery bypass surgery [6]. The mortality rate can be significantly reduced if there is continuos monitoring of heart based on ischaemia symptoms.

Cardiomyocytes need oxygen for proper metabolism, however, an imbalance between oxygen requirement and oxygen supply leads to ischaemia. The lack of oxygen limits the mitochondria of the cardiomyocyte to produce sufficient energy (ATP). Hence, anaerobic glycolysis takes over to produce the required energy. The process of anaerobic glycolysis leads to lactic acid formation, which breaks down immediately to form hydrogen atoms and lactate. The intracellular pH reduces due to increase of acidity in cardiomyocytes. Ischaemia is not only associated with insufficient oxygen supply, but also with inefficient removal of metabolic waste products. The restriction in blood flow also prevents carbon dioxide to get transported away from the cell and leads to carbon dioxide accumulation. Hence, ischaemia leads to i) insufficient oxygen supply, ii) decrease in pH levels (increased acidity), iii) increase in lactate levels and iv) increase in carbon dioxide levels. There is also correlation among tissue lactate, tissue pH and tissue carbon dioxide [7]. Based on previous reports [8], we have selected oxygen and pH measurements as the most efficient technique to detect ischaemia.

In this work, two different sensing layers are fabricated for pH and oxygen in hydrogel matrix. The pH sensitive probe, pyranine, cannot be incorporated directly into the hydrogel, as it gets leached away during measurements. Hence, pyranine is immobilized on the surface of microbeads and then incorporated on the hydrogel matrix. Both pyranine (pH sensitive) and ruthenium (oxygen sensitive) demonstrates absorption at 450 nm (blue light), however they show sensitive detection at different wavelengths. The pH sensing measurements are carried out at 520 nm emission from pyranine and the oxygen sensing measurements are carried out at 610 nm emission from ruthenium complex. Even though seperate sensor layers are fabricated and characterized in pH solution and in air, this research would be extended to fabricate both sensor probes in one single layer and detect pH and oxygen levels in tissues for myocardial ischaemia.

II. EXPERIMENT

A. Choice of sensor matrix and sensing probes

HydroMed D4 is selected as the sensor matrix owing to its proven bio-compatibility and non-essential activation process. The development of HydroMed D4 is efficiently carried out by dissolving it in ethanol. The sensor probes/indicators/fluorescent particles are then introduced into the hydrogel solution to form an integrated system of sensor probes and sensor matrix. Hydrogel layers with incorporated sensor probes have a lifetime of more than 120

Avik Sett* and Robbert Friendwijk* have contributed equally.

days, which makes it a promising candidate for sensing applications [9].

Pyranine (HPTS) is a phenolic luminophore which contains phenol or phenolates as its functional attachment. Photoexcitation of phenolate groups results in fluorescence. A decrease in pH contributes to lesser absorption of the phenolate form leading to reduction in fluorescence. On the contrary, an increase in pH results in enhancement of fluorescence. Pyranine was selected due to its high sensitivity towards pH alterations, large Stokes shift and ease in processing. However, pyranine suffers bleaching and alters the ionic strength of the solution. Hence, proper encapsulation of the pyranine in the sensor matrix is of utmost importance.

Ruthenium particles are chosen as fluorescent probes for oxygen detection owing to its high sensitivity towards oxygen, large stokes shift and good selectivity. In the absence of oxygen, the fluorescence intensity of the ruthenium particles is very high. However, in presence of oxygen, the excited states of the ruthenium complex collides with the oxygen molecules, resulting in fluorescence quenching. The decrease in fluorescence intensity with increase in oxygen content gives an indication of the oxygen content in a given media.

B. *Fabrication of pH and oxygen sensing layers*

For developing the pH sensor, initially 10 g of AmberChrom microbeads was soaked in 10 ml demineralized (DM) water. 35 mg HPTS (pyranine) was dissolved in 100 ml DM water and the microbead solution was added to it. The resulting solution was stirred for 15 hours at 400 rpm. During this process, HPTS got functionalized on the microbeads surface. The microbeads with HPTS was collected through filtration. The hydrogel matrix was prepared by dissolving 1 g HydroMed D4 precursor to 10 ml 90% ethanol. The solution was stirred for about 6 hours to get a uniform hydrogel solution. 3.5 g of the HPTS functionalized microbeads was added to the hydrogel solution. The mixture was stirred for 6 hours to get a well dispersed profile of microbeads in the hydrogel. The solution was then drop casted over a glass slide to prepare the pH sensing layer.

Dichlorotris(1,10-phenanthroline)ruthenium(II) hydrate was selected as the precursor for fabrication of oxygen sensor. 50 mg of the ruthenium complex was dissolved in 10 ml solution of methanol and toluene (4:1). The solution was stirred for 1 hour at 100 rpm. 1 ml of the as prepared ruthenium solution was added to 10 ml of hydrogel solution. The resulting mixture was stirred for an hour at 300 rpm to obtain an uniform mixture of ruthenium particles in hydrogel matrix. The solution was then drop casted over a glass slide to prepare the oxygen sensing layer.

C. *Sensing approach*

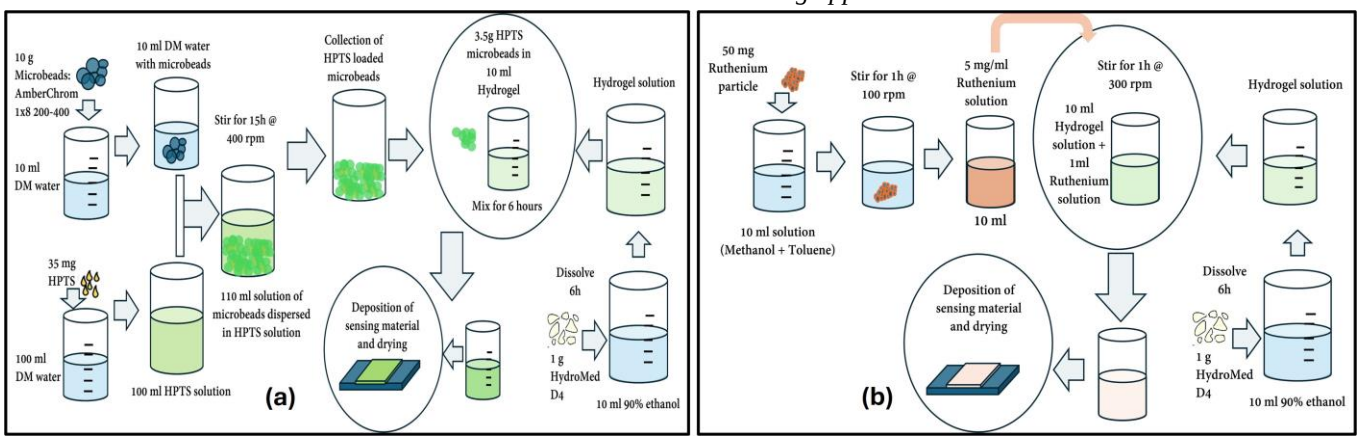

Figure 1: (a) Fabrication steps for pH sensitive hydrogel layer and (b) fabrication steps for oxygen sensitive hydrogel layer

The sensing layers would be attached to the tip of the optical fiber that is used to illuminate the sensor probes with a blue light (450 nm) source as demonstrated in figure 2. The sensing layers would be in contact with the heart tissue, continuously monitoring the pH and oxygen levels during the surgery. The reflected light that contains the fluorescence from the pH (520 nm) and oxygen (610 nm) sensitive probes would be analyzed to monitor the condition of the heart. In case of myocardial ischaemia, there would be lack of oxygen supply and increase in acidity in the heart tissue. Thereby analyzing the pH and oxygen levels would provide a great insight onto the symptoms of myocardial ischaemia. This would facilitate the surgeons to alter the dosage of cardioplegia.

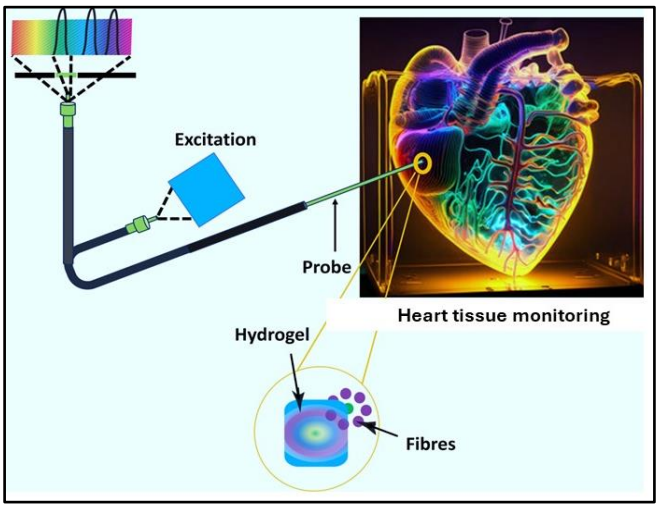

Figure 2: Sensing approach for Myocardial Ischaemia

III. Result and Discussion

The microscopic images of the pH and oxygen sensitive sensing layers are depicted in figure 3(a) and 3(b) respectively. As observed, the HPTS loaded microbeads (figure 3(a)) and ruthenium particles are well dispersed in the hydrogel matrix.

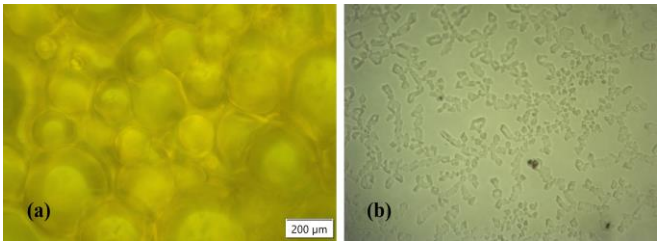

Figure 3: (a) Microscopic images of HPTS loaded microbeads in hydrogel and (b) microscopic images of ruthenium particles in hydrogel

The pH sensor was illuminated with 450 nm LED and the reflected light was recorded for pH detection. With increase in pH levels, the absorption of the sensing layer increases and hence a decrease in intensity at 450 nm is observed in the detector. However, as the fluorescence intensity increases with increase in absorption, figure 4 demonstrates the behavior of the sensor at 520 nm with increase in pH levels. Even though the sensor demonstrates an expected behavior of increased fluorescence intensity with increase in pH, linearity is distorted at higher pH levels. Hence, more optimization is required in the sensor end to achieve a linear performance for better calibration.

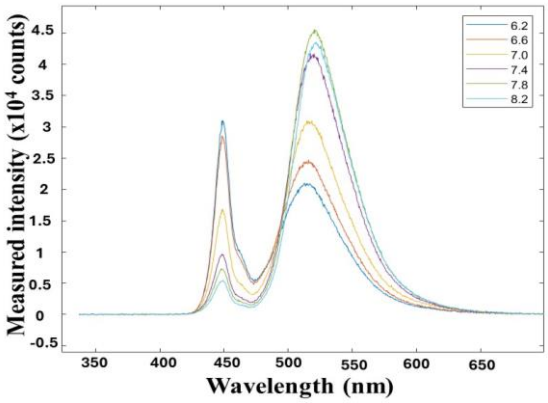

Figure 4: Fluorescence spectra for HPTS loaded microbeads with variation in pH levels.

To better understand the dynamic performance of the pH sensor, the sensor was initially exposed to a solution of pH value 6.6 for fifteen minutes. The sensor was then withdrawn from the 6.6 pH solution and exposed to a solution of pH 7.4. The response time of the sensor was calculated to be 12 seconds, which is apt for measuring continuous change in tissue pH values. The sensor was tested in this range as it is the common pH physiological range for tissues and organs. As the tissue pH would change in an ideal condition during ischaemia monitoring, response time of 12 seconds is appropriate for such detection. Figure 5 demonstrates the transient response of the sensor with changing pH from 6.6 to 7.4.

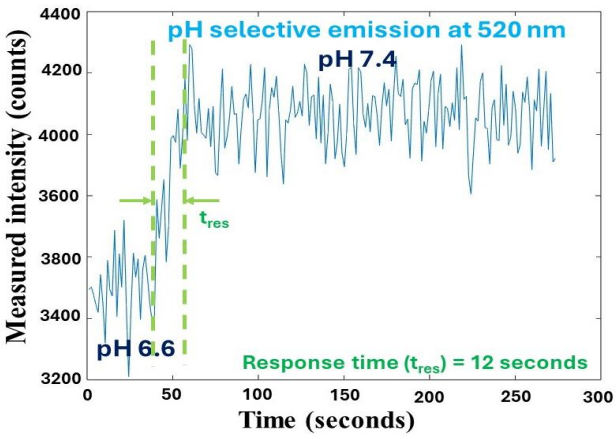

Figure 5: Transient response of the hydrogel sensor with HPTS loaded microbeads.

The ruthenium incorporated hydrogel sensing layer was tested for oxygen detection in air. Even though the real application resides in determining oxygen level in tissues, this experiment was carried out to test the efficacy of the fabricated sensor. During ischaemia, there is restriction in oxygen supply, however, when the tissue is oxygenated it is termed reperfusion. Figure 6 demonstrates the oxygen sensing performance of the ruthenium incorporated hydrogel layer. The baseline is obtained in presence of oxygen in air (21%), by detecting the fluorescence at 610 nm, when exposed to 450 nm blue light. When the oxygen supply is cut off (0%), the sensor responds immediately and shows a higher fluorescence intensity (approximately >15 times). Again when the oxygen levels are restored, the excited states in ruthenium undergoes collision with molecular oxygen and quenches the fluorescence. The repeatability of the sensor shows there is a scope of improvement for stability through better optimization of particle loading and sensor thickness.

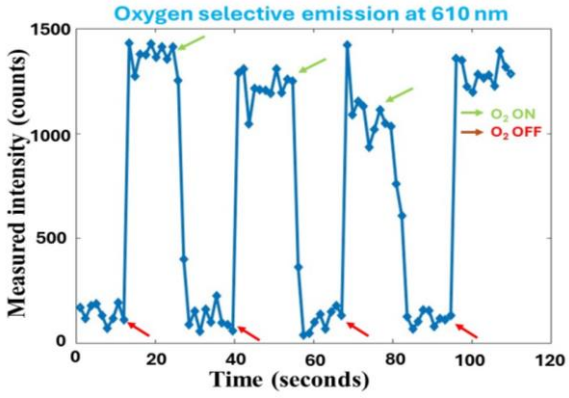

Figure 6: Transient response of the Oxygen sensor with ruthenium in hydrogel.

IV. CONCLUSION

This research work exhibits the successful development of pH and oxygen sensor intended towards detection of myocardial ischaemia. The pH sensor is characterized in

solution where as the oxygen sensor is characterized in air. The sensors demonstrates high sensitivity and fast response. However, future development of this research is planned to develop one single sensor and integrate both the sensor probes in one single layer. This would improve the efficiency of the detection technique. Moreover, in near future, the oxygen sensor would be tested in solutions. At the subsequent stage, pH and oxygen sensor in an integrated form would be tested in tissues for the ultimate application.

REFERNCES

[1] C. Carvajal, A. Goyal, and P. Tadi, Cardioplegia (StatPearls [Internet]). Treasure Island, FL, USA: StatPearls, Jan. 2022.

[2] G. P. Dobson, G. Faggian, F. Onorati, and J. Vinten-Johansen, "Hyper kalemic cardioplegia for adult and pediatric surgery: End of an era?" Frontiers Physiol., vol. 4, p. 228, Aug. 2013.

[3] G. P. Gravlee, Cardiopulmonary Bypass: Principles and Practice. Philadelphia, PA, USA: Wolters Kluwer Health, 2008.

[4] C. Drescher, A. Diestel, S. Wollersheim, F. Berger, and K. R. L. Schmitt, "How does hypothermia protect cardiomyocytes during cardioplegic ischemia?" Eur. J. Cardio-Thoracic Surg., vol. 40, no. 2, pp. 352–359, Jan. 2011.

[5] C. H. Lee et al., "Myocardial injury following aortic valve replacement for severe aortic stenosis," Korean J. Thoracic Cardiovascular Surg., vol. 47, no. 3, pp. 233–239, 2014.

[6] A. T. Turer and J. A. Hill, "Pathogenesis of myocardial ischemia reperfusion injury and rationale for therapy," Amer. J. Cardiol., vol. 106, no. 3, pp. 360–368, Aug. 2010.

[7] A. Steinegger, O. S. Wolfbeis, and S. M. Borisov, "Optical sensing and imaging of pH values: Spectroscopies, materials, and applications," Chem. Rev., vol. 120, no. 22, pp. 12357–12489, Nov. 2020.

[8] M. F. Vriesendorp, "Detecting myocardial ischaemia with optochemical sensing by using a fluorescent hydrogel," M.S. thesis, Dept. Biomed. Eng., Delft Univ. Technol., Delft, The Netherlands, 2021.

[9] X. Ge, Y. Kostov, and G. Rao, "High-stability non-invasive autoclavable naked optical CO2 sensor," Biosensors Bioelectron., vol. 18, no. 7, pp. 857–865, Jul. 2003.