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TECHNICAL PAPER

Ultrasensitive micro ion selective sensor arrays for multiplex heavy metal ions detection

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Abstract

Trace heavy metal ions are probable carcinogens with concentrations at *ppb* levels. Ion selective electrode (ISE) technology is a conventional and widely used method to detect various ions with the advantages as rapid measurement, low power consumption and low cost. However, the detection limit of a conventional bulky ISE device is only able to reach *ppm* level so far, not sensitive enough for practically detecting heavy metal ions. A micro ion selective electrode (μISE) array which can realize multiplex detection of heavy metal ions on one chip is reported in this paper. Its detection limit for Pb^{2+}, Cd^{2+}, AsO_2^-, and Hg^{2+} can reach 1, 3, 10, and 1 ppb, respectively, within the permissible limits of drinking water. The micrometer scale device arrays from microfabrication processes demonstrated enhanced sensitivity, uniformity, and reduced response time (18 s) compared to conventional ISE. Our devices showed superb selectivity, and the performance dependence on temperature and pH values was investigated as well.

1 Introduction

TRACE ion elements of lead (Pb^{2+}), cadmium (Cd^{2+}), mercury (Hg^{2+}), and arsenite (AsO_2^-) can cause numbers of health problems, and are probable carcinogens for human beings with concentrations at ppb levels (Wang et al. 2014). Therefore, it is essential to detect the concentration of these toxic ions in various samples including drinking water and food. The most common and reliable methods for the determination of heavy metal ions include atomic absorption spectroscopy (AAS) (Xie et al. 2008), X-ray fluorescence (XRF) (Ravisankar et al. 2015), inductively coupled plasma-mass spectroscopy (ICP-MS) (Rui and Hao 2012), and inductively coupled plasma-atomic emission spectroscopy (ICP-AES) (Cong and Cai 2010). Although these laboratory-based methods exhibit high performance, the large cost and complicated sample pretreatment prohibit them from wide sensing application.

Ion selective electrode (ISE) technology is a conventional and widely used method to detect various ions with the advantages as rapid measurement, low power consumption and low cost (Malinowska et al. 1994). They generally do not need complicated sample pretreatment and can be used for real time analysis. However, detection limit of a conventional ISE device can only reach ppm level so far (McGraw et al. 2007; Naushad et al. 2014; Gupta et al. 2003; Gupta and Agarwal 2005; Gholivand and Raheedayat 2004; Gupta et al. 2003), not sensitive enough for practically detecting trace heavy metal ions. I, a commercialized bulky ISE device is only able to detect one specific ion. As such, more than one device is needed for multiple heavy metal ions detection, which further limits its applications. Here we used microfabrication technique to largely reduce the geometry size and simplify the complex structure of conventional ISE (Li et al. 2015). Four or even more μISEs can be integrated on one chip, increasing the efficiency of both fabrication and detection. Its detection limit for Pb^{2+}, Cd^{2+}, AsO_2^-, and Hg^{2+} can reach 1, 3, 10, and 1 ppb, respectively, which is able to meet the permissible limits of the guideline for drinking water quality provided by the World Health Organization (WHO). The micrometer scale device arrays derived from microfabrication processes demonstrated enhanced sensitivity, uniformity, and reduced response time compared to conventional ISE.

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2 Experimental

The µISE arrays were fabricated by highly uniform microfabrication technique (Fischer et al. 2015). Metal electrodes were patterned by lift-off process on a glass substrate (Fig. 1a–d). Firstly, negative photoresist NR9-1500PY was spun coated on glass substrate at 3000 rpm for 60 s, followed by alignment, UV light exposure, and development to define the electrode arrays. Then sputtering process was applied to deposit metal layer (10 nm Cr/100 nm Au) on top. The metal electrode arrays were formed on glass after removing the photoresist together with the redundant Cr/Au by acetone. In order to investigate the dependence of the performances on device geometry size, metal electrodes with three different pad sizes (500, 800, and 1200 µm) were fabricated. Finally, glass wafer was diced into small chips with 4 or more electrodes on each one (Fig. 1d). As such, multiplex detection of heavy metal ions on one chip can be realized.

After using O_2 plasma to clean the metal electrodes for 10 min to further remove the photoresist and other organic residue, we spun coated POT (Poly (3-octylthiophene-2, 5-diyl), Sigma-Aldrich) conductive polymer solution (2.5 g/ml in chloroform;, 3-5 µL) on each working electrode with speed of 1000 rpm for 15 s before ionophore coating. POT layer was applied since it is reported to be able to increase the stability of ISE inasmuch as it avoids the interference from O_2 which may result in the potential shift of the device (Sutter et al. 2004). Next, tetrahydrofuran (THF) solvent with different types of ionophore specific for Pb^{2+}, Cd^{2+}, AsO_2^-, and Hg^{2+} were spun coated on different electrodes, respectively (Fig. 1d), with speed 4000 rpm for 40 s. The sample was kept in air at room temperature for 5–10 min to let the solvent, THF, evaporate and form a solid ionophore film. Theoretically, for a certain type of ionophore film, only one kind of ions could be selectively permeate through the film as shown in Fig. 2a. Therefore, ionophore film works as a filter which can block other ions, and increases the selectivity of the sensor.

After introduction of sodium acetate buffer solution (0.1 M, pH 4.6) with various heavy metal ion concentrations at room temperature, potentials between an Ag/AgCl

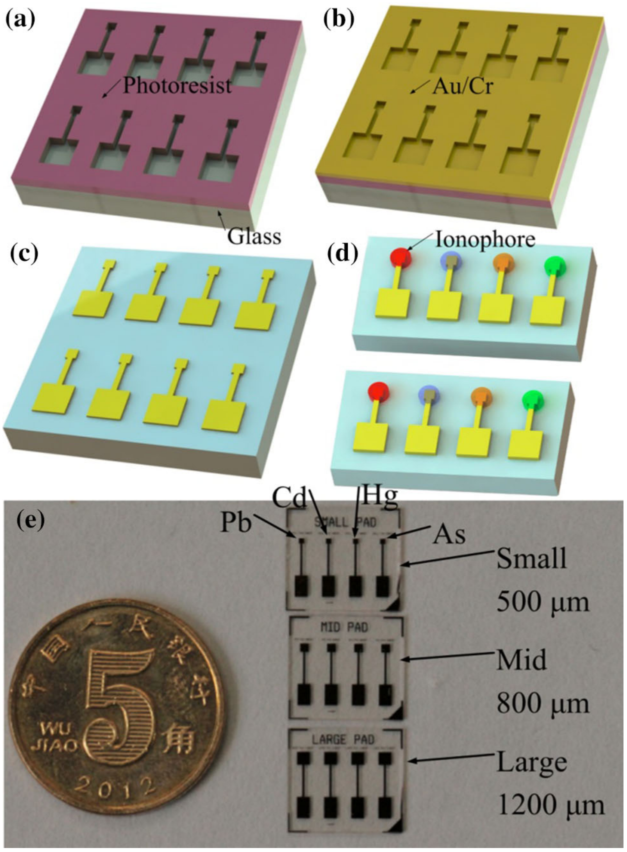

Fig. 1 **a–d** Fabrication process of µISE array. **a** negative photoresist NR9-1500PY was spun coated on glass substrate, followed by alignment and UV light exposure to define the electrode arrays. **b** Sputtering process was applied to deposit metal layer (10 nm Cr/100 nm Au). **c** The metal electrode arrays were formed on glass after removing the photoresist together with the redundant Cr/Au by acetone. **d** Glass wafer was diced into small chips with 4 or more electrodes on each one. Spin-coat the electrodes with POT and ionophore. **e** Photograph of µISE arrays which contains four different ion selective electrodes. Metal electrodes with three different pad sizes (500, 800, and 1200 µm) were fabricated

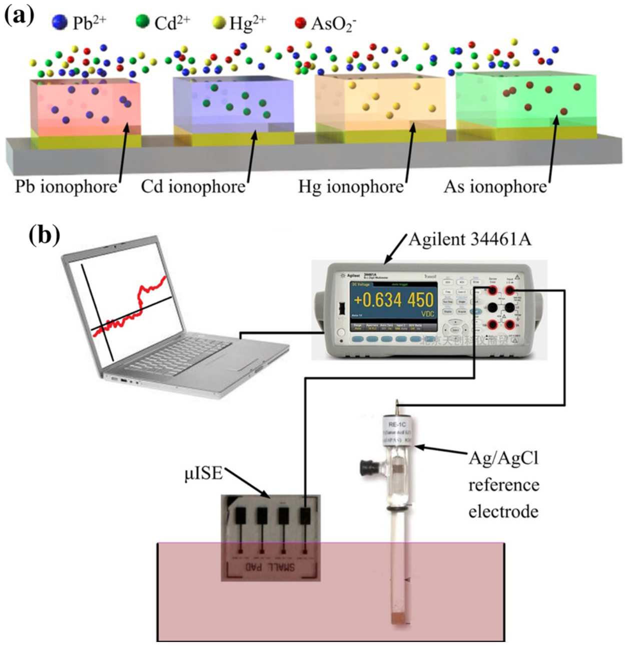

Fig. 2 **a** Schematic view of µISE arrays. Ionophore acts as a filter which only allows a specific type of ions passing through it. **b** µISE array measurement setup. Potentials between an Ag/AgCl reference electrode and corresponding µISE electrodes were measured using an Agilent digital multimeter 34461A

reference electrode and corresponding μISE electrodes were measured using an Agilent digital multimeter 34461A (Fig. 2b). According to the principle of Nernst effect (Gulbault 1981), the potential of reference electrode keeps constant, while the potential of μISE changes with different concentrations of ion detected.

3 Results and discussion

The performance ion selective electrode should follow modified Nernst (Nikolsky) Equation (Gulbault 1981):

$$E = E_0 + \frac{2.303RT}{nF}\log(\gamma N) \tag{1}$$

where E is experimentally observed potential of ISE, E_0 is the potential under standard conditions, R is the gas constant (8.31 J $K^{-1}mol^{-1}$), T is the thermodynamic temperature (in K), n is an integer with sign and magnitude corresponding to the charge of the principal ion, F is the Faraday constant (9.65×10^4 C mol^{-1}), $\gamma$is the activity coefficient of the ion, N is the concentration of the ion. According to Eq. 1, the potential of ISE should increase with higher concentrations of ion detected. In our experiment, as shown in Fig. 3a, when the Pb^{2+} concentration increased from 10 ppb to 100,000 ppb, a clear potential increase of μISE was observed, indicating that modified Nernst (Nikolsky) Equation can be applied to μISE as well. This result also suggested that the Pb^{2+} can be effectively detected over wide concentration range.

Spin coating, a standard and highly uniform microfabrication technique, was chosen in our experiment to form ionophore layer on metal electrodes. To investigate the influence of ionophore coating method, we tested devices based on spin coating and drop casting (a conventional method for bulky ISE devices), respectively. All the devices tested had identical geometry size. The thicknesses of drop-casted ionophore were typically in the orders of millimeters, while spin-coated ionophore film were much thinner (in the orders of micrometers), so ions detected can pass through it more easily. As a result, devices with spin-coated ionophore demonstrated much shorter response time than drop-casted ionophore shown in Fig. 3b. We fitted the curve with equation (Li et al. 2015):

$$V = V_f - (V_f - V_0)e^{-t/\tau} \tag{2}$$

where V is the instantaneous potential difference between ISE and reference electrode, V_0 is the initial potential difference after Pb^{2+} introduction, V_f is the final potential difference when the output signal is stable, t is the time, and τ is time constant. The extracted time constants for ISE devices based on spin-coated and drop-casted ionophore were 18 s and 145 s (for 1000 ppb Pb^{2+}), respectively (Fig. 3b). Notably, larger response time constants were observed with smaller Pb^{2+} concentration (Fig. 3c). Additionally, the thickness of drop-casted ionophore film varies from device to device, while spin-coated ionophore has highly uniform thickness, which is responsible for the improved uniformity of the sensors as shown in Fig. 3d. Therefore, spin-coating method can not only enhance the response rate but also improve the uniformity of the sensor.

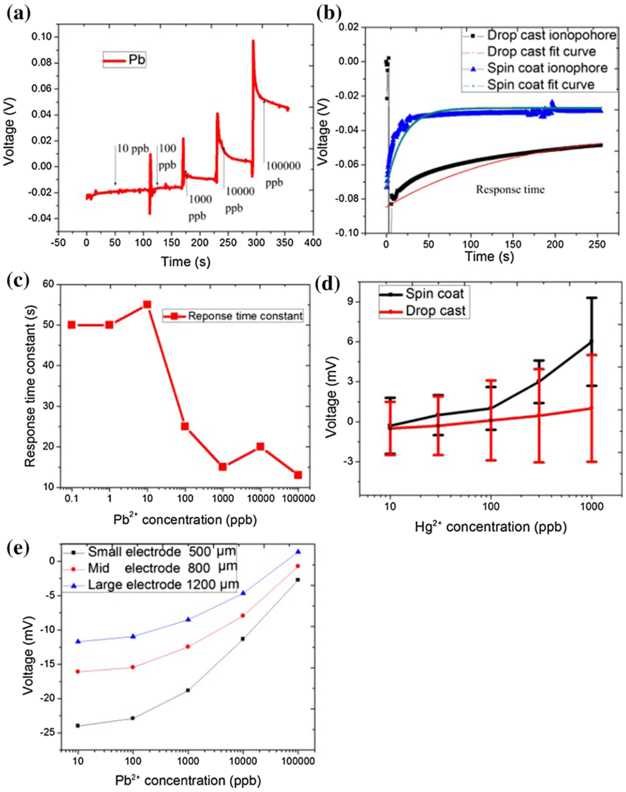

Fig. 3 **a** μISE's response to solutions with different concentrations of Pb^{2+}. When the Pb^{2+} concentration increased from 10 to 100,000 ppb, a clear potential increase of μISE was observed. **b** Response time of electrode with drop casted ionophore is about 8 times larger than that of electrode with spin-coated ionophore (18 s vs 145 s). **c** The response time constant is smaller with higher Pb^{2+} concentration. (d) Electrode with spin coated ionophore has better uniformity. (d) Sensitivity of small, mid, and large electrode is 8.63, 7.21, and 6.04 mV/decade, respectively, which indicated a trend that reducing the size of ISE can enhance its sensitivity

In order to investigate the dependence of the performances on device geometry size, metal electrodes with three different pad sizes (500, 800, and 1200 μm) were measured (Fig. 3e), and their sensitivities extracted from linear region were 8.63, 7.21, and 6.04 mV/decade, respectively, which indicated a trend that reducing the size of ISE can enhance its sensitivity. We assume that the ion concentration gradient after equilibrium is different at the edge area of ionophore film from that at the center. When the size of ISE devices reduces to micrometer scale, the edge effect becomes prominent, and it can affect the entire output of the sensor (increase sensitivity). This is one of our major motivations of exploring μISE.

Detection limit of a sensor is generally defined as three times the standard deviation of its noise (defined by international union of pure and applied chemistry (IUPAC)) (Currie 1995). Micro ISE's noise we measured (22 μV, Fig. 4a) was much smaller than that of regular ISE reported (0.6-0.8 mV). We assume the simplicity of our device structure avoids some interfaces which may introduce noise. Because of the low noise and enhanced sensitivity, we were able to achieve ultrasensitive detection of heavy metal ions. When we switched the solution from sodium acetate buffer to 1 ppb Pb^{2+}, a potential shift of 1.1 mV was observed as shown in Fig. 4b. This value was large than three times the standard deviation of μISE's noise. As such, μISE is capable of detecting Pb^{2+} at least down to 1 ppb. Additionally, the μISE's detection limits for Cd^{2+}, AsO_2^-, and Hg^{2+} can reach 3, 10, and 1 ppb, respectively (Fig. 4c, d, e). Selectivity is critical for ISE to identify each type of ions correctly and reduce the chance of misleading (Li et al. 2015). Micro ISE array demonstrated excellent ion selectivity. Lead working electrode's response to Pb^{2+} was much larger than that to Cd^{2+}, AsO_2^-, and Hg^{2+}, indicating it is only sensitive to Pb^{2+} (Fig. 5a). Similar results were observed for working electrodes coated with cadmium, arsenic, and mercury ionophore (Fig. 5b, c, d). The results displayed in Fig. 5 demonstrate the good selectivity of μISE. It also proves that the potential change of our sensor was caused by the ion interaction instead of other factors in environment (Li et al. 2015).

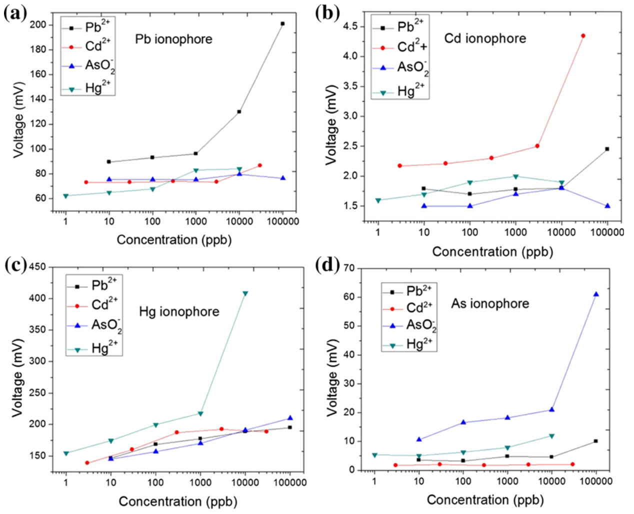

Fig. 5 Selectivity of μISE. **a** Lead working electrode's response to Pb^{2+} was much larger than that to Cd^{2+}, AsO_2^-, and Hg^{2+}. **b** Cadmium working electrode's response to Cd^{2+} was much larger than that to Pb^{2+}, AsO_2^-, and Hg^{2+}. **c** Mercury working electrode's response to Hg^{2+} was much larger than that to Cd^{2+}, AsO_2^-, and Pb^{2+}. (**d**) arsenite working electrode's response to AsO_2^- was much larger than that to Cd^{2+}, Pb^{2+}, and Hg^{2+}

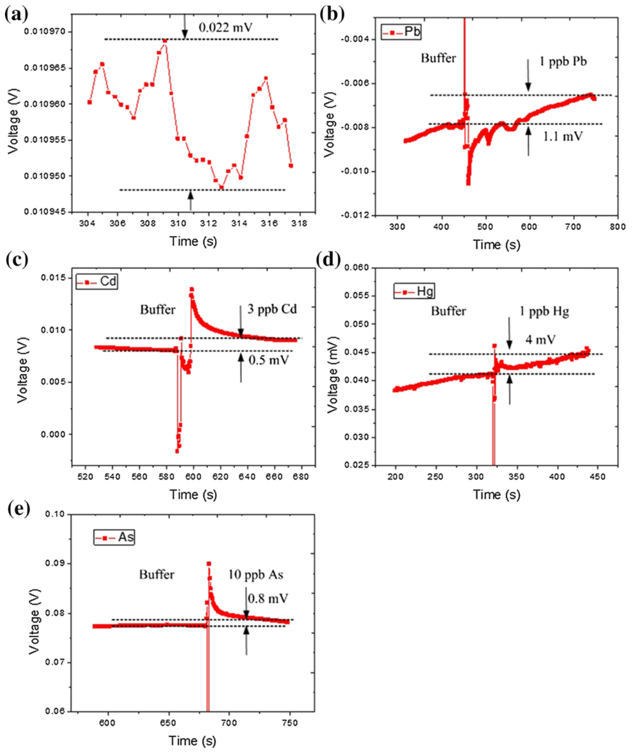

Fig. 4 **a** Noise of μISE is only 22 μV. **b** Detection limit for Pb^{2+} can reach 1 ppb. **c** Detection limit for Cd^{2+} can reach 3 ppb. **d** Detection limit for Hg^{2+} can reach 1 ppb. **e** Detection limit for AsO_2^- can reach 10 ppb

The environment's influence on the sensor was also investigated. Similar to regular ISE, μISE array's output signals were sensitive to temperature variation. According to Eq. 1, higher temperature can result in larger potential value, and higher temperature can also increase the activity coefficient of the ion, which further increases the potential. Our experimental result in Fig. 6(a) is consistent with this theory. The results indicate that the device is able to work under a wide range of temperature value after calibration. The performance of μISE can also be influenced by H^+ or OH^-. Thus, pH dependent of device was tested over the pH range 1–7 for 1 ppb heavy metal ions. Figure depicts that the pH dependence of the potentials is insignificant in the pH range of 3–5 for devices based on Cd^{2+}, AsO_2^-, and Hg^{2+} ionophore, and insignificant in the pH range of 4–7 for devices based on Pb^{2+} ionophore. Therefore, sodium acetate buffer solution (0.1 M, pH 4.6) we used can minimize the influence of pH value variation, and it is suitable for μISE to detect heavy metal ions, as shown in Fig. 6(b).

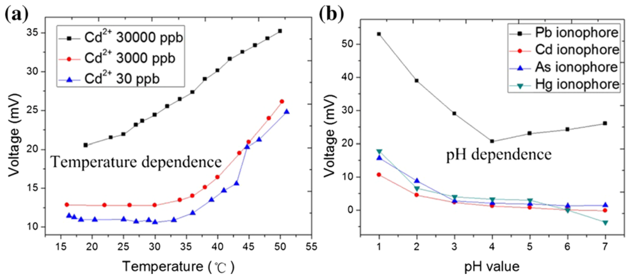

Fig. 6 **a** Temperature dependence of μISE. Higher temperature can cause higher potential of μISE. **b** pH dependence of μISE. Figure depicts that the pH dependence of the potentials is insignificant in the pH range of 3–5 for devices based on Cd^{2+}, AsO_2^-, and Hg^{2+} ionophore, and insignificant in the pH range of 4–7 for devices based on Pb^{2+} ionophore

4 Conclusion

We investigated a new μISE array realizing multiplex detection of heavy metal ions on one chip. Micromanufacture processes including photolithography and lift-off were used to fabricate the micro chip with a high potential for integration. The micro device array using microfabrication processes demonstrates enhanced sensitivity, uniformity, and reduced response time, compared to conventional ISE. Its detection limit can reach *ppb* level, within the permissible limits of drinking water. The device demonstrates superb selectivity, and the performance dependence on temperatures and pH values was also investigated.

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