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In-situ detection of cadmium with aptamer functionalized gold nanoparticles based on smartphone-based colorimetric system

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ABSTRACT

Cadmium is a heavy metal pollutant in environment with high toxicity that severely threats human health. A simple and sensitive method for rapid detection of cadmium ions in water sample is of significant importance. In this paper, a colorimetric method based on aptamer-functionalized gold nanoparticles (AuNPs) for specific recognition were proposed to realize Cd^{2+} detection. AuNPs aggregate in high-salt solutions because of the shielding of salt to electrostatic repulsion among AuNPs, while aptamers can strengthen the stability of AuNPs and avoid the aggregation. After adding Cd^{2+} ions, the specific interaction between aptamers and Cd^{2+} leads to a decrease of free aptamers, which weakens the stability of the AuNPs and results in the color change of the solution. The colorimetric change can be rapidly captured and analyzed by a self-developed smartphone-based colorimetric system (SBCS) within 10 min, which implements the quantitative detection of Cd^{2+}. The results show that Cd^{2+} ions can be detected with high selectivity and sensitivity with a linear range of 2–20 μg/L and a detection limit of 1.12 μg/L. Compared with other methods, the proposed approach features high sensitivity, high simplicity, easy implementation and high throughout, which provides a promising means for in-situ determination of Cd^{2+} in practical applications.

1. Introduction

Environmental heavy metal pollution is one of the most concerned issues of the public today, in which cadmium is a common environmental pollutant with high toxicity. Cadmium ions are generally discharged into the environment from industrial and domestic wastewater. Through food chains and water intake, Cd^{2+} ions will accumulate in human organs such as lung, kidney and liver, resulting in acute or chronic poisoning and even cancer [1,2]. Therefore, it is urgent and of great significance to develop a method for detecting Cd^{2+} in a rapid and sensitive manner.

Several analysis methods have been developed for Cd^{2+} ions determination in water samples, including atomic absorption spectroscopy, inductively coupled plasma mass spectrometry, electrochemical method, immunoassay, and enzyme inhibition method, nucleic acid aptamer method [3–7]. In spite of their wide detection range, high selectivity and sensitivity, these methods have disadvantages of being bulky, costly, complicated, time-consuming and non-portable. Since multi-microplate reader is too huge and inconvenient for on-site detection, many biochemical analysis platforms combined with smartphone have been developed combining with the colorimetric method [8,9]. And based on these biochemical analysis platforms many substances can be detected rapidly and conveniently [10–12], with a good analytical performance in terms of the dynamic range, sensitivity, precision and detection limit.

Colorimetric approach is an attractive method because of its simplicity, short detection time and low cost. Particularly, Au nanoparticles (AuNPs) draw great attentions from the public due to its superior advantages of surface plasmon resonance (SPR) and high extinction coefficient, which macroscopically presents a specific solution color depending on the interparticle distance with high sensitivity [13,14]. Many studies have reported the colorimetric detection of heavy metal

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ions such as Hg^{2+}, Pb^{2+}, Cu^{2+} based on AuNPs [15–20]. For Cd^{2+} detection, Guo et al. [21] proposed a simple and label-free colorimetric method in water and digested rice samples based on the coordination between Cd^{2+} and 4 × glutathione (GSH) as a spherical shaped complex. Li et al. [22] designed a colorimetric method with peptide to obtain the aggregation of peptide-modified gold nanoparticles (peptide-AuNPs) triggered by the interaction between peptides and Ag^{+}. The detection limit is as low as 7.4 nM with a linear range of 10–1000 nM. Among different recognition molecules, aptamer is an extremely ideal recognition molecule, which can lead to the change in colorimetric signals by specific binding to heavy metal ions [23,24]. It has significant advantages of high sensitivity, good selectivity, high stability, non-toxicity and easy for massive production.

In this paper, we proposed a simple, rapid, high-throughput method for Cd^{2+} ions determination in water samples with aptamer functionalized AuNPs using a smartphone-based colorimetric system (SBCS). AuNPs would aggregate in high-salt solutions because excess salt can shield the electrostatic repulsion between AuNPs [25,26]. Aptamers can strengthen the stability of the AuNPs and avoid the aggregation. Cd-aptamer is employed as a specific recognition molecule which can strongly interact with Cd^{2+}. Therefore, different interaction between Cd^{2+} and Cd-aptamers-AuNPs can lead to different degrees of aggregation of the AuNPs [24], which results in the color change used for quantitative detection of Cd^{2+}. Besides, a self-developed SBCS was employed to capture the color change of aptamer-AuNPs solutions and analyze data with image processing algorithms for convenient detection of Cd^{2+}.

2. Materials and methods

2.1. Material and reagents

The oligonucleotide with sequence 5'-ACCGACCGTGCTGGACTCT GGACTGTTGTGG.

TATTATTTTTGGTTGTGCAGTATGAGCGAGCGTTGCG-3' was synthesized by GenScript Biotech Corp (Nanjing, China) according to the reported work [23]. Tetrachloroauric (III) acid hydrate ($HAuCl_4{\cdot}4H_2O$, > 47.8%) was purchased from Shanghai Reagent Company of China (Shanghai, China). Trisodium citrate (99.0%), sodium chloride (NaCl) and other reagents were purchased from Aladdin (shanghai, China). Unless otherwise noted, all the reagents were of analytical grade and used as obtained. The ultrapure water with a resistivity of 18.4 MΩ cm (Millipore, USA) was used in all experiments.

Transmission Electron Microscope (TEM) images were obtained with a JEM-2100 microscope at acceleration voltage at 200 kV. A multi-microplate reader USD51400 (Molecular Devices, America) was employed to record the Ultra violet-visible absorption spectra of aptamer-AuNPs in Cd^{2+} detection. The values of assay were detected by a self-developed smartphone based colorimetric reader system.

2.2. Smartphone-based colorimetric reader system

In brief, the principle of colorimetric assay is that AuNPs aggregate under the high-NaCl conditions, leading to the color change of AuNPs solution (Fig. 1). The nucleic acid aptamer has a stem-loop structure [23], capable of specifically recognizing Cd^{2+} ions. The negatively charged citrate is adsorbed to the surface of the AuNPs, and the electrostatic repulsion keeps the AuNPs in a stable dispersion state. Under high-salt conditions, the AuNPs will aggregate to different degrees, and the color of AuNPs changes from red to purple and finally to gray. Nevertheless, aptamer can protect AuNPs from the aggregation, because the exposed base on the surface of the aptamer can be easily adsorbed onto the surface of AuNPs. And the electrostatic repulsion generated by a large number of negatively charged aptamer phosphate backbones inhibits strong van der Waals attraction and enhances the stability of AuNPs to salt-induced aggregation, allowing the solution to remain dispersed [23,27]. Upon the addition of Cd^{2+}, aptamer-AuNPs can undergo aggregating due to the specific interaction between the aptamer and Cd^{2+}, and result in a significant aggregation of AuNPs solution with the apparent color change [28].

The color changes are analyzed by a self-developed SBCS, which consists of a smartphone (iPhone 4s) as detection instrument and portable accessory as illumination provider. The portable accessory includes a 96-well microplate loading station, a wide-angle lens, a dark room, and a piece of low-power electroluminescent sheet. The wide-angle lens is placed above the dark room and in good contact with the camera of the smartphone. The 96-well microplate loading station is used to place the reaction vessel. The illumination needed for detection in dark room is provided by electroluminescent sheet.

Based on the Objective-C language, the smartphone software contains image extraction and data analysis software. The detection process is shown in Fig. 2. Firstly, the 96-well microplate is placed on the loading platform, and the colorimetric image is collected by the smartphone put on the designated containment. Subsequently, the acquired image is analyzed by the image processing algorithm. A standard curve of color and Cd^{2+} concentration is established to calculate the concentration of the added Cd^{2+}. The image processing algorithm employs the RGB color model in the mean pixel intensity calculation, where R,G,B stands for red color channel, green color channel and blue color channel, respectively. We extract the pixel of red channel and blue channel from the color model and used the ratio of A_R to A_B (A_R/A_B) to analyze the image date (A_R and A_B are defined as the difference in pixel value of R channel and B channel contrast with the blank hole, respectively). The linear relationship between the detected values and the Cd^{2+} concentrations is obtained and used to quantitative analysis based on the calibrated working curve. Compared with the multi-microplate reader, which is expensive and bulky, the SBCS has advantages of no need for additional instruments, small size and easy operation, which exhibits great potential in rapid and high-throughput detection of Cd^{2+}.

2.3. Synthesis of AuNPs

AuNPs were synthesized by the citrate reduction of $HAuCl_4{\cdot}4H_2O$, according to the reported method of Frens in 1973 [29]. An aqueous solution of 1% $HAuCl_4{\cdot}4H_2O$ (4.2 mL) and ultrapure water (95.8 mL) were brought to a refluxing solution, heated to boiling with rapid stirring for 10 min. Then 10 mL of a 1% (w/w) trisodium citrate solution was quickly added, and as a result, the color of solution turned from light yellow to final red. Further, the mixture was kept boiling for an additional 20 min, and allowed to cool to room temperature with stirring and stored in a refrigerator at 4 °C before use. The synthesized AuNPs were characterized by transmission electron microscopy (TEM) and UV–vis spectroscopy.

2.4. Colorimetric detection of Cd^{2+}

Before Cd^{2+} detection, the aptamer was centrifuged at 6,000 rpm for 15 min, and dissolved in pure water. Then it was heated at 90 °C for 5 min and rapidly allowed to cool to room temperature for reshaping. Diverse concentrations of Cd^{2+} (2–20 μg/L) were obtained by serially diluting the stock solution to test the sensitivity limits of aptamer-AuNPs. Firstly, 10 μL nucleic acid aptamer and 20 μL Cd^{2+} solutions with different concentrations were added to the 96-well microplate and incubated for 20 min. While the blank group added 20 μL ultrapure water instead of Cd^{2+} solution. Then 160 μL AuNPs was added to the above mixture and equilibrated for another 10 min. Last but not least, the final volume of all the reaction mixture was regulated to 200 μL by adding 10 μL NaCl solution and incubated at room temperature for several minutes. All experiments were repeated three times, respectively. In addition, we explored the selectivity of our proposed strategy for Cd^{2+} over other potential co-existing ions (Pb^{2+}, K^{+}, Cu^{2+}, Ca^{2+},

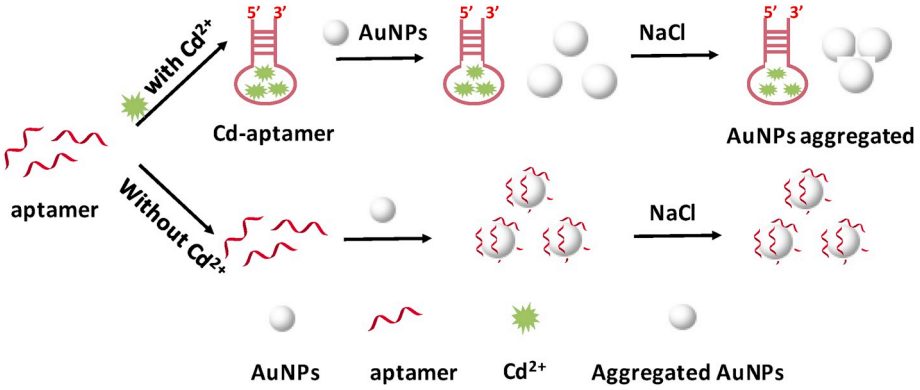

Fig. 1. Colorimetric detection principle based on AuNPs.

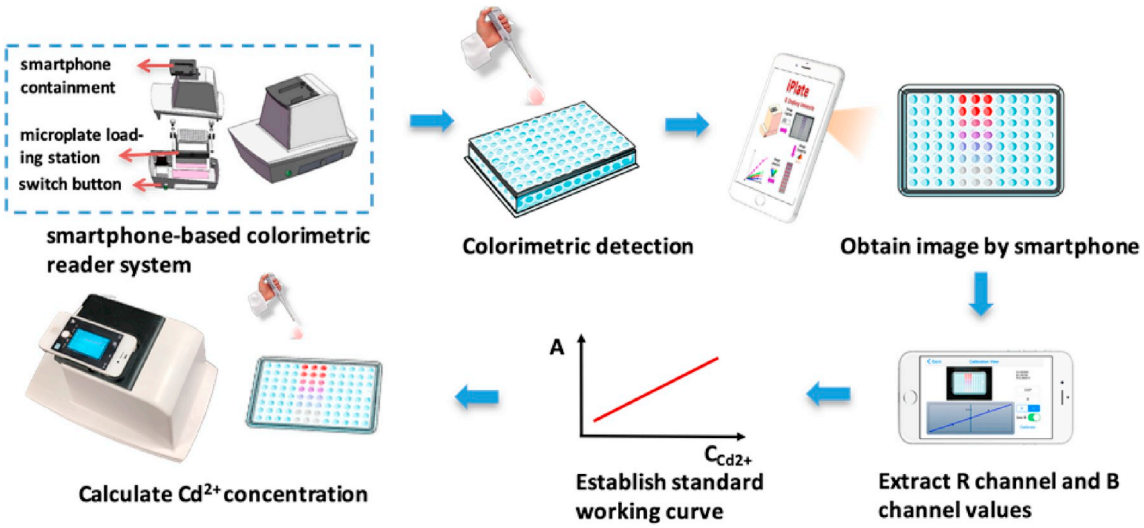

Fig. 2. Detection process of smartphone based colorimetric reader system.

Mg^{2+}, Na^{+}). The Cd^{2+} concentration was 10 μg/L, while co-existing ions were set as 10 fold Cd^{2+} concentration.

The recovery experiments were accomplished using Cd^{2+}-spiked tap water. The procedure of Cd^{2+} detection in tap water samples is similar to that of the colorimetric detection of Cd^{2+} above. Compared with the standard curve of colorimetric response against Cd^{2+}-spiked tap water samples, the Cd^{2+} concentrations in the samples could be calculated.

3. Results and discussion

3.1. UV–vis spectra and TEM images of aptamer-AuNPs

The proposed method was characterized by transmission electron microscopy (TEM) and UV–vis spectroscopy from 400 nm to 800 nm. As shown in Fig. 3, a characteristic SPR peak of AuNPs was observed in the spectrum at approximate 520 nm (Fig. 3A), since AuNPs are negatively charged due to adsorption of citrate on the surface, and the aggregation of electron oscillation intensity will form a characteristic plasmon resonance absorption peak. With the addition of Cd^{2+}, the color of the solution changes from red to purple, which is in accordance with the decrease of the absorbance at 520 nm and the increase at 740 nm. The corresponding TEM observations were shown in Fig. 3B(a). The picture shows that AuNPs were uniformly dispersed and the average particle diameter of AuNPs is about 15 nm (Fig. 3B(a)).

Aptamer has effect on the stability of AuNPs in high-salt conditions (Fig. 3B(b)) because the exposed base on the surface of the aptamer can be easily adsorbed onto the surface of AuNPs, and the electrostatic repulsion generated by a large number of negatively charged aptamer phosphate backbones inhibits strong van der Waals attraction and prevents the stability of AuNPs to from salt-induced aggregation, allowing the solution to remain dispersed.

However, when the Cd^{2+} was added to the aptamer-AuNPs solution, the AuNPs aggregated and the color of solution turned purple, further supported by TEM image (Fig. 3B(c)). Because the aptamer and Cd^{2+} combined to form a composite structure, and the amount of aptamer bound to the AuNPs surface reduced, resulting in significantly aggregated. It was clear that the absorption value at 520 nm apparently decreased and that at 740 nm increased. The absorption values of the solution at 520 nm and 740 nm corresponded to the quantities of dispersed and aggregated AuNPs. Therefore, the state of dispersed to aggregated AuNPs can be presented by ratio of the absorption value at 740 nm to that at 520 nm (A_{740nm}/A_{520nm}).

3.2. Parameters optimization

To obtain the optimum condition of the detection system, we optimized several parameters regarding the reaction time of the mixture, concentration of aptamer and concentration of NaCl. Firstly, NaCl-induced aggregation of AuNPs was investigated, because NaCl concentration plays an important role in the stability of the AuNPs, which could shield the electrostatic repulsion between AuNPs, resulting in the aggregation of AuNPs. The ratio of colorimetric response in the different concentrations of NaCl was shown in Fig. 4A after NaCl solution

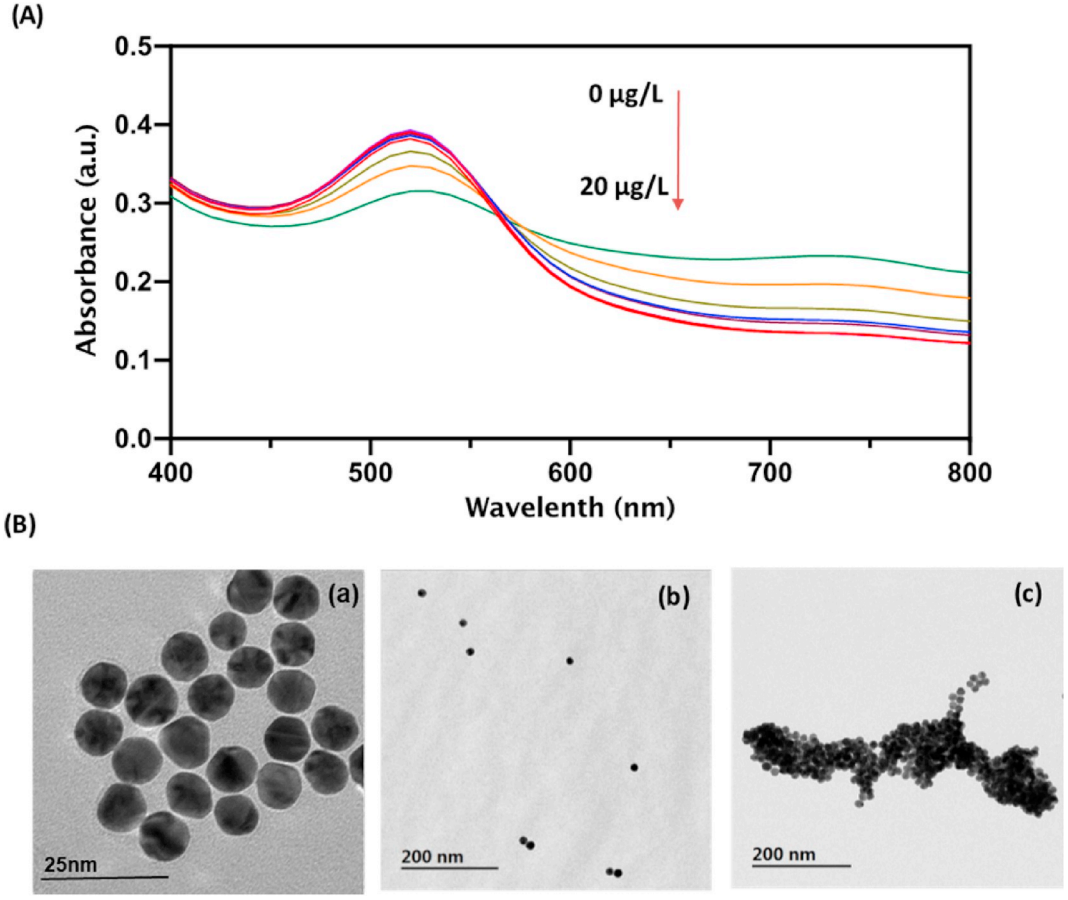

Fig. 3. (A) UV–vis spectra of the aptamer-AuNPs at the Cd^{2+} concentration range of 0–20 μg/L (B) TEM image of the (a) AuNPs and the aptamer-AuNPs in the (b) absence and (c) presence of 20 μg/L Cd^{2+}.

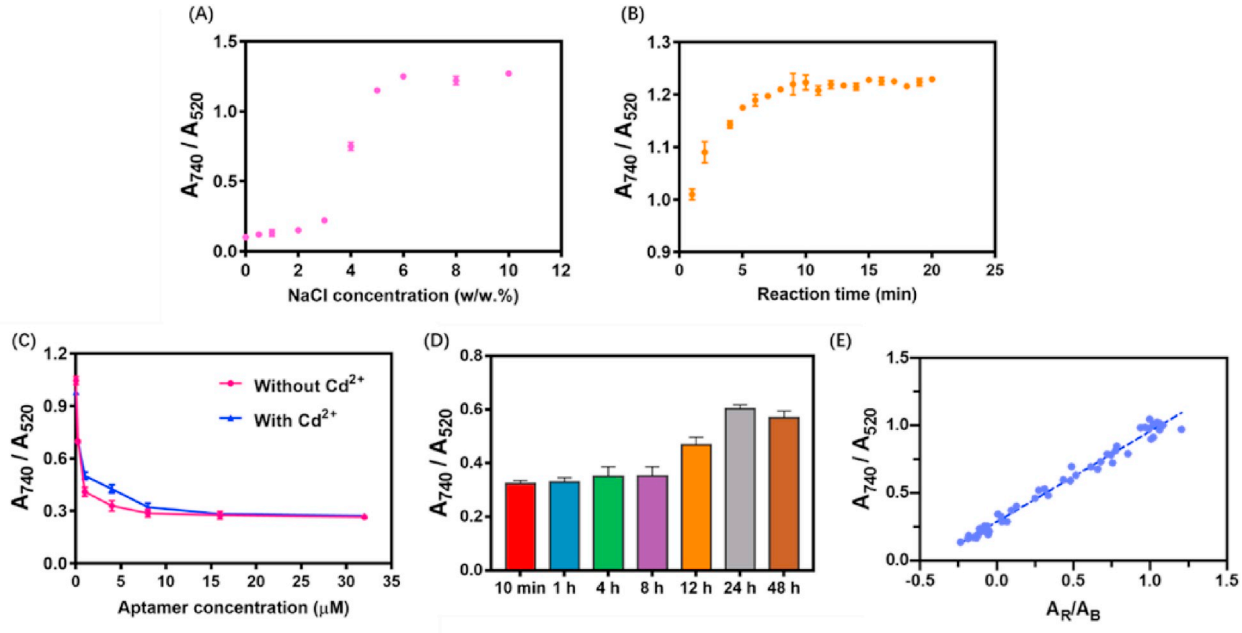

Fig. 4. (A) Colorimetric response of NaCl concentration ranging from 0% to 10% (w/w). (B) Effect of different reaction time at the range of 1 min–21 min. (C) Effect of different aptamer concentration in the presence (10 μg/L) and absence of Cd^{2+} ranging from 0 to 32 μM. (D) The reaction time of aptamer and AuNPs. (E)Correlation of the colorimetric response between the SBCS and multi-microplate reader. All the experiments were repeated 3 times.

was added to the Unmodified AuNPs. As the NaCl concentrations ranging from 2% (w/w) to 6% (w/w), the value apparently increased and the color of the AuNPs gradually changed from red to purple and finally to gray, indicating different degrees of aggregation. When below the concentration of 2% (w/w), the value was low, indicating that AuNPs dispersed well in the solution. On the contrary, it reached maximum

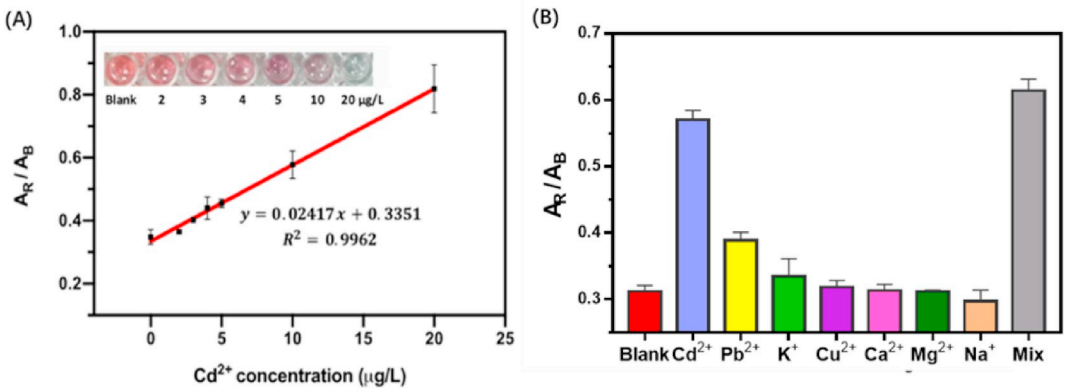

Fig. 5. (A) Colorimetric response linearity of the assay at the Cd^{2+} concentration range of 2–20 μg/L. (B) Colorimetric response of aptamer-AuNPs with several metal ions (100 μg/L), Cd^{2+}(10 μg/L), and the mixture (10 μg/L Cd^{2+}, six metal ions with 100 μg/L each). The error bars represent standard deviations based on three independent measurements (n = 3).

Table 1
Comparison of different UV–visible detection methods toward Cd^{2+}.

Detection method/Material	LOD (μg/L)	Linear range (μg/L)	Portability	High throughput	Ref.
glutathione-AuNPs	560	/	No	No	[21]
2,6-dimercaptopurine-AuNPs	3.66	84–336	No	No	[31]
chalcon carboxylic acid-AuNPs	25.76	25–356	No	No	[32]
DNA aptamer-AuNPs	0.52	1.12–448	No	No	[24]
chitosan dithiocarbamate-AuNPs	7.06	5.6×10^3–5.6×10^4	No	No	[33]
aptamer-AuNPs based on SBCS	1.12	2–20	Yes	Yes	This work

Table 2
Determination of Cd^{2+} in tap water samples using the proposed method.

Samples	Spiked concentration (μg/L)	This colorimetric system		Microplate reader	
		Determined conc. (μg/L)	Recovery%	Determined conc. (μg/L)	Recovery%
1	5	5.18	116.4	5.21	104.3
2	10	11.32	113.2	10.96	109.6
3	10	11.61	116.1	10.83	108.3
4	20	21.63	108.15	20.12	100.6
5	20	23.56	117.8	22.15	110.8

value and remained basically unchanged with the NaCl concentration higher than 6% (w/w), revealing that AuNPs aggregated almost completely in high-salt conditions. Therefore, NaCl concentration of 6% was selected.

We investigated the effect of reaction time between NaCl and AuNPs, and the colorimetric response was measured every 1 min within a time range of 1–21 min (Fig. 4B). After the addition of NaCl, it rapidly formed a blue-gray solution under the action of the salt solution, and the blue-gray gradually became deeper in the subsequent 10 min, and the value of the test value continued to increase. The color of the solution did not change greatly After 10 min, and the response of the assay remained stable. Therefore, 10 min was applied as the reaction time to the detection system for the following experiments.

The effect of aptamer concentration was investigated as well to obtain the best concentration of aptamer. The value in the presence (10 μg/L) and absence of Cd^{2+} and in the presence of different concentrations of aptamer was shown in Fig. 4C. It was evident that with the increase of the concentration of aptamer, the colorimetric response increased gradually and when the aptamer concentration was 16 μM, the response with and without Cd^{2+} were reaches a plateau, indicating that the color of AuNPs did not change greatly when the concentration of aptamer is above 8 μM. Since the aptamer could be electrostatically adsorbed to the surface of the AuNPs by the exposed positively charged. Thereby AuNPs was stabilized to salt-induced aggregation. Comparing the results with and without Cd^{2+}, the difference between the two groups caused by added Cd^{2+} reached the maximum value at the concentration of 4 μM, which means the highest sensitivity of the assay. Therefore, aptamer concentration of 4 μM was selected for the further study. Besides, the reaction time of aptamer-AuNPs was also investigated. AuNPs and aptamers were mixed for different times (10 min, 1 h, 4 h, 8 h, 12 h, 24 h, 48 h) and then the color changes were analyzed after NaCl solution was added (Fig. 4D). It can be seen that before 8 h, only a slight change can be observed in A_{740}/A_{520}, indicating that the aptamer-AuNPs is relatively stable in the period from 10 min to 8 h. After 8h, A_{740}/A_{520} increases obviously indicating the aggregation of AuNPs and cannot be used to detect the Cd^{2+}. Therefore, we choose 10 min for the aptamer-AuNPs reaction, and then NaCl solution was added to was added to study the performance of the proposed method. What's more, it also shows the stability of the aptamer-AuNPs.

3.3. Colorimetric reader system validation

The correlation of the colorimetric response between SBCS and multi-microplate reader was analyzed. SBCS used the ratio of R channel value to B channel value (A_R/A_B) to express the degree of the aggregation, while multi-microplate reader applied the ratio of absorbance values at 740 nm and 520 nm (A_{740}/A_{520}). The results (Fig. 4E)

showed that the colorimetric response detected by SBCS and multi-microplate reader were linear, with a linear regression correlation coefficient of 0.9841.

3.4. Aptamer-AuNPs based sensor detection of Cd^{2+}

To determine the detection limit of the colorimetric assay, different concentrations of Cd^{2+} solutions were prepared from 2 to 20 μg/L by serially diluting the stock solution. The color of the AuNPs gradually changed from red to purple and finally gray with the Cd^{2+} concentrations ranging from 2 to 20 μg/L. We used the ratio of R channel value to B channel value (A_R/A_B) to express the degree of the aggregation as mentioned above. The ratio of colorimetric response definitely increased as the Cd^{2+} concentration increased, revealing that concentration was depend on the colorimetric response (A_R/A_B). Fig. 5 (A) showed that the response of the assay was fitted to linear, with a linear regression correlation coefficient of 0.9984 at the Cd^{2+} concentrations range of 2–20 μg/L. The linear equation is $A_R/A_B = 0.02417C_{[Cd2+]}(\mu g/L) + 0.3351$. Based on a previous report, 3σ rule was used to determine the detection limit of the proposed method as low as 1.12 μg/L, which is lower than the allowed Cd^{2+} concentration limit (5 μg/L) defined by the United States Environmental Protection Agency (USEPA) in drinkable water. The results indicate that the proposed method can be potentially used to detect Cd^{2+} in aqueous solution with high sensitivity.

3.5. Selectivity for the determination of Cd^{2+}

To identify the selectivity of the colorimetric method against Cd^{2+}, cations including Pb^{2+}, K^+, Cu^{2+}, Ca^{2+}, Mg^{2+}, Na^+ were tested and set as 10 fold concentration of Cd^{2+}. Fig. 5 (B) showed the colorimetric response of the assay against Cd^{2+} and other ions. As expected, Cd^{2+} led to an evident increase values when the other ions did not cause significant colorimetric response except for Pb^{2+}. Nevertheless, there was a slight response resulting from Pb^{2+}, which was considerably lower than the response from Cd^{2+} although the concentration of Pb^{2+} ions was 10 fold higher than the concentration of Cd^{2+}. The reason for the slight colorimetric response of Pb^{2+} ions might be attributed to its specific affinity for the G group, since Pb^{2+} promoted a G-rich sequence to form a "G-quadruplex" structure under suitable conditions [30]. When the mixed solution is detected, only slight change can be observed compared to the response of Cd^{2+} even with 10 fold interfering metal ions of Cd^{2+}, indicating that the sensor has a good selectivity. The present method is also compared with the other UV–visible methods (Table 1). It was observed that the proposed method was sensitive towards Cd^{2+}. In addition, compared to the UV spectrophotometers, which could only test one sample at a time, our system could simultaneously detect 96 samples and it took less than 10 min for image acquisition and analysis. So it had the advantage of portability, high throughput, and was especially suitable for simultaneous detection of a large number of samples.

3.6. Practical applications

In order to confirm the practical application of the proposed method, we prepared water samples from the tap water and then collected a series of samples by spiking them with different concentrations of Cd^{2+}. Each measurement was done in triplicate and analyzed by the proposed method. The analytical results of Cd^{2+} in tap water samples were shown in Table 2, indicating good agreement with those obtained from the multi-microplate reader.

4. Conclusions

In this paper, a simple, rapid, high-throughput method is proposed for Cd^{2+} ions detection in water samples, which employs aptamer-AuNPs as a specific recognition molecule A self-developed SBCS was developed to capture the colorimetric image of AuNPs solution before and after adding Cd^{2+} and analyze data within 10 min. As a result, Cd^{2+} can be easily recognized and determined. The detection limit of the colorimetric system is 1.12 μg/L, which is below the allowable limit (5 μg/L) according to the USEPA in drinking water. The results validate that our method is effective for rapid, convenient and high-throughput detection of Cd^{2+} ions with high selectivity. The approach paves a promising platform for in-situ and quantitative detection of Cd^{2+} in practical applications.

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