Anal. Bioanal. Electrochem., Vol. 12, No. 2, 2020, 238-249

Analytical &
Bioanalytical
Electrochemistry

2020 by CEE
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Full Paper

Extended-Gate Field-Effect Transistor based Sensor for Detection of Hyoscine N-Butyl Bromide in its Pharmaceutical Formulation

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Received: 15 December 2019 / Received in revised form: 20 January 2020 /
Accepted: 23 January 2020 / Published online: 29 February 2020

Abstract- A novel recognition method for selective determination of the hyoscine N-Butyl bromide (HBB), an antispasmodic agent for smooth muscles, was devised using extended gate field-effect transistor (EG-FET) as transducing unit. For this purpose a PVC membrane, containing hyoscine n-butyl-tetraphenyl borate ion-pair as recognition component, was coated on Ag/AgCl wire, which was connected to the extended metal gate. In optimal conditions, the linear range for HBB was 10^{-8}-10^{-5} $molL^{-1}$ with limit of detection 1.7×10^{-9} $molL^{-1}$. The proposed sensor was applied in real sample, it showed fast response with high accuracy, and therefore it could be used as HPLC detector in the pharmaceutical samples in quality control.

Keywords- Ion Sensitive Field Effect Transistors sensor, Hyoscine N-Butyl bromide, PVC membrane

1. INTRODUCTION

Hyoscine N-Butyl Bromide (HBB) is a hyoscine derivative, which is an antispasmodic agent for smooth muscles and used in treatment of spasmodic conditions such as disorders of the gastrointestinal tract peptic ulcer, urinary tract [1] and for suppression of postoperative nausea and vomiting [2]. For its importance, numbers of analytical methods have been developed for determination of HBB, such as spectrophotometry [3-5], high performance liquid chromatography (HPLC) [6-8], capillary electrophoresis [9, 10] and electrochemical methods including symmetric and asymmetric potentiometric membrane sensors [11,12]. In recent years, among electrochemical sensors for determination of drugs, ion sensitive field effect transistors (ISFET) have attracted much attention due to ability of chip-circuit design, miniaturization, low cost, fast response and sensitivity [13].

ISFET are the subset of potentiometric sensors, but ISFETs are very less affected by distortions arises from the environmental potential noise, because the input potential source (gate) is attached to the transducer (FET) [14]. They are capable of converting any little electrical field in vicinity of the gate to detectable current, such as any species carrying charge the same as ions. The operational characteristic of ISFET is similar to Metal-Oxide-Semiconductor (MOSFET), except in ISFET the metal gate is substituted by an ion sensitive membrane (ISM) [14]. However, ISFET sensors are opened to chemical attack from various species existing in the solution. For overcoming this problem, extended gate field effect transistor (EGFET) developed [15]. EGFET is subset of ISFET, but in EGFET the sensing element is deposited on the gate, which is extended from the insulated transducing FET. This configuration is less temperature sensitive and enables us to dispose damaged gate [13,16-18]. Different sensitive membrane such as PVC membrane can be used as a coating layer for the extended gate.

In recent years for designing of ISFs, polyvinylchloride (PVC) matrix is widely used. PVC has two roles [19]; it contains the component of the membrane together and raises the effective dielectric constant of the membranes to ~10, which is appropriate for potentiometric sensors.

In this study, we designed a coated gate EGFET for determination of HBB. The sensitive coating layer of the proposed sensor is based on the membrane with PVC as matrix and ion pair of HBB-sodium tetraphenyl borate as sensitive element for exchanging HBB cations in the solution of the sample. The designed membrane is coated on Ag/AgCl wire electrode. This electrode is connected to the extended gate of the FET. Characterizations of the sensor were examined and optimum conditions were obtained for selectivity and plotting the calibration curve. The sensor was successfully applied for measurement of HBB in its pharmaceutical formulation.

2. EXPERIMENTAL DETAILS

2.1. Chemicals and reagents

All materials and reagents were of analytical grades and at the highest available purity. They include: high-molecular weight polyvinylchloride (Fluka Co.), the chloride salts of the necessary cations, hydrochloric acid (HCl), tetrahydrofuran (THF), dibutyl phthalate (DBP), sodium tetraphenyl borate (NaTPB) (Merck Co.). HBB was donated by pharmacology department of Medical Sciences/University of Tehran. All solutions were prepared by double distilled water.

For preparation of ion-pair, aqueous solutions with certain amount of NaTPB and HBB were prepared separately and were mixed with each other gradually to form insoluble ion-pair complex. Fig. 1 shows the structure of this ion-pair. Stock 100 ml of solutions of 0.01 $molL^{-1}$ of HBB, NaCl, KCl, $CaCl_2$, NH_4Cl and $Mg(NO_3)_2$ were prepared. Other standard solutions were made by diluting certain amount of these stock solutions.

2.2. Preparation of the real sample

Ten tablets of pharmaceutical HBB, containing 10 mg of HBB/tablet, were weighted and average weight of one tablet was calculated. Then, these ten tablets were finely powdered and average weight of one tablet was dissolved in distilled water and then filtered through filter paper into a 100 mL volumetric flask.

2.3. Preparation of the membrane coated electrode

The sensor consisted of a fabricated sensitive electrode, which was connected to the extended gate of the commercial FET (CD4007). The sensing electrode was an Ag/AgCl wire coating with PVC membrane. The Ag/AgCl wire was made by sweeping of potential on the Ag wire through cyclic voltammetry with PalmSens potentiostat (Palm Instrument BV, the Netherlands). For this purpose, the Ag wire with 0.6 mm diameter was polished with sandpaper until a shiny surface was revealed. Then wire was rinsed with distilled water several times. Three-electrode system was consisted of Ag wire as the working electrode, graphite counter electrode and the Ag/AgCl reference electrode. In addition the HCl solution of 0.01 M was used as the electrolyte solution. The potential was swept between 0 to 0.5 V and only one cycle was applied. Therefore, the Ag wire was covered with a thin layer of AgCl.

For preparation 10 gram of the coating PVC membrane, 20% (w/w)PVC, 73% (w/w)DBP, 2% (w/w) NaTPB and 5% ion-pair were weighted and mixed uniformly in 2.0 mL fresh THF. This solution was evaporated slowly on heater at 50 °C temperature, till an oily mixture was formed. Each of the used components has an important role in the membrane operation [20,21]. Then, the coated Ag wire with AgCl was dipped in this oily mixture 5 times and each time for 2 second. After removing the electrode from the mixture, for drying, it was maintained at room temperature for at least 12 h. Finally, for conditioning, it was soaked in 1×10^{-3} $molL^{-1}$ HBB about 48 h.

It should be noted that the used ion-pair is the sensing element, which responses to the HBB cation in the solution of the sample via its ion exchange ability according to the equation (1). Also, NaTPB is the conductive component of the membrane. While, the nature and the amount of the plasticizer (DBP) is a prominent issue to obtain a symmetric membrane, which could influences the slope of calibration curve, linear range and selectivity of the membrane [21]. In addition, it prompts homogenous dissolution and diffusion mobility of the ion-pair in the PVC matrix of the proposed membrane [23].

$$HBB^{+}_{\text{(aqueous sample solution)}} + TPB^{-}_{\text{(membrane)}} \leftrightarrow HBB^{+}\text{-}TPB^{-} \qquad (1)$$

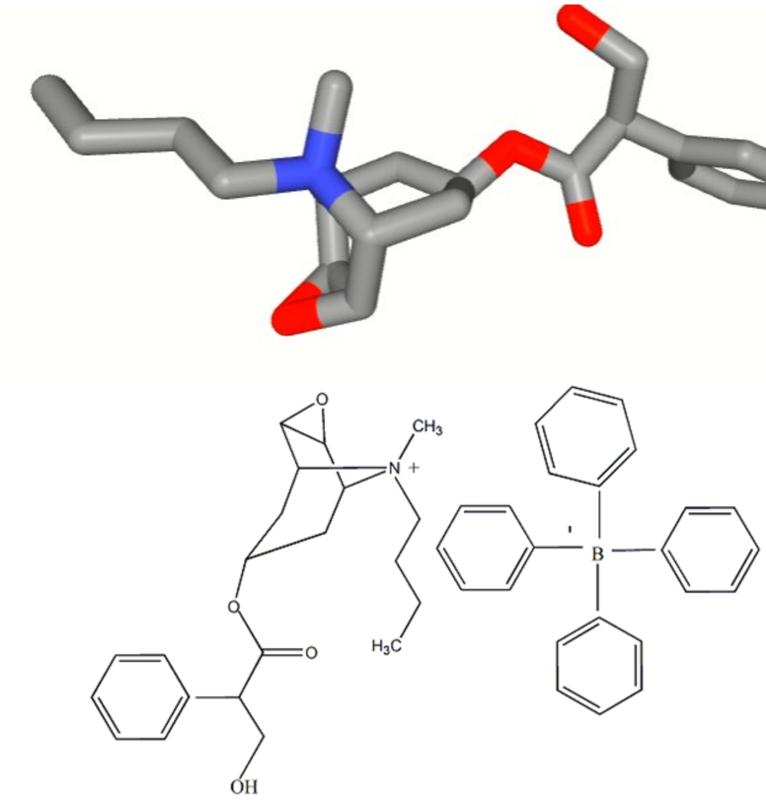

Fig. 1. 3D Chemical structure of HB and the ion-pair (HBB-TPB)

2.4. Apparatus and measurement circuit

Practically, an EGFET consists of two parts; a sensing element and a FET, which is electrically connected to the extended gate. Similarly, here, the sensing element was a coated Ag-AgCl electrode with HBB-TPB membrane. This electrode was connected to the gate of a commercial MOSFET (Fig. 2). The MOSFET was an n-channel enhancement mode MOSFET with low-leakage current (CD4007). The potential changes arising from the accumulation of the charges on the sensing electrode were transferred to the gate of the MOSFET [16]. The potential change on the gate results in change of the source to drain current which were measured as the analyte signal.

Theoretically, the ideal current-voltage relation for the n-channel enhancement mode MOSFET in no saturation region can be expressed as follows:

$$I_{DS} = K_n [2(V_{GS} - V_T) V_{DS} - V^2_{DS}] \quad (2)$$

where I_{DS} is the current between source and drain, K_n is the conduction parameter, V_{DS} is the drain to source voltage and V_{GS} is the applied voltage to the gate. V_T is the threshold voltage, which is the minimum required potential across the gate to turn the ISFET on. $K_n=\mu_n C_i W/2L$ (μ_n is the electron mobility in the inversion layer, C_i is the insulator capacitance per unit area, and W/L is the width to length ratio of the channel) is a constant value, which is related to the intrinsic properties of the ISFET. V_T is also a constant value that depends on the intrinsic properties of MOSFET [24].

For an ISFET, V_{GS} is applied by the reference electrode and the ideal current-voltage relation is the same as equation (2) [25]. According to the equation (2), if the value of V_{DS} is kept constant and the value of V_{GS} is biased well above the value of V_T, then the value of I_{DS} increases linearly with the applied potential, which is related to the analyte accumulation on the surface of the sensing electrode (as well as the concentration of the drug in the solution).

For the fabricated sensor, using an external voltage source, the value of V_{GS} was applied to the reference electrode (V_{ref}), which was located in the vicinity of the drug sensitive electrode in the sample solution.

It is noteworthy to note that there is a difference in values of V_{GS} and V_{ref} due to the potential drop in the electrolyte. That is why only the value of V_{ref} could be reported and expect the value of V_{GS} to follow this value with an offset. Thus, the whole experimental cell consisted of a solution, where in the reference electrode and the sensing electrode were immersed (Fig. 2). The values of V_D and V_{DD} are used against a known resistor (R_{sense}) in order to calculate I_{DS}. Finally, the values of V_D and V_{DD} were flowed by an analog-to-digital converter (ADS1256 from Texas Instruments). Fig. 2 shows the schematic diagram of the measurement set up for the drug concentration.

The acquired data were processed in the computer in order to remove the existing noise that may adversely affect the results. In order to achieve the highest possible performance of the ADC, careful handling of the signals was required. The applied gate voltage is needed to achieve a highly stability with minimum the noise. Therefore, shielding of the signal path, stabilization of the temperature (25 °C) and protection against light and the other vibrations were practiced throughout the whole experiment. Furthermore, a filtered, regulated voltage source powered by a battery was used to achieve lower noise at the gate biasing circuit.

3. RESULTS AND DISCUSSION

3.1. Sensor characterization

For testing the performance of the ISFET sensor, different values of V_{ref} and V_{DD} were applied to the setup with the cell just containing distilled water, and then I_{DS} was measured as the electrode signal. Fig. 3 shows the effect of V_{ref} voltage on the curve of I_{DS} versus V_{DD}. As demonstrated, when the voltage of V_{DD} is higher than 4 V the ISFET reaches the saturation region. Therefore, for the main measurements, the optimum voltage of V_{DD}=4.5 V was used to have the maximum amplification for I_{DS} in different values of V_{ref}.

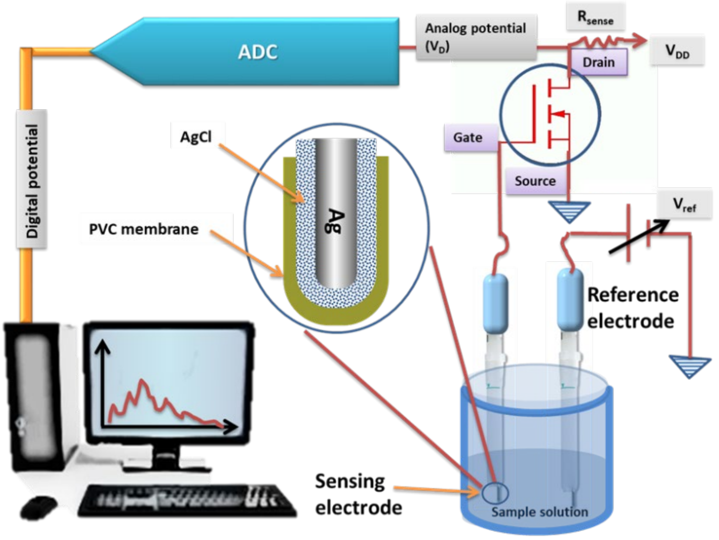

Fig. 2. Schematic diagram of the operational measurement set up for analyte

Fig. 4 displays the plotted curve for I_{DS} against V_{ref} (at V_{DD}=4.5 V). The curve data indicates that for turning the ISFET on, the voltage of 1.7 V should applied to the reference electrode (V_T=1.7 V). The value of V_{ref} higher than V_T voltage leads to the linear relation between V_{ref} and I_{DS} (as expected from equation (2)).

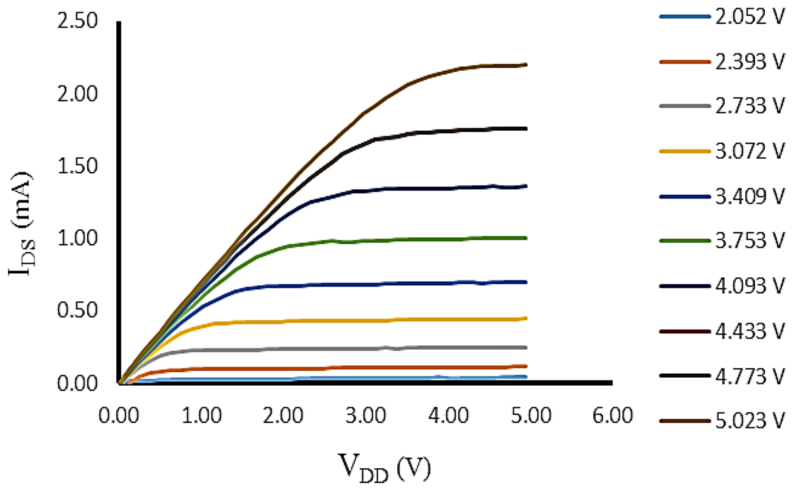

Fig. 3. I_{DS} versus V_{DD} at different V_{ref} for the fabricated sensor in the distilled water

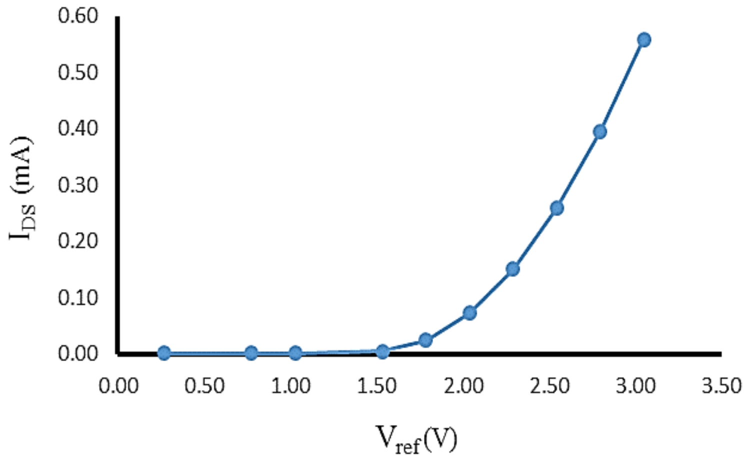

Fig. 4. Variation of I_{DS} versus V_{ref} at constant V_{DD} of 4.5 V for the fabricated sensor in the distilled water

In order to obtain optimum value of V_{ref} (to have the best sensitivity), the calibration curves were plotted at different voltages of V_{ref} at the constant V_{DD} of 4.5 V. For determination of HBB, the exact volumes of the standard HBB solution were added in to the experimental cell containing 25 mL distilled water, to obtain desired concentrations of HBB. The ion-pair complexes existing in the membrane, response to the HBB cations in the solution according to the cation exchange ability of the ion-pair as described in the section 2.3. As a result, the accumulation of positive charges (HBB cations) on the membrane could lead to potential that is more positive across solution/sensor.

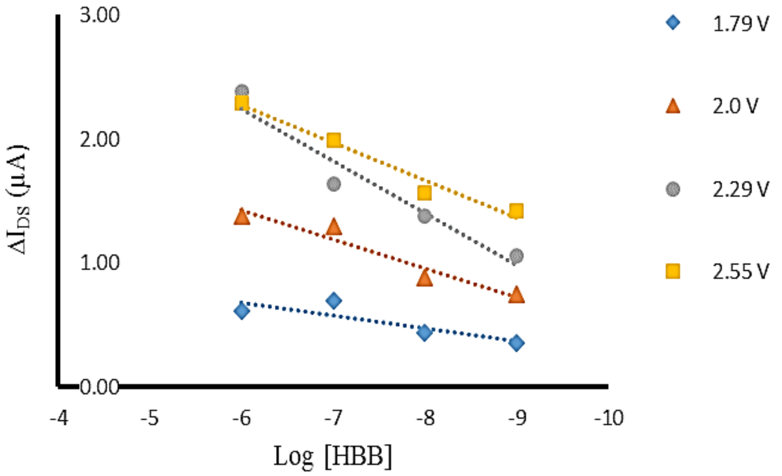

Fig. 5. I_{DS} versus different concentrations of the HBB in aqueous solution for different values of V_{ref} at the constant V_{DD} of 4.5 V

This potential transferred to the gate of the ISFET. Consequently, the value I_{DS} changed as described in section 2.4, which was proportional to the HBB concentration. The analyte signal (ΔI_{DS}) was calculated based on the equation (3);

$$\Delta I_{DS} = I_{DS} - I^{o}_{DS} \qquad (3)$$

where I_{DS} is the current of the ISFET electrode in the solution containing concentration of HBB and I^{o}_{DS} is the current of the electrode in the blank solution. Fig. 5 shows the obtained calibration data in form of ΔI_{DS} versus the different concentrations of HBB. It can be seen that the best sensitivity was obtained at V_{ref}=2.29 V, where the calibration curve of HBB has the highest slope. Consequently, the V_{ref}=2.29 V was selected as the optimum voltage for determination of detection limit of the system.

3.2. HBB measurement

Fig. 6 shows the change of I_{DS} in time, when the concentration of HBB was increased at optimum values of V_{ref} and V_{DD}. As shown, for each concentration of HBB increment, the value of I_{DS} increases sharply and between 10 second to 2 minutes (for the lowest concentration of HBB, 10^{-8} molL^{-1}, and 10 seconds, the highest HBB concentrations, 2×10^{-5} molL^{-1}).

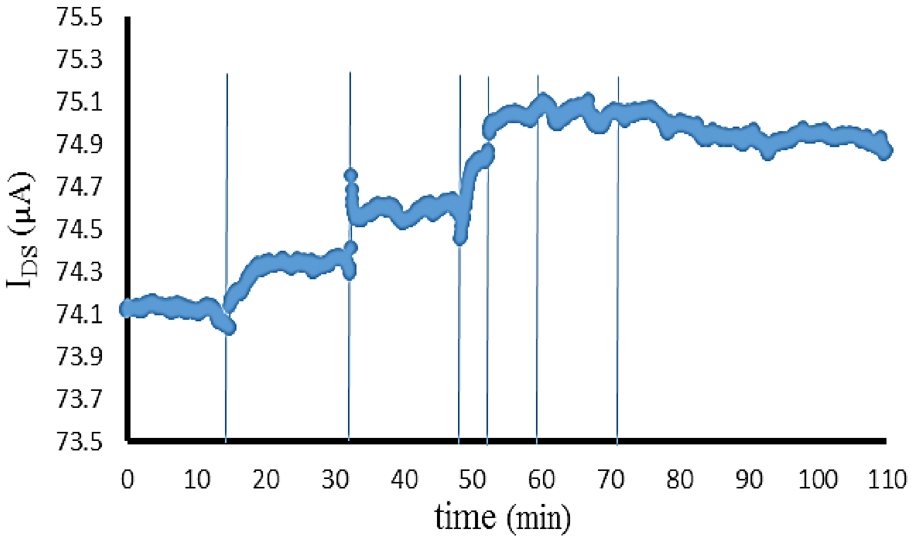

Fig. 6. I_{DS} versus time. Each vertical line shows one addition of HBB standard solution in to the cell. The additions make the concentration of HBB in the cell 10^{-8}, 10^{-7}, 10^{-6}, 2×10^{-6}, 10^{-5} and 2×10^{-5} molL^{-1} respectively in time

In the measurements, and the adsorption of HBB on the surface of the sensor reached to equilibrium, where the value of I_{DS} reached to a plateaus. Therefore, the signal (ΔI_{DS}) for the calibration curve (Fig. 7) was measured after 2 minutes after addition of HBB in to the cell.

Under the optimum conditions, the obtained linear range was 1.0×10^{-8}-2×10^{-6} $molL^{-1}$ and the calculated detection limit (DL) was 1.7×10^{-9} $molL^{-1}$. This sensor exhibits sensitivity of 322.92 nA $decade^{-1}$ of the HBB concentration. For determination of repeatability of the sensor, five standard solutions of HBB with the concentration of 3×10^{-8} $molL^{-1}$ were tested. The calculated RSD of the response of the sensor was 3.9%. The features of the proposed sensor are compared with previous reported potentiometric ion selective electrodes in Table 1.

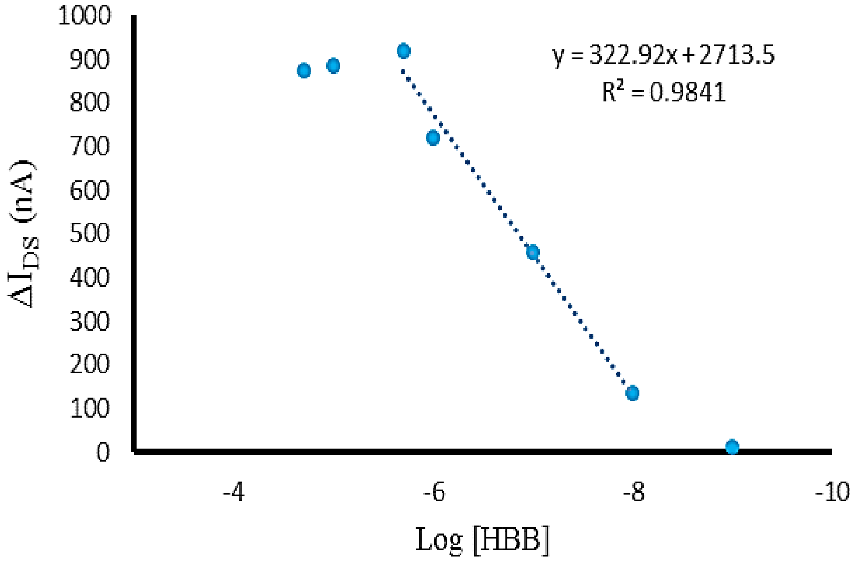

Fig. 7. Calibration plot of HBB at constant V_{ref}=2.29 V and constant V_{DD}=4.5 V

Table 1. Comparison of the features of the proposed sensor with previously reported HBB potentiometric sensors

Sensor type	**detection limit ($molL^{-1}$)**	**Linear range ($molL^{-1}$)**	**Slope of the calibration curve**	**Ref.**
Potentiometric PVC membrane sensor	10^{-7}	1.0×10^{-7}–1.0×10^{-3}	55.6 (mV/decade)	[12]
Potentiometric PVC membrane sensor	1.80×10^{-7}	1.00×10^{-6}–1.00×10^{-2}	54.57 (mV/decade)	[26]
Potentiometric PVC membrane sensor	4.90×10^{-7}	1.00×10^{-6}–1.00×10^{-2}	51.51 (mV/decade)	[27]
Potentiometric carbon paste sensor	8.50×10^{-9}	3.00×10^{-8}–1.00×10^{-2}	59.55 (mV/decade)	[28]
In this work	1.7×10^{-9}	1.00×10^{-8}–2×10^{-6}	322.92 (nA/decade)	Present work

3.3. Selectivity

In definition, selectivity of a sensor is the specificity of the sensor toward a specific analyte in the presence of other interfering ions, which is the most important feature of the sensor.

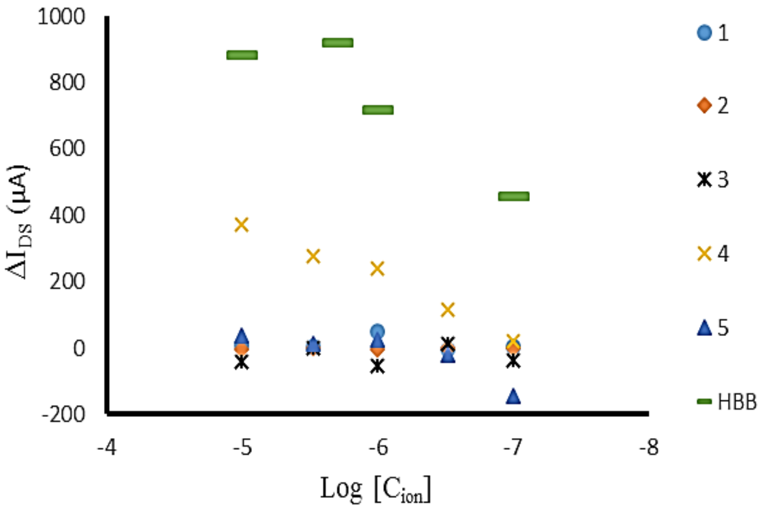

Fig. 8. ΔI_{DS} versus Log [C_{ion}] in the solution of HBB with concentration of 10^{-8} molL^{-1} 1: Na^+, 2: k^+, 3: NH_4^+, 4: Mg^{2+}, 5:Ca^{2+}

Practically, for determination the selectivity of the sensor respect to HBB, the concentration of the interfering ions in the solution of 10^{-8} molL^{-1} HBB was increased gradually and the ΔI_{DS} was measured. This test was done for Na^+, K^+, NH_4^+, Ca^{2+} and Mg^{2+} up to the concentration of 10^{-5} molL^{-1} (which is 5 times higher than the highest concentration of HBB in its calibration curve). The results of the tested ions are shown and compared with HBB in Fig. 8. All the tested ions did not affect the response of the sensor significantly. However, at higher concentration of Mg^{2+} ion has an affect the sensor signal due to the higher charge density, which may be absorbed on the membrane via ion exchange ability of the ion pair.

3.5. Application of the sensor to pharmaceutical formulation

For testing HBB in the pharmaceutical formulation, the stoke solution of the tablet as described in part 2.2 was prepared. Measurement of the tablet solutions were done by standard addition method [28]. For this purpose 1.1 µL of tablet stoke solution was added to the cell containing 25 mL of the blank solution. Then different volumes of standard solution of HBB were added to the cell according to standard addition method. This measurement procedure was done for 5 times. The mean amount of HBB per tablet was 9.42 mg with RSD of 5%.

4. CONCLUSION

Here, we constructed ISFET sensor by using an EG-FET (MOSFET) successfully, for selective determination of HBB. The selectivity of the sensor was examined in the presence of most interfering ions, leading to obtain selectivity feature of the sensor to be 1000 times toward to HBB. This sensor have superior advantages in comparison to the pervious devised ISE sensors, such as low detection limit about nanomolar, simple design and easy operatory. The response of the sensor is very fast for concentrations above ~10^{-7} molL^{-1} of HBB. Thus, in the linear range of 1.00×10^{-8}–2×10^{-6} molL^{-1} of HBB, the ISFET sensor could be used as a detector for HPLC or it could be used in flow injection technique. Therefore, the proposed ISFET sensor can be an excellent candidate for using in quality control of pharmaceutical industry. As the FETs are very small, the proposed sensor can be applied to construct portable measurement device.

Acknowledgements

The authors are grateful to the Research Council of University of Tehran for the financial support of this work.

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