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DEVELOPMENT OF EXTENDED GATE FIELD EFFECT TRANSISTOR (EGFET) FOR QUANTIFICATION OF PHOSPHORUS MASS REMOVED FROM CHRONIC KIDNEY PATIENTS IN HEMODIALYSIS SESSIONS

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Abstract: Hemodialysis is a procedure that seeks to remove excess fluids and substances accumulated in the body of patients with kidney failure (chronic kidney disease). Excess substances such as phosphorus are harmful to the body, and the control of its serum level in chronic kidney disease patients during hemodialysis represents a challenge for nephrologists. The elevated level of phosphate in the blood (hyperphosphatemia) is associated with death cases in chronic kidney disease patients. This work presents the development of an extended gate field effect transistor (EGFET) for phosphorus mass quantification in the final total dialysate (FTD) extracted during the hemodialysis process. Initially, an electrolyte-insulating-semiconductor device (EIS) was manufactured to be connected to the gate of a commercial MOSFET to form the EGFET. For the EIS device, thin aluminum oxide films (Al_2O_3) deposited on a structure composed of a thin layer of silicon oxide (SiO_2) on the silicon substrate were used. In addition, a reference electrode was manufactured containing an ion-selective membrane based on poly vinyl alcohol, along with the insertion of an organic compound diethylenetriamine to be used in the EGFET. The results indicated the phosphate concentration in the range of zero to 7 mg/dL in FTD and a sensitivity of 97 mV/(mg/dL), confirming that the EGFET is an innovative solution for real time measurement of phosphate concentration in FTD for the quantification of the phosphorus mass that is removed from the chronic renal patient during the hemodialysis session.
Keywords: EGFET, (Al_2O_3), hemodialysis, phosphate, thin films.

INTRODUCTION

Hemodialysis removes phosphate by diffusion and convection, but in general, it is not enough to maintain a neutral balance [1]. The removal limitation of excess phosphate during the dialysis procedure is mainly due to the kinetics between the intra and extracellular compartments [2]. Phosphate removal occurs mainly in the first 60 to 90 minutes of the hemodialysis session, decreasing right after it [3]. This is due to the fact that phosphate exist in large quantities in the intracellular compartment and, as the phosphate is removed from the blood to the dialysate, there is a phosphate transfer from the intracellular to the blood compartment, slowly than its removed by hemodialysis instead [4]. The main determinant aspect of the phosphate amount removed is its serum level at the beginning of hemodialysis. When in excess, the blood phosphate ion binds to circulating calcium, forming calcium phosphate, an insoluble substance that precipitates in blood vessels. The final result is the calcification of these vessels, obstructing blood flow [5], favoring cardiovascular diseases and thus increasing the risk of heart attack and stroke, which are the main death causes of patients with kidney failure.

Therefore, the phosphate concentration analysis in the post-hemodialysis liquid (final total dialysate) is essential for chronic renal patients. In this context, an EGFET device sensitive to the phosphorus ion was made to be used to measure the phosphate concentration in the FTD solution in real time. Firstly, a phosphate ion sensitive EIS device was developed, which can be connected to a MOSFET gate. The EIS device was built in the same way as a MOS capacitor (metal-oxide-semiconductor capacitor), but the metallization was not performed (oxide window) and a polymeric insulator based on methoxy propanol acetate was deposited on

it (SU8-25), having an opening window, thus allowing the solution to come in contact with the oxide, as illustrated in Fig. 1.

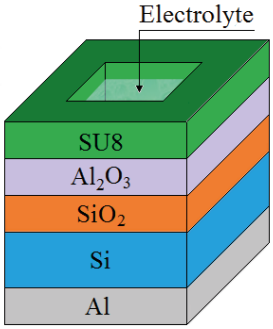

Fig. 1: Representation of the EIS device.

Then, the manufactured EIS device was connected to the gate of a commercial MOSFET model IRF540, as presented in Fig. 2.

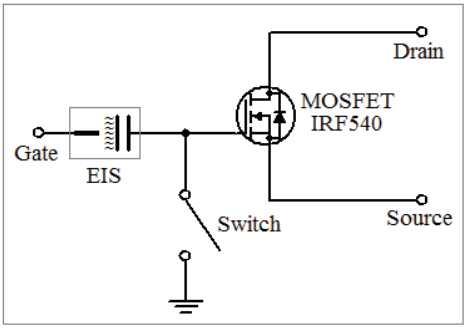

Fig. 2: Schematic representation of EGFET.

Due to the electrical fluctuations that may occurs in the transistor gate, a switch was used, to ground the device, in order to discharge the MOSFET between one measurement and another, thus avoiding possible accumulated residual charges. The I_{DS} current as a function of the V_{DS} voltage is practically the same as that of the MOSFET [6].

$$I_{DS} = \frac{1}{2}\mu C_{OX}\frac{W}{L}\left[2(V_{REF} - V_{T_{EGFET}})V_{DS} - V_{DS}^2\right] \quad (1)$$

Where the oxide capacitance (C_{OX}) is defined by:

$$C_{OX} = \frac{C_{Al_2O_3} \times C_{SiO_2}}{C_{Al_2O_3} + C_{SiO_2}} = \frac{\varepsilon_{OX} A}{t_{OX}} = \frac{\varepsilon_{OX} A}{t_{Al_2O_3} + t_{SiO_2}} \quad (2)$$

And, ε_{OX} is defined as:

$$\varepsilon_{OX} = \frac{\varepsilon_{Al_2O_3}\varepsilon_{SiO_2}\left(t_{Al_2O_3} + t_{SiO_2}\right)}{\varepsilon_{SiO_2} t_{Al_2O_3} + \varepsilon_{Al_2O_3} t_{SiO_2}} \quad (3)$$

The contribution of the voltages that appear due to the interface between the electrolyte and the ion-selective membrane is presented in the threshold voltage of the EGFET, and the electrolyte and the reference electrode [7], [8]:

$$V_{T_{EGFET}} = V_{T_{MOSFET}} + V_{REF} + \phi_{SOL} - \frac{\Phi_{REF}}{q} - \phi \quad (6)$$

In equation 6, V_{REF} is the reference electrode potential, Φ_{SOL} is the electrolyte surface dipole potential, Φ_{REF} is the work function of the reference electrode, q is the elemental charge, and ϕ is the electrolyte/membrane interface potential ion-selective [9], [10].

MATERIALS AND METHODS

EIS DEVICE MANUFACTURING

For EIS device fabrication, type P silicon wafer with crystallographic orientation <100> and with resistivity from 1 to 10 Ω/cm were used. Thin films of amorphous aluminum oxide deposited on a structure composed of a thin silicon oxide layer (passivation layer) on the silicon substrate were used, thus forming an $Al_2O_3/SiO_2/Si$ structure. Silicon oxide was obtained by dry oxidation in a conventional oven at 1000 ºC for 30 minutes, thus obtaining a thickness of about 14 ηm. Aluminum oxide was obtained by ALD (Atomic Layer Deposition), and presented a thickness of 20 ηm.

Aluminum (Al) was used to form the lower electrode of the EIS device. This electrode was obtained by sputtering, having 300 ηm tick. A polymeric insulator known as SU8-25 was deposited on the aluminum oxide

layer through the photogravure method, forming a structure having a well with walls, as illustrated in Fig. 1, allowing the solution to contact the oxide only in that region. Fig. 3 contains a schematic representation of the EIS device fabrication steps.

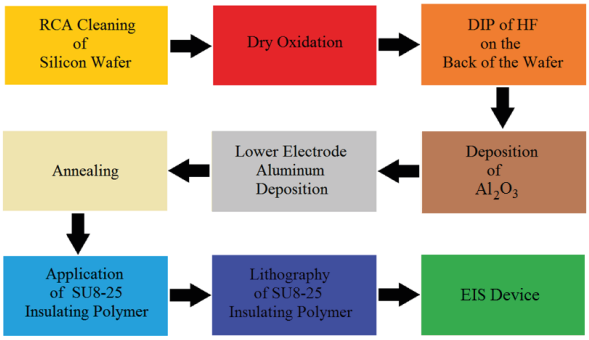

Fig. 3: Steps in the EIS device production process.

The SU8-25 layer thickness is approximately 40 µm, and the opening area in the photoresist has a diameter of 4 mm. Fig. 4 shows the image of a complete EIS device.

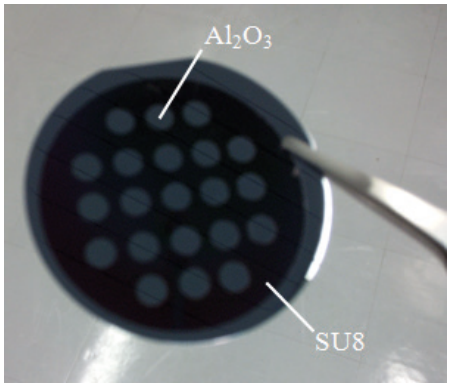

Fig. 4: Image of the completed EIS device.

EGFET REFERENCE ELECTRODE FABRICATION

The reference electrode used in EGFET is composed of a plastic tube containing an ion-selective polymeric membrane, which in turn is formed by the polyvinyl alcohol polymer (PVA) with the addition of the ionophore diethylenetriamine and a copper electrode, as shown in Fig. 5.

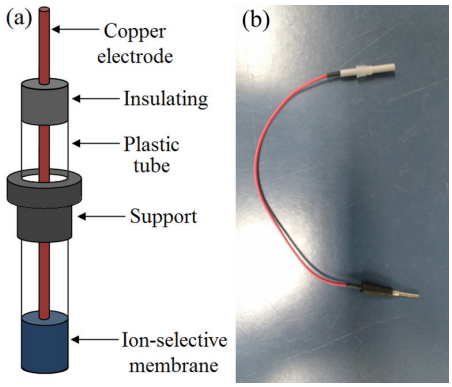

Fig. 5: (a) Illustration of the reference electrode used in the manufactured EGFET, (b) electrode image.

ION-SELECTIVE POLYMERIC MEMBRANE MANUFACTURING

In this work, polyvinyl alcohol (PVA) was used as a polymeric matrix [11]-[14]. The membranes were prepared by solubilizing 2 g of PVA in 40 ml of deionized water and 4 ml of isopropyl alcohol at approximately 85 °C under constant mechanical stirring. After decreasing the temperature of the PVA mixture to approximately 45 °C, 75 µL of 25% glutaraldehyde and concentrated hydrochloric acid (HCl), the latter being the catalyst, were added to promote crosslinking of the PVA. This mixture was stirred briefly and placed in an oven for 24 h at 70 °C [15], [16]. To increase the selectivity between the ion-selective membrane and the phosphate ion, 10 µL of diethylenetriamine was added to the PVA, which behaves as an ionophore for the phosphate ion [17], [18].

RESULTS AND DISCUSSION

PHOSPHATE CONCENTRATION MEASUREMENTS IN FTD

For the phosphate concentration measurements in the final total dialysate (FTD), I_{DS} versus V_{DS} curves were obtained. Different concentrations of phosphate dissolved in the FTD solution were used. In this characterization, the voltage applied to the EGFET reference electrode was set to 3,45 V. For this measurements, a 10 µL drop of phosphate solution dissolved in the FTD was placed on the surface of the EIS device (electrolyte) for each analyzed concentration (zero to 7 mg/dL). Thus, an MOS structure of the electrolyte/Al_2O_3/Si type (EIS device) was obtained. The reference electrode was placed in contact with the electrolyte. The body contact was made in the Si substrate pressed on the metal base of the testing station. Then, the measurement of I_{DS} x V_{DS} in EGFET was started for each drop of phosphate solutions dissolved in FTD with concentrations ranging from zero to 7 mg/dL, varying V_{DS} from zero to 1 V, having a fixed 3,45 V on the reference electrode. Fig. 6 shows the I_{DS} versus V_{DS} curves as a function of the phosphate concentration.

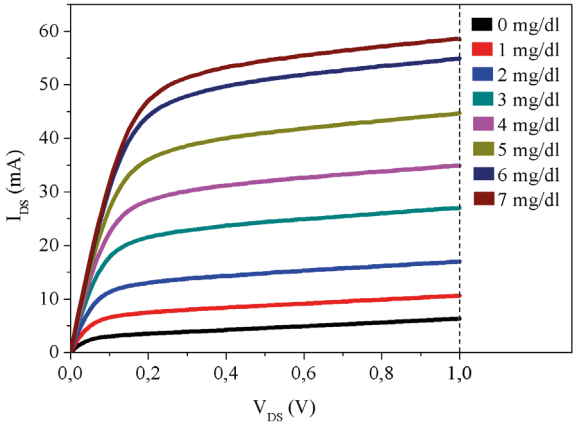

Fig. 6: I_{DS} x V_{DS} curves as a function of the phosphate concentration in FTD solution. All measurements were performed using an EGFET.

In fig. 6, the I_{DS} measurement of the FTD solution without adding the phosphate salt (zero mg/dL) was performed to verify the selectivity of the ion-selective membrane, that is, the interference in the measurement of other ions in the solution. The saturation current (I_{DS}) for the measurement with zero phosphate concentration in the FTD was approximately 6,3 mA, and for the measurement with 1 mg/dL it was approximately 10,6 mA. That is, the measurement with the concentration of 1 mg/dL, was approximately 68% higher than the measurement in FTD with zero phosphate concentration. It is also possible to extract the saturation I_{DS} values for each phosphate concentration values in FTD solution, and thereby obtaining the I_{DS} curve as a function of phosphate concentration in FTD solution, as shown in Fig. 7.

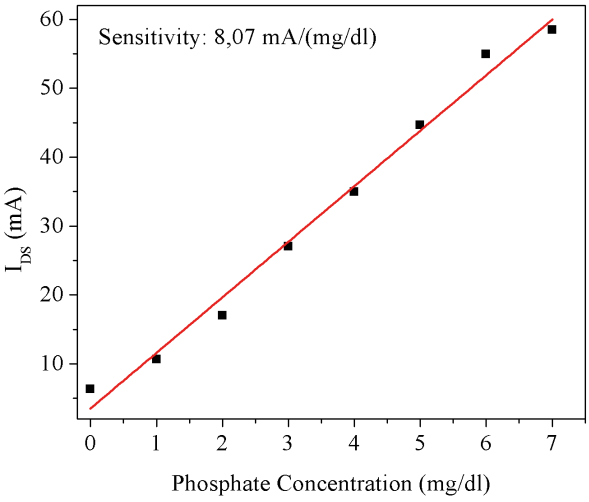

Fig. 7: I_{DS} values as a function of the phosphate concentration in FTD solution.

In Fig. 8, we have the I_{DS} x V_{GS} curves, showing the threshold voltages (V_T) for each phosphate concentrations in the FTD.

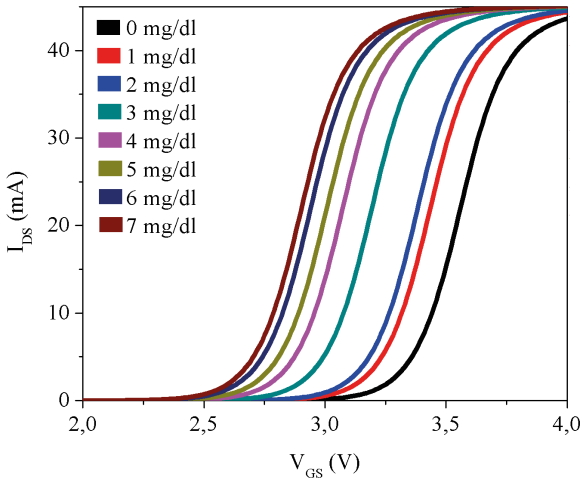

Fig. 8: I_{DS} x V_{GS} as a function of the phosphate concentration in FTD solution.

From the I_{DS} x V_{GS} by I_{DS} it was possible to extract the V_T value for each concentration values. When plotting these V_T values as a function of phosphate concentration, we obtained the EGFET sensitivity value as a function of the phosphate concentration in FTD solution, as shown in Fig. 9, and thus obtaining the EGFET sensitivity value.

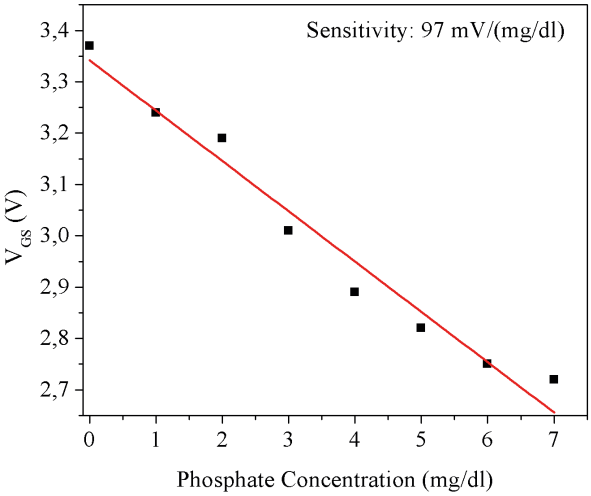

Fig. 9: V_{GS} values as a function of the phosphate concentration in FTD solution used to calculate the EGFET device sensitivity.

We can see in Fig. 9 that the sensitivity of EGFET was 97 mV/(mg/dL). This voltage sensitivity obtained is too close to that one's presented for ISFETs devices [19].

EGFET CALIBRATION AND TESTING

The EGFET device testing was performed in samples of the final total dialysate (FTD) provided by the Department of Clinical Medicine (Nephrology) of the Faculty of Medical Sciences at the State University of Campinas, and the result was compared with that one's obtained from chemical analysis done in dedicated laboratory. Tab. 1 shows the result of the laboratory analysis of the FTD sample.

Substance	Calcium	Phosphor	Magnesium	Potassium	Sodium
Concentration (mg/dL)	4,70	2,31	1,28	9,78	312,66

Tab. 1: Laboratory analysis results of the FTD sample.

For the EGFET calibration, an FTD solution with a phosphate salt (Na_2HPO_4) concentration of 2,31 mg/dL was prepared, and then the I_{DS} x V_{DS} was obtained (sample A). In the same way, a sample (B) was collected at the output of the hemodialysis machine and the I_{DS} x V_{DS} of the FTD sample was raised and laboratory analysis was performed. Fig. 10a shows the $I_{DS\,x}$ V_{DS} curves for samples (A) and (B) obtained, and Fig. 10b shows the I_{DS} x V_{DS} curve adjusted for the sample (A).

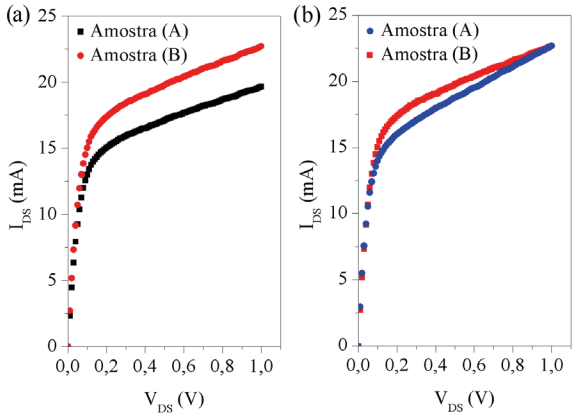

Fig. 10: I_{DS} x V_{DS} as a function of the phosphate concentration in FTD solution for samples (A) and (B), and I_{DS} x V_{DS} adjusted for the sample (A).

Even though both samples have the same chemical characteristics, according to the I_{DS} x V_{DS} curves, we notice that there is a difference in the maximum I_{DS} current of approximately 3,0 mA between samples. That shows the need for an EGFET calibration since the results of current measurements for the two samples should be the same or very close to each other. This calibration was performed by empirically adjusting the voltage at the EGFET reference electrode until the I_{DS} curve of the sample (A) overlapped the I_{DS} curve of the sample (B), as shown in Fig. 10b. This calibration must be performed every time a series of measurements is started. Samples A and B are chemically identical, but sample B was selected as the standard sample for calibration. We noticed in Fig. 10b, that the adjusted I_{DS} curve of the sample (A) was not entirely superimposed on the V_{DS} by I_{DS} curve of the sample (B), however, this is not critical, the most important thing is that the maximum I_{DS} current of both curves are the same, since the maximum I_{DS} current that will be correlated with the phosphate concentration.

CONCLUSION

In this work, the EGFET device proved to be an efficient solution for the measurement of the phosphate concentration, being a good alternative for ISFET replacement. EGFET allows greater flexibility when choosing the MOSFET device and also in the flexibility of changing the EIS device, without the need to fully manufacture another device. Also in this work, a selectivity was shown by both the aluminum oxide and the ion selective membrane, which allowed to clearly measure the phosphate ion concentration in solution of the final total dialysate (FTD) having a sensitivity of 97 mV/(mg/dL). The measurements results carried out on the prepared FTD solutions were approximately 15% off the results obtained from the FTD solutions made by chemical analysis. This difference was easily reduced to approximately 4,4% by only adjusting the voltage at the EGFET reference electrode. The EGFET formed by a MOS transistor and an EIS device, composed of aluminum oxide and a reference electrode containing a selective membrane [20], proved to be very promising solution to measure the concentration of phosphate in FTD in real time and also for quantifying the mass of phosphorus that is removed from the chronic renal patient in hemodialysis sessions. It has also brought a significant contribution regard to the phosphorus concentration level control in chronic renal patients, according to works related in the literature [21], which shows the significance of controlling the phosphorus concentration in patients with chronic kidney failure. Generally, this concentration in dialysis patients should be between 2,7 and 5,5 mg/dL [22], [23]. The fabricated device is able to monitor at real time such concentrations.

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