Talanta 198 (2019) 412–416

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

A portable and quantitative biosensor for cadmium detection using glucometer as the point-of-use device

Lingwen Zeng[a,b], Junyu Gong[a], Peisen Rong[a], Chengshuai Liu[c], Junhua Chen[d,*]

[a] School of Food Science and Engineering, Foshan University, Foshan 528000, China
[b] Institute of Environment and Food Safety, Wuhan Academy of Agricultural Science, Wuhan 430065, China
[c] State Key Laboratory of Environmental Geochemistry, Institute of Geochemistry, Chinese Academy of Sciences, Guiyang 550081, China
[d] Guangdong Key Laboratory of Integrated Agro-environmental Pollution Control and Management, Guangdong Institute of Eco-environmental Science & Technology, Guangzhou 510650, China

ARTICLE INFO

Keywords:
Cadmium ion
Biosensor
Personal glucose meter
Point-of-use
Signal amplification

ABSTRACT

As an ubiquitous heavy metal pollutant, cadmium ion (Cd^{2+}) is detrimental to food and human health even at low concentrations. Conventional methods require costly instruments and cannot meet the requirements of on-site analysis. Here we report the use of a personal glucose meter (PGM) as the point-of-use (POU) device for portable and quantitative detection of Cd^{2+}. The specific recognition between the aptamer and Cd^{2+} trigger the recycling signal amplification process by exonuclease III (Exo III). After successive hybridization and cleavage reactions, numerous single-stranded DNA were liberated on the surface of the magnetic bead. An invertase-conjugated DNA that is complementary to the single-stranded DNA is introduced into the sensing system. After magnetic separation, the invertase conjugates hydrolyze sucrose into glucose, thus establishing direct conversion of Cd^{2+} concentration to glucose amount, which can be directly quantified by a PGM. Thanks to the synergistic signal amplification of Exo III and invertase, the POU device greatly improves the sensitivity for Cd^{2+} analysis, with a detection limit of 5 p.M. With the advantages of portability, cost-effectiveness, wide availability, and ease of use, the PGM-based detector has the potential to be used by the public as a routine tool for reliable and quantitative detection of Cd^{2+}.

1. Introduction

Cadmium ions (Cd^{2+}) are recognized as highly toxic heavy metals that can be found in water, soil, and agricultural products [1]. Chronic exposure to Cd^{2+} even at low concentrations is detrimental to human health and could cause many serious diseases and several types of cancers [2]. According to the U.S. Environmental Protection Agency (EPA) guidelines, the maximum contaminant level (MCL) for Cd^{2+} in drinking water is 5 ppb [3]. In China, the maximum permitted concentration for Cd^{2+} in rice has been set at a level of 0.2 mg/kg [4]. Therefore, sensitive detection of Cd^{2+} is of considerable significance for food safety and human health.

Over the years, traditional methods for the detection of Cd^{2+} have been developed, including atomic adsorption spectrometry (AAS) [5], atomic fluorescence spectrometry (AFS) [6], and inductively coupled plasma mass spectrometry (ICP-MS) [7]. Although these methods can realize accurate quantification of Cd^{2+}, time-consuming sample pre-treatment steps, costly instruments, and complicated operation are generally required, which makes them challenging for routine measurement. Recently, several elegant biosensors have been designed for monitoring of Cd^{2+} using fluorescent [8–10], electrochemical [1,11–13], and Raman techniques [14,15]. Although these biosensors for Cd^{2+} detection are cheaper and faster than traditional methods, most of them are associated with laboratory-based instruments or customized devices which are not easily accessible to the public for point-of-care (POC) diagnosis and on-site detection. Colorimetric methods and lateral flow devices have been employed for Cd^{2+} detection by the naked-eye without instrumentation [3,16,17]. However, they can only achieve qualitative or semi-quantitative results based on color observation, whose accuracy may vary among different people or may be affected under different light conditions.

One ideal device that can meet the above challenge is the personal glucose meter (PGM) [18–21]. PGMs detect glucose by measuring the redox reaction of glucose dehydrogenase (GDH). A consumable element containing chemicals that react with glucose in the drop of blood is used for each measurement. For some models this element is a plastic

* Corresponding author.
E-mail address: 222chenjunhua@163.com (J. Chen).

https://doi.org/10.1016/j.talanta.2019.02.045
Received 26 October 2018; Received in revised form 29 January 2019; Accepted 9 February 2019
Available online 10 February 2019
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test strip with a small spot impregnated with GDH, pyrroloquinoline quinone (PQQ), and other components. The glucose in the blood reacts with an enzyme electrode containing GDH. GDH is reoxidized with an excess of a mediator reagent (PQQ). The mediator in turn is reduced by reaction at the electrode, which generates an electric current. The total charge passing through the electrode is proportional to the amount of glucose that has reacted with the enzyme. During the redox process, PQQ is reduced to a green polymer, which causes the color changed from yellow to green on the round control window on the back of the test strip. Such color changes can be observed by the naked eye. As a widely used personal diagnosis device for POC testing, PGM benefits from its portable pocket size, low cost (as low as $10 for a meter and $0.5 per test), simple operation, reliable quantitative results, and the easy accessibility to the public worldwide [22–27]. However, PGMs can detect only glucose as the target. Recently, Lu's group reported a smart design by combining invertase with a PGM for quantitative detection of non-glucose targets [28–32]. Yang et al. developed a novel sensing platform that combines a glucoamylase-trapped aptamer-cross-linked hydrogel with a PGM for cocaine and ATP detection [33]. Inspired by such pioneering work, we explore the new application of a PGM for Cd^{2+} monitoring. The main challenge is the relatively low sensitivity of the PGM for the analysis of trace levels of heavy metal ions [31]. To further upgrade the detection sensitivity, signal amplification is usually needed. Herein, we propose a strategy for portable quantification of Cd^{2+} with high sensitivity using Exo III as the signal amplification catalyst [34–36], invertase as the linker, and PGM as the POU device.

2. Materials and methods

2.1. Chemicals and materials

Sulfosuccinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC), invertase from baker's yeast (*S. cerevisiae*), sucrose, and Tris(2-carboxyethyl)phosphine hydrochloride (TCEP) were purchased from Sigma-Aldrich, Inc. (St. Louis, MO). Streptavidin-coated magnetic beads (2.8 μM in diameter) were purchased from Life Technologies, Inc. (Grand Island, NY). Exo III was purchased from New England biolabs, Inc. (Ipswich, MA). Amicon-10K/100 K centrifugal filters were purchased from Millipore, Inc. (Billerica, MA). The personal glucose meter (ACCU-CHEK) and test strips were obtained from Roche Disgnostics, Inc. (Mannheim, Germany). Other reagents were of analytical grade and obtained from standard reagent suppliers. Ultrapure water with a resistivity of 18.2 MΩ/cm was used to prepare all the solutions. All the DNA used in this work was synthesized and purified by Sangon Biotech. Co., Ltd. (Shanghai, China) and their sequences were listed in Table S1 (Supporting Information).

2.2. Preparation of DNA-invertase conjugation

40 μL of 1 mM DNA5, 5 μL of 1 M sodium phosphate buffer (pH 5.5), and 5 μL of 25 mM TCEP were mixed and incubated at room temperature for 1 h. The mixture was purified by Amicon-10K using buffer A solution (0.1 M NaCl, 0.1 M sodium phosphate buffer, pH 7.3) for three times. For invertase conjugation, 1 mg of sulfo-SMCC was mixed with 500 mL of 20 mg/mL invertase in buffer A solution. After vortexing for 5 min, the solution was placed on a shaker for 1 h at room temperature. The mixture was then centrifuged and the insoluble excess sulfo-SMCC was removed. The supernatant was washed three times by Amicon-100K using buffer A solution. The TCEP-activated DNA5 and the sulfo-SMCC-activated invertase were mixed and incubated for 48 h at room temperature. To remove the unreacted DNA5, the mixture was further purified by Amicon-100K for three times using buffer A solution.

2.3. Procedures for Cd^{2+} detection

100 μL of 2.5 mg/mL streptavidin-coated magnetic beads (SA-MBs) was washed three times by the washing buffer solution (20 mM PBS, 0.05% Tween-20, pH 7.4). After magnetic separation, the SA-MBs were resuspended in 100 μL buffer A solution. 300 nM DNA1 was added into the SA-MBs solution and incubated on a shaker for 40 min. The coverage of DNA1 on MBs is about 240 nM (Fig. S1, Supporting Information). Then 500 nM DNA2 was added and incubated for 30 min. The resulting SA-MBs-DNA1-DNA2 complex was washed three time using the washing buffer solution to remove the excess DNA2 and dispersed in 100 μL buffer A solution. 200 nM DNA3-DNA4 duplex was mixed with different Cd^{2+} concentrations and incubated at room temperature for 30 min. Then the mixture and 2.5 units/μL Exo III were added into the SA-MBs-DNA1-DNA2 solution and incubated for 40 min at room temperature. After magnetic separation, the solid residue was resuspended in buffer A solution. The DNA-invertase conjugation was then added into the resuspension and incubated at room temperature for 20 min. After magnetic separation to remove the unbound invertase conjugation, 0.5 M sucrose was added and incubated for 20 min. The final solution was detected by a PGM and a test strip. The test strip is the consumable of the PGM. Each strip is used once and then discarded. The PGM readout and the test strip color change can be obtained simultaneously. For each Cd^{2+} detection, the test strip was inserted into the PGM to harvest the electric signals. Meanwhile, on the round control window on the back of the test strip, the color changed from yellow to green. Such color changes can be observed by the naked eye at the same time. 5 μL of the final reaction solution was added onto the sample pad and the test strip was inserted into the PGM. After 30 s, we can read the PGM signal. Meanwhile, the color change can be observed by the naked eye on the round control window on the back of the test strip.

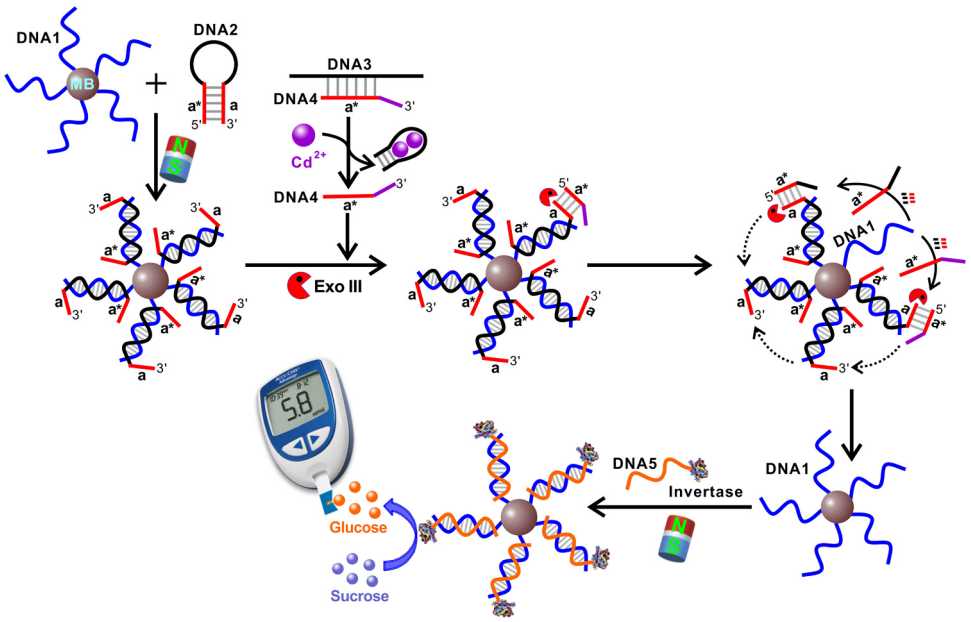
2.4. Analysis of real water samples

The lake water was obtained from Baiyun Lake. The river water samples were collected from Pearl River. The pond water was taken from our institute. Those water samples were filtered with 0.22 μm microfiltration membrane to remove the solid impurities and suspension. The concentration of Cd^{2+} was detected using our proposed sensor. Also, ICP-MS assay was employed to verify the sensor results.

3. Results and discussion

3.1. Mechanism of the assay

The assay mechanism of the PGM-based POU device for Cd^{2+} detection is illustrated in Scheme 1. DNA1 is first immobilized on the surfaces of magnetic beads (MB), and then hybridized with a hairpin nucleic acid (DNA2) to form the partial duplex DNA probe. After magnetic separation to remove excess DNA2, the obtained sensing probe (DNA1-DNA2) with the protruding 3′ end cannot be digested by Exo III which specifically cleaves double-stranded DNA with blunt or recessed 3′ termini. In the absence of the target Cd^{2+}, domain a* of DNA4 is occluded by hybridization with the anti-Cd^{2+} aptamer (DNA3), which prevents the interaction between DNA2 and DNA4 to form a blunt 3′-terminus. The introduction of Cd^{2+} to the sensing system induces dehybridization between DNA3 and DNA4, and segment a* of DNA4 is exposed to bind with segment a of DNA2. Such a binding generates a blunt 3′-terminus of DNA2. By virtue of the ability to mediate 3′ blunt-end cleavage of double-stranded DNA, Exo III can selectively digest DNA2 in a 3′ to 5′ direction, so that the trigger DNA4 will be released to hybridize with a secondary probe DNA2 on MB to initiate a new cleavage reaction. At the same time, the 5′-end fragment of DNA2 (containing domain a*) is also released during each cleavage process, which can be used as a new activator sequence to trigger the successive digestion of DNA2. Thus, in the presence of Cd^{2+}, the autonomous, autocatalytic cleavage of DNA2 is activated, which leads to the effective generation of numerous single-stranded DNA1 on MB. By hybridization with DNA5, the DNA5-invertase conjugates on MB can



Scheme 1. Schematic representation of the assay mechanism for Cd^{2+} detection based on PGM-based POU device. DNA is represented as different lines. DNA1-DNA5 were marked with different colors. Domain a is complementary to domain a* . MB, magnetic beads; Exo III, exonuclease III.

efficiently catalyze the hydrolysis of sucrose into glucose, which is quantified by a glucose meter. Because the concentration of target Cd^{2+} is proportional to the amount of DNA-invertase conjugates attached on MB, the readout in the PGM can be used to quantify Cd^{2+} concentration.

3.2. Feasibility of the design

To verify the feasibility of the designed PGM sensor for Cd^{2+} detection, the PGM signals were recorded in a series of control experiments. As shown in Fig. 1, in the absence of Cd^{2+}, the sensing probes (DNA1-DNA2) on the surface of MB were kept intact and failed to be activated for the signal amplification process because the domain a* of DNA4 is blocked. Thus, the DNA5-invertase conjugates couldn't be captured on MB and no sucrose was converted into glucose (histogram a). The results indicated that excess DNA2 can hybridize with DNA1 with high efficiency to make sure that no free DNA1 can be used for invertase strand (DNA5) binding in the absence of Cd^{2+}. In the absence of Exo III, no cleavage reaction toward the DNA1-DNA2-DNA4 complex was occurred and no obvious response can be observed in the PGM sensor (histogram b). Without introducing the DNA5-invertase conjugate to the sensing system, the PGM readout was too low to be detected (histogram c). Only in the presence of Cd^{2+}, Exo III, and DNA5-invertase conjugate, a remarkable enhanced PGM readout can be obtained (histogram d). This signal increase can be attributed to the fact that lots of sucrose has been converted into glucose by the invertase. Furthermore, the color change in the test strip of the PGM was also recorded (inset in Fig. 1). When Cd^{2+}, Exo III, and DNA5-invertase conjugate were all in the reaction solution, an obvious green color can be observed. In other control experiments, the color remained yellow. The novelty of this work is the design of segment a* in DNA2. As shown in Fig. S2 (Supporting Information), when DNA2 containing domain a* , the PGM readout of the sensing system toward 50 nM Cd^{2+} is much higher than that of DNA2 without a* sequence. The above results demonstrated the feasibility of our proposed sensing strategy for Cd^{2+} detection.

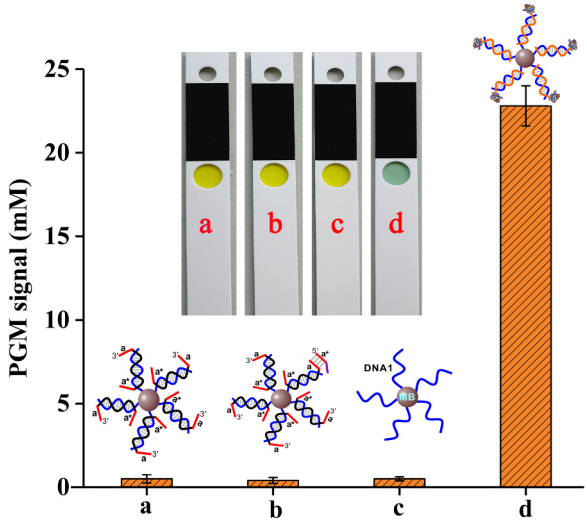


Fig. 1. The response of the PGM-based sensor under different conditions: (a) without Cd^{2+}; (b) without Exo III; (c) without DNA5-invertase conjugate; and (d) in the presence of Cd^{2+} (50 nM), Exo III, and DNA5-invertase conjugate. Inset: the corresponding color change of the test strip. The corresponding error bars represent the standard deviation of three independent measurements.

3.3. Optimization of the experimental conditions

To acquire an optimal sensing performance of the PGM-based sensor for Cd^{2+} detection, some experimental parameter such as the reaction temperature of the system, the incubation time with Exo III, and the concentration of sucrose were optimized. Since the enzyme activity and the affinity of DNA hybridization were temperature dependent, the effect of the reaction temperature on the sensor performance was first investigated. As shown in Fig. S3 (Supporting Information), in the presence of 50 nM Cd^{2+}, the PGM signals increased with increasing the temperature from 4° to 37°C and then decreased when the temperature was higher than 37 °C (blue histogram). On the other hand, the background signals (black histogram) increased gradually along with the elevated temperature from 4° to 45°C. At high temperature, the activity of the enzyme will be reduced and the DNA hybridization will be disturbed. To obtained the best signal-to-noise (S/N) ratio (red line), 25 °C was considered as the optimum reaction temperature.

The incubation time with Exo III that controlled the efficiency of the

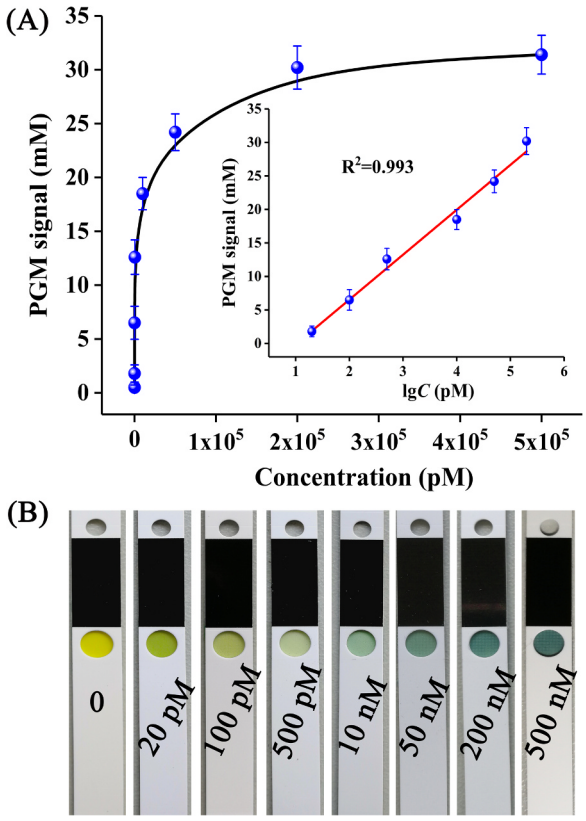


Fig. 2. (A) Analytical performance of the PGM-based sensor for Cd^{2+} detection. Inset: Calibration curve of the PGM reading vs. Cd^{2+} concentration. (B) Photographs of the color changes in the test strips of the PGM under different concentrations of Cd^{2+}. The corresponding error bars represent the standard deviation of three independent measurements.

signal amplification process had a significant effect on the behavior of the PGM-based sensor. As shown in Fig. S4 (Supporting Information), the PGM signals elevated gradually with the increase of the incubation time at the early stage and tended to be a maximum at 40 min, indicating that the cleavage reaction by Exo III can be completed within 40 min. Thus, 40 min was selected as the optimum incubation time.

As the concentration of sucrose is strongly related to the sensitivity of the sensor, we further optimized this parameter. As shown in Fig. S5 (Supporting Information), the PGM signals increased with the increase of the concentration of sucrose and then reached a plateau after 0.5 M. This indicated that 0.5 M sucrose is enough to be hydrolyzed by the invertase conjugates. Thus, 0.5 M sucrose was chosen for the following experiments.

3.4. Analytical performance for Cd^{2+} detection

Under the optimal experimental conditions, the analytical performance of the proposed PGM-based sensor for Cd^{2+} detection was investigated. As shown in Fig. 2A, the PGM readings increased gradually with the increase of the Cd^{2+} concentrations. The calibration curve exhibited a good linear relationship between the PGM signals and the logarithm of Cd^{2+} concentrations in the range from 20 p.M. to 200 nM. The regression equation is: $y = 6.7 \times - 6.8$ ($R^2 = 0.993$), where y is the PGM readings and x is the logarithm of Cd^{2+} concentrations. The detection limit was calculated to be 5 p.M. based on $3\sigma_b$/slope, where σ_b was the standard deviation of the blank samples. Since the maximum permissible amount of Cd^{2+} in drinking water is set by the EPA to be 5 ppb, the detection range and detection limit of the PGM-based sensor is suitable for Cd^{2+} detection in water samples. The high sensitivity of this assay can be attributed to the cyclic cleavage reaction by Exo III,

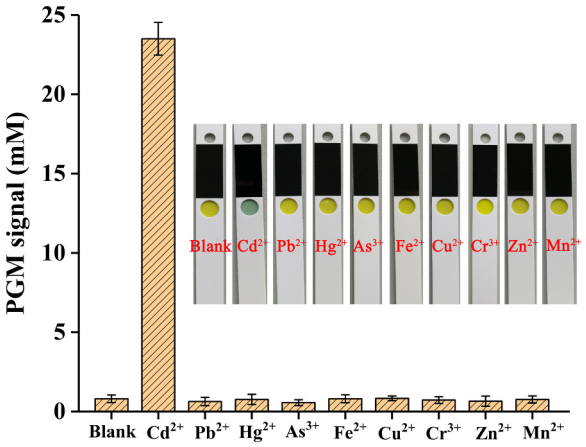


Fig. 3. Selectivity investigation of the PGM-based sensor for Cd^{2+} and other interfering ions. Cd^{2+}: 50 nM; other interfering ions: 100 nM. The corresponding error bars represent the standard deviation of three independent measurements.

the multiple conversion efficiency of invertase, and the low background signal by magnetic separation. Moreover, the color changes in the test strips of the PGM were also recorded in Fig. 2B. With the Cd^{2+} concentration increased, the colors in the strips were changed gradually from yellow to green, indicating that more sucrose were converted to glucose by the invertase. Thus, the PGM-based sensor can provide the digital readout and naked-eye color observation for Cd^{2+} detection.

3.5. Selectivity of the assay

To evaluate the selectivity of the PGM-based sensor for Cd^{2+} detection, several other heavy metal ions including Pb^{2+}, Hg^{2+}, As^{3+}, Fe^{2+}, Cu^{2+}, Cr^{3+}, Zn^{2+}, and Mn^{2+} were also investigated using the same analytical procedure. The concentration of Cd^{2+} used in this test was 50 nM and the concentration of the interfering ions was 100 nM. As shown in Fig. 3, only the target Cd^{2+} can cause the color of the test strip to change from yellow to green and significant PGM signal can be observed. In contrast, almost no color change in the test strips was observed in the presence of the interfering ions and no distinct PGM reading can be obtained. The results indicated that our proposed sensing system is highly sensitive for Cd^{2+} detection. Such high specificity and anti-interference ability of the PGM-based sensor can be attributed to the high binding capability of the aptamer-ligand interaction.

3.6. Real sample analysis

To validate the applicability and accuracy of this assay, the PGM-based sensor was applied to the detection of Cd^{2+} in real water samples, including lake water, river water, and pond water. The concentrations of Cd^{2+} in those water samples were also certified by the ICP-MS standard method. The determination results were summarized in Table S2 (Supporting Information). The data indicated that no significant difference existed between the sensing strategy and the ICP-MS method, confirming the reliability and practicality of the PGM-based sensor for Cd^{2+} detection in real samples.

4. Conclusions

In conclusion, this work has demonstrated a simple and general method for portable and quantitative detection of Cd^{2+} using a commercially available PGM as the POU device. The approach is based on target-triggered signal amplification process to capture DNA-invertase conjugates on MB. After magnetic separation, the invertase can effectively catalyze the conversion of sucrose into glucose, which can be

directly monitored by a PGM. The novelty of our work is that the capture strand for invertase (DNA1 strand) can be continuously recovered by Exo III-mediated recycling signal amplification process. In this approach, the design of DNA2 strand is smart: a* domain could regenerate from every dehybridization event. After successive hybridization and cleavage reactions, numerous single-stranded DNA (DNA1) were available on the surface of the magnetic beads. Due to the recycling cleavage reactions of Exo III and efficient conversion capability of invertase, significantly amplified response signals for highly sensitive detection of Cd^{2+} down to 5 p.M. can be achieved. In addition, this POU sensor shows excellent selectivity for Cd^{2+} from other competing metal ions. This portable device has been successfully applied to the determination of Cd^{2+} in water samples with reliable results compared with the ICP-MS technology. Moreover, the PGM-based Cd^{2+} sensor offers several advantages of simple operation, low cost, user-friendliness, and quantitative signal output, making this sensing system particularly suitable for routine on-site monitoring by the public. The sensor also possesses good extensibility for other targets detection by simply substituting specific molecular recognition elements.

Acknowledgements

Financial support was provided by the NSFC (31671933), the Guangdong Natural Science Funds for Distinguished Young Scholars (2016A030306012), and the Local Innovative and Research Teams Project of Guangdong Pearl River Talents Program (2017BT01Z176).

Conflict of interest

The authors declare that they have no conflicts of interest to this work.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.talanta.2019.02.045.

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