Low-cost fabrication of indium tin oxide (ITO) FETs for sodium detection in electrolytes and human urine

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Here, robust and low-cost sodium sensors based on the ion-sensitive field-effect transistor (ISFET) are fabricated using indium tin oxide (ITO) thin film. The effect of the presence of oxygen during the sputtering of the ITO thin film is characterized on the sensitivity of sodium ion (Na⁺) detection. A sodium ionophore III membrane is applied on the ITO substrate to fabricate ISFET (ITO-ISFET). The results reveal that the increase in the oxygen gas flow rate (0–1 sccm) with a fixed argon flow rate at 20 sccm during sputtering increased the sensitivity of ITO-ISFET from 15.8 to 100.9 mV/decade. In addition, the proper condition with a nearly Nernstian slope is at 0.4 sccm oxygen flow rate. Furthermore, the experimental results reveal that the sensors exhibit a high sensitivity of 38.5 ± 2.1 mV/decade in a wide range (10⁻¹⁰ to 10⁻¹ M). The limit of detection (LOD) of ITO-ISFET is 1.8 nM, which is lower than the minimum allowable Na⁺ level in the human body and urine. Furthermore, the proposed ITO-ISFET has the capability to detect Na⁺ in real human patient urine without any dilution process.

Introduction: Several advanced materials have been extensively employed as robust materials to prepare sensors for the determination of ions. In the medical field, sodium ions (Na⁺), found in the human blood and extracellular fluid, play an important role in maintaining the electrolyte balance, fluid balance, and pH (acid/alkaline) balance in the body. In the human body (blood plasma), the normal Na⁺ concentration is 135–145 mmol/L. The increase in Na⁺ concentration above 145 mmol/L causes hypernatremia and concentration below 135 mmol/L causes hyponatremia [1]. Therefore, it is essential to monitor the Na⁺ concentration in the human body. We may also need a sodium urine test after getting abnormal results on a Na⁺ blood test, which can identify acute kidney failure. However, the measurement of the urine is cumbersome, inconvenient, and challenging. Hence, a robust, easy, and accurate monitoring of Na⁺ is important.

Indium tin oxide (ITO), a transparent thin film produced from indium (III) oxide (In₂O₃) and tin (V) oxide (SnO₂), has been extensively utilized in biosensor studies owing to its unique properties such as good optical transparency, wide potential window, high electrical conductivity, substrate adhesion, and low capacitive current. Several methods, such as sputtering, spin coating, ion plating, dip coating, and pulsed laser deposition, are commonly used for depositing ITO thin film. Among these methods, the sputtering method is considered a simple and compatible fabrication method for depositing high-quality ITO thin films with high electrical properties [2].

Field-effect transistor (FET) as a potentiometric biosensor has gained increasing attention due to its advantageous analytical properties such as simple procedural instruments, low cost, and rapid analysis time. FET for ion sensing application was first developed by Bergveld, and is referred to as ion-sensitive FET (ISFET) [3]. The current magnitude of the ISFET depends on the charge density (concentration) of the analyte molecules on the gate surface. Several studies have reported the Na⁺ detection of graphene- and silicon-based ISFETs [4, 5]. The objective of this work is to investigate the effect of the oxygen gas flow rate at room temperature sputtering of ITO thin film on the sensitivity to Na⁺. The ITO thin films were deposited on the glass substrate by radio frequency (RF) magnetron sputtering under the same argon flow rate, temperature, power, and working pressure. ITO thin films were deposited with different oxygen flow rates. Furthermore, the obtained results revealed that the developed ITO-ISFET could be utilized to determine Na⁺ concentration in real human urine samples.

Experiment: ITO thin films were deposited by an RF magnetron sputtering system (KVS-2000, Korea) with the ITO target containing 90 wt% In₂O₃ and 10 wt% SnO₂ for 15 min at a power of 100 W. The base pressure and working pressure were set at 5 × 10⁻⁶ and 1.75 × 10⁻³ Torr, respectively. Argon and oxygen gases were used as sputtering reactive gases. The ITO thin films were deposited at 0, 0.2, 0.4, 0.6, 0.8, and 1 sccm oxygen flow rate with fixed argon flow rate at 20 sccm. All the samples were sputtered at 25°C.

Gold was deposited on the ITO thin film surface using a thermal evaporator to define the drain and source electrodes, which created a total width and length of the ITO-ISFET at 10.5 mm × 5 mm. The gate channel was 5 mm in width and 500 µm in length, as shown in Figure 1. An Ag/AgCl electrode was used as a reference electrode. To apply a bias to the electrodes, conductive wires were bonded to the drain and source electrodes using silver paste. Finally, drain and source electrodes were covered with epoxy resin to protect the electrodes from the electrolyte. This simple hand-made fabrication and the sputtering of thin film at 25°C allow high production and lower ISFETs fabrication cost.

The ion-selective membrane (ISM) was prepared by following the preparation in [6]. Briefly, 2 wt% of sodium ionophore III was mixed with 65 wt% bis(2-ethylhexyl) sebacate and 33 wt% poly(vinyl chloride) high molecular weight, and the mixture was dissolved in 1 mL tetrahydrofuran (THF). Then, the gate channel was coated with 3 µL of the ISM mixture, and stored at 25°C for 24 h, to allow all THF to evaporate. Finally, the gate channel area of the FET was fully covered by the ISM.

The gate–source voltage (VGs) was fixed at 0.5 V. The gate–source voltage (VGs) was swept from −1.0 to 2.0 V. The sensitivity and limit of detection (LOD) of Na⁺ in 50 mM Tris-HCl buffer solution were evaluated in the ITO-ISFETs fabricated with different oxygen flow rates by varying the concentrations of NaCl solution from 10⁻¹⁰ to 10⁻¹ M. The sensitivity measurements in Tris buffer solution were obtained using five hand-made ITO-ISFETs. Before measuring, the ITO-ISFET was soaked in 0.1 M NaCl solution for 30 min to activate the ISM, followed by immersion in DI water for 15 min.

The Na⁺ sensitivity of the ITO-ISFET was evaluated in the four human urine samples. The real human patient urine was provided by Keimyung University School of Medicine (IRB No. 2015-03-018). The ion concentration of patient urine samples was characterized using an ISE-based analytical equipment (ADVIA 2400, SIEMENS Healthcare, USA) at Keimyung University Dongsan Hospital. The urine condition of the four real human patient samples is shown in Table 1. All the real patient urine samples were tested without any additional dilution process.

Table 1. The ion concentration (Na⁺, K⁺, Cl⁻, and Cr³⁺) and Na⁺/K⁺ ratio in human urine samples

| Subject no. | u-Na⁺ (mM) | u-K⁺ (mM) | Na⁺/K⁺ ratio | u-Cl⁻ (mM) | u-Cr³⁺ (mM) |
|-------------|-------------|------------|---------------|-------------|-------------|
| S058        | 226.0       | 50.9       | 4.4           | 145.0       | 133.0       |
| S060        | 152.0       | 51.0       | 3.0           | 76.0        | 177.0       |
| S066        | 25.0        | 30.6       | 0.8           | 22.0        | 64.9        |
| S061        | 95.0        | 15.3       | 6.2           | 76.0        | 39.2        |
Result and discussion: Field emission scanning electron microscopy (FE-SEM) was used to characterize the surface morphology of deposited ITO thin films at different gas flow rates. The grain size of the deposited ITO thin films decreased with an increase in the oxygen flow rate, as shown in Figure 2a. When the oxygen flow rate increased (0 to 0.2, 0.4, 0.6, 0.8, and 1 sccm), the thicknesses of the deposited ITO thin films were 67.2, 60.9, 44.9, 37.8, 33.8, and 26.3 nm, respectively, as shown in Figure S1 in Supporting Information. Furthermore, the growth rate of the ITO films significantly decreased from 4.5 to 1.8 nm/min with an increase in the oxygen flow rate (Figure 2). Argon as a rare-gas ion has a higher sputtering rate compared to the reactive oxygen gas ions. The higher oxygen gas flow rate increases the affinity of the electronegative oxygen to attract electrons, which reduces the plasma density, thus, causing fewer positive argon ions. In addition, the increase in the flow rate of oxygen disturbed the bombardment of argon ions to the ITO target [7]. Therefore, the increase in the flow rate of oxygen into the sputtering chamber reduces the sputtering rate, thus, reducing the thickness of the thin film. The energy dispersive X-ray spectroscopy (EDS) was used to determine the chemical elements present in the ITO thin film. The relative ratio of oxygen present in the ITO thin film is proportional to the increment of oxygen flow rates (Table S1 in Supporting Information).

The electrical properties of the ITO thin films were measured by the oxygen flow rate. Figure 3a indicates that the increase in the oxygen flow rate causes a reduction in the carrier concentration from 10^{19} to 10^{16} cm^{-3}. In contrast, the ITO thin film sheet resistance increased with an increase in the oxygen flow rate (Figure 3b). The sheet resistance shows the opposite trend with carrier concentration. The increase in the sheet resistance was due to the decrease in the thickness and grain size of the ITO thin film. The change in the sheet resistance was also caused by the redundant oxygen that is usually chemisorbed on the surface and bonded at the defects [7].

The membrane containing sodium ionophore III had adequate sensitivity and selectivity in whole blood, plasma [8], and aqueous solutions. This ionophore has high lipophilicity, allowing it to interact with and be highly maintained by the hydrophobic membrane. Other research also showed that this ionophore has excellent stability for several months [9]. The sensitivity of the ITO-ISFET to Na^{+} was evaluated by the shift of the $V_{GS}$ and calculated directly from the $I_{DS}$-$V_{GS}$ curve using the constant-current method.

As the fabricated ITO-ISFET is an n-type semiconductor, when Na^{+} is captured through the ISM onto the gate channel surface, Na^{+} induces a positive gating effect, thus decreasing the ITO electrical resistance. As the concentration of Na^{+} increases, the $V_{GS}$ shifts in the negative direction (Figure S2 in Supporting Information). The increment in the $\Delta V_{GS}$ with an increase in the oxygen flow rate could be attributed to a decrease in free carrier density in the ITO thin film. If the oxygen flow rate increases in the sputtering chamber, the oxygen atom ratio of the ITO film deposited on the glass substrate increases relative to the tin or indium atom, and the negative charge on the surface of the ITO film also increases due to the increase of the oxygen atom in the ITO film. The negative charge of the ITO film accelerates the movement of the Na^{+} ions trapped in the ISM on the gate channel towards the surface, and Na^{+} ions sensitivity increases on the ITO-ISFET, as shown in Figure 4a. However, the higher oxygen atom ratio increased the sheet resistance of the ITO film due to the decrease in oxygen vacancy, as shown in Figure 3b. Furthermore, as shown in Figure 2a, as the oxygen flow rate increased, the average grain size of the ITO thin film gradually decreased, thus, resulting in a higher surface-to-volume ratio of the sensing area. Consequently, we hypothesized that the higher surface-to-volume ratio of the smaller grain size results in an increase in the sensitivity of the ITO-ISFET to Na^{+}. However, according to the experimental results, when the oxygen flow rate exceeded 0.6 sccm, the Na^{+} sensitivity was higher than the lower oxygen flow rate, but the reproducibility of the ITO-ISFET deteriorated (Figure 4a).

The Na^{+} sensitivity of the ITO-ISFET deposited at an oxygen flow rate of 0.4 sccm was 55.2 ± 2.3 mV/decade (ranging from 10^{-4} to 10^{-1} M), which is close to the Nernstian response (Figure S2 in Supporting Information). We conducted the real-time detection of Na^{+} at a range of 10^{-4} to 10^{-1} M in 50 mM Tris buffer solution. The real-time detection response of the ITO-ISFET (5 min for each concentration) to Na^{+} is shown in Figure 4b. We defined the hysteresis voltage as the difference between the first and second $V_{GS}$ of the 10^{-2} M NaCl solution. The hysteresis voltage of the ITO-ISFET in 10^{-2} M NaCl solution was 5.2 mV, which was lower than that of the ITO-ISFET in pH solutions at 8.3 mV [10]. Therefore, we chose 0.4 sccm oxygen flow rate to deposit the ITO thin film in the sputtering process and fabricate the ITO-ISFET for Na^{+} detection. We also evaluated the LOD of the ITO-ISFET in 50 mM Tris buffer solution. The working range of the ITO-ISFET was 10^{-10} to 10^{-1} M, and the sensitivity was found to be 58.5 ± 2.1 mV/decade. The LOD of the ITO-ISFET sensor was 1.8 nM, as shown in Figure 4c. The stability over time of the ITO-ISFETs is observed (Figure S6 in Supporting Information). We conclude that the ITO-ISFETs at 0, 0.2, and 0.4 sccm are more stable compared to ITO-ISFETs at 0.6, 0.8, and 1 sccm.

Other cations such as potassium ion (K^{+}) and calcium ion (Ca^{2+}) are known to interfere in the detection of Na^{+}. Figure S4 in Supporting Information shows the responses of the ITO-ISFET to K^{+} and Ca^{2+}.  

![Figure 2](image-url) The (a) grain size and the (b) growth rate of the ITO thin films deposited by various oxygen flow rates from FE-SEM images

![Figure 3](image-url) The (a) carrier concentration and the (b) sheet resistance of the ITO thin films deposited by various oxygen flow rates

![Figure 4](image-url) The sensitivity ITO-ISFET to Na^{+} (a) in 50 mM Tris buffer solution (NaCl concentration is from 10^{-4} to 10^{-1} M) at different oxygen flow rates (0–1 sccm), (b) real-time measurement in 50 mM Tris buffer solution (for the ITO-ISFET at 0.4 sccm oxygen flow rate), and (c) the limit of detection (LOD) of the ITO-ISFET in 50 mM Tris buffer solution
were 226, 152, and 25 mM, respectively. The ratios between Na
added to the urine sample (S061). The initial concentration of Na
and urine samples of four patients. A specific concentration of NaCl was
selective to Na
in the urine samples. For example, sample no. S066 had a higher
sensitivity of the ITO-ISFET to Na
Fig. 5
The sensitivity of ITO-ISFET to Na
sensing of the electrical signal. Other ions such as chlorine (Cl
−)
and proteins present in urine also affect the sensing of electrical signals. Regardless of the factors interfering with the sensing
signal, the ITO-ISFET sensor was still selective to Na
+ as shown in

**Figures 5a and 5b**. To evaluate the stability in real human patient urines, ITO-ISFETs were washed and measured in DI water between each different concentration. There was no significant shift in the ΔVGS measured in DI water before and after the measurement of Na
+ in the urine. The sensitivity of the ITO-ISFET was 0.4 mV/mM in human urine, as shown in

(Figure 5b and Figure S5 in Supporting Information). This indicates that our sensor stably detects Na
+ in human urine even without any dilution process.

**Conclusion:** The Na
+ sensitivity of the ITO-ISFET was investigated and characterized by different oxygen flow rates in the sputtering process. The ITO-ISFET sputtered at 25°C in the presence of oxygen gas showed higher Na
+ sensitivity compared to the ITO-ISFET at 0 sccm oxygen flow rate. The condition that gave the highest reproducibility and the result close to the Nernstian response was at 0.4 sccm oxygen flow rate. The devices were able to detect Na
+ concentration in the range of 1.8 × 10
−9
 to 0.1 M with the sensitivity at 58.5 ± 2.1 mV/decade. It is comparable with the existing commercial Na
+ ion sensor with the sensitivity at 54.5 ± 3 mV/decade and detection range from 2 × 10
−6
 to 0.1 M [11]. The ITO-ISFET was also tested on human urine without any additional dilution process. Although there were many interferences from other ions and proteins, the ITO-ISFET selectively detected Na
+ in human urine. The ITO-ISFETs exhibited reliable sensing performance in buffer solutions and human urine. The established ITO-ISFETs appear to be suitable biosensors for sodium detection in undiluted human urine and electrolytes.

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**Figures 5a and 5b** are not visible in the provided text.

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