



Highly sensitive fluorescence detection of copper ion based on its catalytic oxidation to cysteine indicated by fluorescein isothiocyanate functionalized gold nanoparticles

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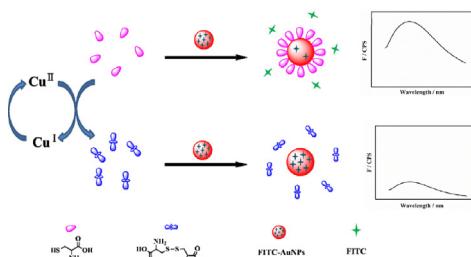


HIGHLIGHTS

- A fluorescent probe for Cu²⁺ has been developed by FITC functionalized gold nanoparticles.
- Cysteine could replace FITC from the surfaces of gold nanoparticles and Cu²⁺ could catalyze O₂ oxidation of cysteine.
- The fluorescent probe provides high sensitivity toward Cu²⁺ in drinking water as a real sample.

GRAPHICAL ABSTRACT

A highly sensitive fluorescent sensor for Cu²⁺ based on its catalytic oxidation of cysteine and cysteine-induced increase in fluorescence intensity of FITC-AuNPs.



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ABSTRACT

An innovative fluorescence method for sensitive detection of copper ion (Cu²⁺) was developed based on fluorescein isothiocyanate functionalized gold nanoparticles (FITC-AuNPs). Due to the stronger binding affinity of isothiocyanate functional group to gold, FITC molecules could adsorb on the surface of AuNPs, forming a simple fluorescence resonance energy transfer (FRET) system, and the fluorescence intensity of FITC was remarkably quenched. Upon adding cysteine, FITC could be displaced from the surface of AuNPs because the formation constant (K_f) of Au–S linkage ($K_f(AuS^-) = 4 \times 10^{35}$) was much higher than Au–SCN linkage ($K_f(Au(SCN)^2-) = 10^{23}$), leading to the recovery of fluorescence intensity. However, Cu²⁺ could catalyze O₂ oxidation of cysteine, and the generated disulfide cystine could not remove FITC from AuNPs' surface. Therefore, the recovery of fluorescence intensity was much weaker when compared with that of in the absence of Cu²⁺. And on the basis of this principle the concentration of Cu²⁺ could be detected quantitatively. Under optimal conditions, our method exhibited high selectivity toward Cu²⁺ and provided a good linear relationship in the range of 1.0–17.0 nM with the detection limit of 0.37 nM calculated by 3σ/S. Furthermore, complicated synthetic procedures and poor water solubility could be ignored in this proposed fluorescent sensor.

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1. Introduction

As an indispensable trace element in human body, copper ion (Cu²⁺) plays an important role in the development and function of

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internal organs [1], such as brain, liver and heart. And it also activates the formation of hemoglobin and promotes the absorption and utilization of iron [2]. However, the excessive accumulation of copper is confirmed to be poisonous to humans, in that it can lead to neurodegenerative diseases probably by its involvement in the generation of active oxygen species [3,4]. Accordingly, the safe limit of Cu^{2+} is 1.3 ppm ($\sim 20 \mu\text{M}$) in drinking water recommended by U.S. Environmental Protection Agency (EPA) [5]. The common analytical methods adopted for Cu^{2+} measurement include atomic emission spectrometry (AES) [6], atomic absorption spectrometry (AAS) [7], inductively coupled plasma mass spectrometry (ICP-MS) [8] and electrochemistry assay [9]. In spite of high selectivity and sensitivity, these methods often require professional operational skills, tedious sample pretreatments and a long analysis time. As a consequence, there has been growing interest in developing new methods for monitoring Cu^{2+} with high selectivity and sensitivity.

Recently, numerous chemosensors and biosensors have been designed based on nano-materials, e.g. gold nanoparticles (AuNPs) [10–12], gold nanorods (AuNRs) [13–15], carbon dots (CDs) [16–18] and quantum dots (QDs) [19,20]. Among various nano-materials, AuNPs have attracted a great deal of attention for chemical and biological analysis over past decades. Due to their unique optical properties, especially localized surface plasmon resonance (LSPR) [21], AuNPs were widely applied in colorimetric [10,11], fluorescent [22], surface-enhanced Raman scattering [23] and electrochemistry assays [24]. What's more, possessing higher extinction coefficient than those of common organic dyes in the ultraviolet and visible regions [25], AuNPs are emerging as efficient quenchers for fluorophores.

On account of high sensitivity and relative versatility, fluorescent assay has been gained comprehensive attention. However, complicated synthetic procedures and poor water solubility limit the application of most of existing fluorescent methods, which are only based on the design and synthesis of organic compounds. AuNPs have opened up a new alternative for the fabrication of fluorescent chemosensors. Because of AuNPs' high extinction coefficient, fluorophores attached to the surfaces of AuNPs will be quenched by fluorescence resonance energy transfer (FRET) [26]; when added analytes which have much stronger affinity with AuNPs, fluorophore molecules will be replaced, leading to the increase of fluorescence intensity. So far, AuNPs-FRET-based assay has been used to develop sensors for the detection of metal ions [27], inorganic anions [28], small organic molecules [29] and biomolecules [30].

Herein, a simple and sensitive method for fluorescence detection of Cu^{2+} in aqueous solution at room temperature was proposed based on fluorescein isothiocyanate functionalized gold nanoparticles (FITC-AuNPs). The fluorescence of FITC switched off when attached to the surfaces of AuNPs through forming Au–SCN linkage; upon adding cysteine, FITC was replaced because the Au–S linkage was stronger than Au–SCN linkage, and the fluorescence turned to switch-on. Yet, the oxidation of cysteine by O_2 could be catalyzed with the existence of Cu^{2+} , resulting in the formation of disulfide cystine [31,32]. At this point, the recovery of fluorescence was weakened when adding AuNPs. Based on this principle, the quantitative analysis of Cu^{2+} could be realized and this proposed method also showed high sensitivity toward Cu^{2+} over other metal ions.

2. Materials and methods

2.1. Chemicals

Fluorescein isothiocyanate (FITC, 96%), $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ and $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ were purchased from Aladdin. Hydrogen

tetrachloroaurate (III) hydrate ($\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$), sodium citrate, cysteine, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, MgCl_2 , CaCl_2 , FeCl_3 , NiCl_2 , ZnCl_2 , $\text{Cd}(\text{ClO}_4)_2$, LiCl , MnCl_2 , KCl , BaCl_2 , AgNO_3 , $\text{Pb}(\text{NO}_3)_2$ and HgCl_2 were obtained from Sinopharm Chemical Reagent Company Limited (Beijing, China). All the reagents were of analytical grade and used without any future purification.

2.2. Apparatus

Solutions were prepared with double-deionized water ($18.2 \text{ M}\Omega \text{ cm}$ specific resistance) obtained by a Cascada LS Ultrapure water system (Pall Corp., USA). Transmission electron microscope (TEM) images were captured on a JEM-1230 electron microscope (JEOL Ltd., Japan) operating at 100 kV. UV-vis absorption spectra were collected on a Thermo Scientific NanoDrop 2000C spectrophotometer (Gene Company Ltd., USA). The fluorescence spectra were recorded on a Fluoromax-4 spectrofluorometer with a xenon lamp and 0.5 cm quartz cells (HORIBA Scientific, Japan).

2.3. Synthesis and modification of AuNPs

All glasswares used in the following experimental procedure were bathed in freshly prepared 3:1 $\text{HCl}-\text{HNO}_3$, rinsed thoroughly with double-deionized water and dried in air. AuNPs were prepared by the citrate-mediated reduction of HAuCl_4 according to Frens' method [33]. Typically, 100 mL of 1.0 mM HAuCl_4 was introduced into a three-necked flask and heated to reflux with stirring. Then 10 mL of 38.8 mM sodium citrate was rapidly added to the boiling solution, resulting in a color change from pale yellow to deep red. The solution was kept boiling for another 30 min, and then cooled to room temperature with continuous stirring. The concentration of the obtained AuNPs solutions was estimated to be 12 nM according to Beer's law ($A = \varepsilon bc$), where the colorimetric cuvette had a path length (b) of 1 cm and the extinction coefficient (ε) of 13 nm AuNPs at 520 nm is $2.78 \times 10^8 \text{ M}^{-1} \text{ cm}^{-1}$.

A stock solution of 1.0 mM FITC was prepared in ethanol absolute. Then, 50 μL of the prepared FITC solution was added to the 50 mL AuNPs solution with stirring, and the mixture was equilibrated in the dark at room temperature.

2.4. Fluorescence detection of Cu^{2+}

A stock solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.01 M) was prepared in double-deionized water, and different concentrations of Cu^{2+} solution was acquired by diluting the stock solution accurately. For Cu^{2+} detection, 10 μL various concentrations of Cu^{2+} solution was added to 890 μL $\text{Na}_2\text{HPO}_4-\text{NaH}_2\text{PO}_4$ buffer (10 mM) at a pH of 6.8 containing 3.0 μM cysteine; the mixture solution was incubated at room temperature for 30 min. Then 100 μL FITC-AuNPs was added to the mixture solution. 10 min later, fluorescence spectra were collected at 514 nm with an excitation wavelength of 490 nm.

To measure the selectivity of the developed method, other metal ions instead of Cu^{2+} were detected in a similar way under the same optimized conditions.

2.5. Fluorescence sensing of Cu^{2+} in drinking water

The drinking water was obtained locally and 5-fold diluted, then this water sample was used to prepare 10 mM $\text{Na}_2\text{HPO}_4-\text{NaH}_2\text{PO}_4$ buffer at a pH of 6.8 spiked with standard Cu^{2+} solutions leading to different final concentrations. 10 μL of 300 μM cysteine was dissolved in 890 μL above buffer solution. After incubation for 30 min, 100 μL FITC-AuNPs was added to the solution and the mixed solution was equilibrated for another 10 min before spectra measurement.

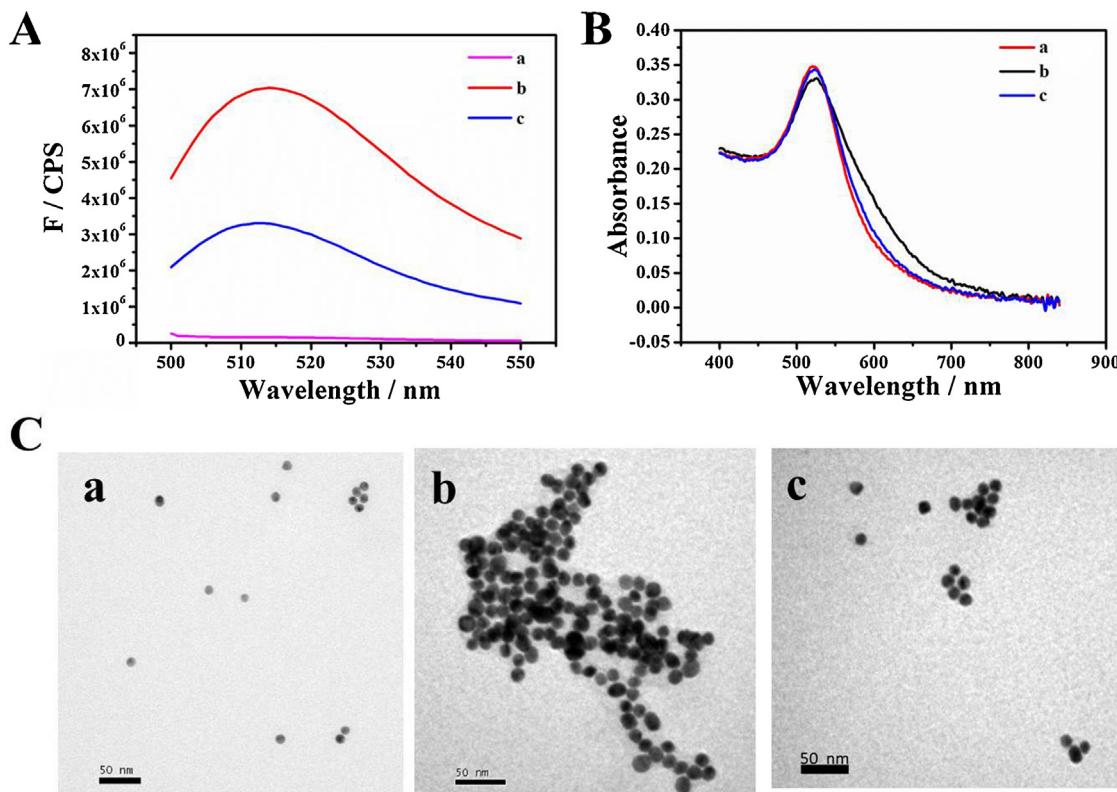


Fig. 1. (A) Fluorescence spectra, (B) UV–vis absorption spectra and (C) TEM images of (a) FITC-AuNPs, and the mixture solution of FITC-AuNPs and cysteine in the absence (b) and presence (c) of 20 nM Cu²⁺. (For interpretation of the references to color in text, the reader is referred to the web version of this article.)

3. Result and discussion

3.1. Characterization of FITC-AuNPs

FITC-AuNPs were synthesized by adding an optimum concentration of FITC to citrate modified AuNPs. Due to coordinately unsaturated gold atoms at the surface of AuNPs which own unoccupied orbitals available for nucleophiles to donate electrons, the isothiocyanate functional group of the FITC molecule, known as the strong nucleophile, could displace citrate ions from the surface of AuNPs and form stable complexes ($K_f(Au(SCN)_2^-) = 10^{23}$) with gold (I) [34]. The UV–vis absorption spectrum of FITC-AuNPs exhibited an intense characteristic LSPR peak at ~520 nm (Fig. 1B, curve a), and the color of the as-synthesized FITC-AuNPs suspension was remained wine red, indicating a good mono-dispersion of FITC-AuNPs in water. TEM image (Fig. 1C, image a) proved that the average particle size of FITC capped AuNPs was 13 nm.

In order to further demonstrate that FITC was modified on the surface of AuNPs, 100 μL FITC-AuNPs was diluted to 1.0 mL by 10 mM Na₂HPO₄-NaH₂PO₄ buffer at a pH of 6.8. At this time the concentration of FITC was equal to 0.1 μM. For purpose of remove AuNPs, the mixture solution was separated by centrifugation and the fluorescence intensity of obtained supernatant was recorded. Compared with that of 0.1 μM FITC prepared by 10 mM Na₂HPO₄-NaH₂PO₄ buffer (Fig. S1, black line), the fluorescence intensity of supernatant (Fig. S1, red line) was much lower, meaning the successful modification of FITC to AuNPs.

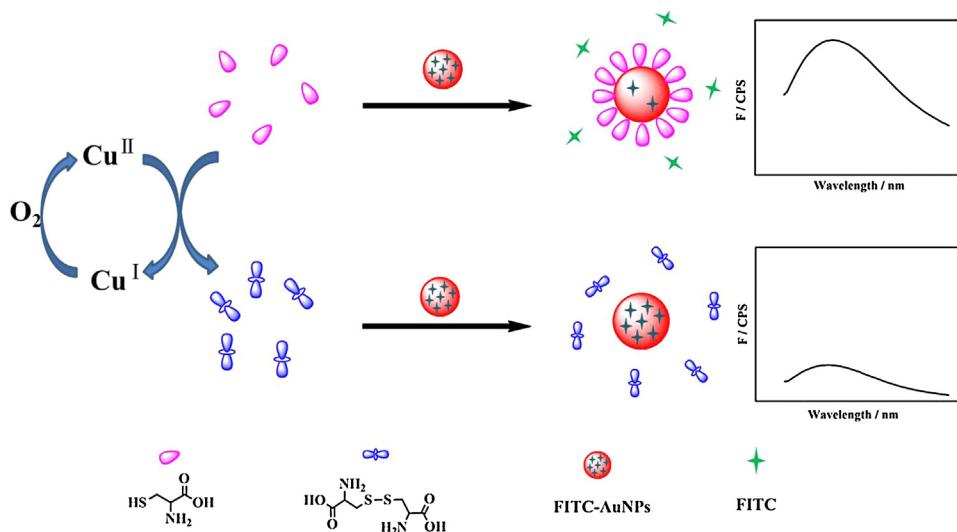
Moreover, the concentration of FITC was of great importance to carry out this sensing study. The optimal concentration of FITC should satisfy that not only enough FITC was required to saturate the surface of AuNPs, but also no free FITC was dispersed in the solution. In this work, the concentration of FITC was investigated by adding various amounts of FITC to 5 mL AuNPs. As shown in Fig. S2, the fluorescence intensity enhanced extraordinarily upon

increasing concentration of FITC up to ~1.0 μM, which could be attributed to the presence of free FITC molecules. Additionally, the fluorescence intensity was dramatically quenched at concentrations below 1.0 μM, indicating almost all the FITC molecules were adsorbed on AuNPs surface. Thus, the concentration of 1.0 μM was chosen as the optimum concentration of FITC to conduct the following experiments.

3.2. Sensing mechanism

Scheme 1 illustrates the sensing mechanism for fluorescence detection of Cu²⁺. By virtue of AuNPs' high extinction coefficient, when FITC was capped on the surface of AuNPs, a simple FRET system was composed in which AuNPs and FITC act as the acceptor and donor, respectively. As a consequence, the fluorescence intensity of FITC was remarkably quenched (Fig. 1A, curve a). Upon addition of sulphydryl-containing cysteine, which has higher binding affinity of Au-S linkage ($K_f(AuS^-) = 4 \times 10^{35}$) than that of Au-SCN linkage ($K_f(Au(SCN)_2^-) = 10^{23}$) [35], FITC molecules were effectively replaced and released to reaction solution, leading to the recovery of fluorescence intensity (Fig. 1A, curve b). However, the presence of Cu²⁺ could catalyze the oxidation of cysteine by O₂, resulting in the formation of disulfide cystine. The detailed catalytic reaction equations [31] were shown in Eq. (S1). With the addition of FITC-AuNPs, the generated disulfide cystine could not displace FITC molecules from the AuNPs' surface, leading to the weak recovery of fluorescence intensity (Fig. 1A, curve c).

To further demonstrate the proposed sensing mechanism, UV–vis absorption spectra and TEM images were also displayed. As indicated in Fig. 1B (curve a), the addition of cysteine induced the aggregation of FITC-AuNPs, leading to the decline of LSPR peak at 520 nm along with the emergence of a long wavelength band. This result was because that cysteine could be attached to the surface of AuNPs through forming Au–S bonds, and aggregation of



Scheme 1. Schematic illustration of fluorescent sensing Cu^{2+} based on its catalysis to cysteine by FITC-AuNPs.

AuNPs occurred by electrostatic interaction among cysteine capped AuNPs. However, the presence of Cu^{2+} could catalyze the oxidation of cysteine by O_2 , and the aggregation of FITC-AuNPs was inhibited (Fig. 1B, curve c). These results were confirmed by TEM images, revealing aggregated FITC-AuNPs in the presence of cysteine (Fig. 1C, image b), and slightly aggregated FITC-AuNPs when cysteine was first treated with Cu^{2+} (Fig. 1C, image c).

Furthermore, the role of dissolved oxygen to the oxidation of cysteine has also been discussed. As shown in Fig. S3, when bubbling N_2 to remove dissolved oxygen during the reaction, the fluorescence intensity (black line) was stronger in contrast to that unbubbling N_2 (red line). The results indicated that the oxidation of cysteine needs the participation of oxygen. The dissolved oxygen at 25 °C was 8.25 mg/mL (~258 μM), which could meet the needs of catalytic oxidation reaction.

3.3. Optimization of experimental conditions

The sensitivity of this proposed method was closely related to experimental parameters including pH, concentration of cysteine, the catalytic reaction time and the responsive time. The value of $F - F_{\text{blank}}$ was explored to evaluate experiments, where F and F_{blank} indicated the fluorescence intensities at 514 nm of reaction solution with or without Cu^{2+} , respectively.

To investigate the effect of pH to the value of $F - F_{\text{blank}}$, the experiment was performed in the pH ranging from 6.0 to 8.0 obtained by adjusting the ratio of NaH_2PO_4 to Na_2HPO_4 . As seen in Fig. S4A, the value of $F - F_{\text{blank}}$ was found to be pH-dependent. On one hand, the fluorescence intensity of FITC increased with increasing concentration of hydroxide ion because the pK_a for FITC was 6.4 [22]. On the other hand, hydrogen ion could be propitious to catalytic reaction because it would involve the reaction of $\text{O}_2^{\cdot-}$ and $\text{RS}^{\cdot-}\text{Cu}^{\text{I}}$. Considering the above two factors, an optimum pH at 6.8 was chosen for Cu^{2+} in the following experiments.

The concentration of cysteine played an important role in this sensing strategy, therefore, it was necessary to evaluate the effect of the concentration of cysteine. Fig. S4B showed the value of $F - F_{\text{blank}}$ in different concentrations of cysteine. It was noted that the value of $F - F_{\text{blank}}$ gradually increased in the range from 1.0 μM to 3.0 μM ; when the concentration was higher than 3.0 μM , the value exhibited a downward trend. Meanwhile, the concentration of FITC in the sensing system was 0.1 μM , which means higher than 0.1 μM of the given cysteine was required theoretically in order to completely displace the FITC molecules from the AuNPs surface. As the results

indicated, we chose 3.0 μM of cysteine to carry out the experiments, and the quantitation for Cu^{2+} was rationally feasible.

Effects of the catalytic reaction time and the responsive time were also considered for improving the sensitivity toward Cu^{2+} . As illustrated in Fig. S4C, the value of $F - F_{\text{blank}}$ gradually increased with the catalytic reaction time before 30 min and then varied slightly. And for the responsive time, it can be deduced that the FITC displacement with cysteine was completed within 10 min (Fig. S4D). Hence, all the following tests were carried out with a catalytic reaction time of 30 min and a responsive time of 10 min, respectively.

3.4. Selectivity and sensitivity for Cu^{2+}

In order to investigate the selectivity of this proposed method toward Cu^{2+} , other metal ions, including 10.0 μM Li^+ , K^+ , Ca^{2+} , Mg^{2+} , Ba^{2+} , Zn^{2+} , Fe^{3+} , Cd^{2+} , Mn^{2+} , 1.0 μM Pb^{2+} , Ni^{2+} and 100 nM Ag^+ , Hg^{2+} were examined under optimum conditions. As illustrated in Fig. 2, only Cu^{2+} had a distinct fluorescence quenching by comparison with that of blank and the presence of other metal ions. These results clearly showed our approach could selectively detect Cu^{2+} over other metal ions.

We further explored the analytical performance of this assay for the determination of Cu^{2+} . Under optimized detection conditions, the fluorescence spectra of reaction solution with different

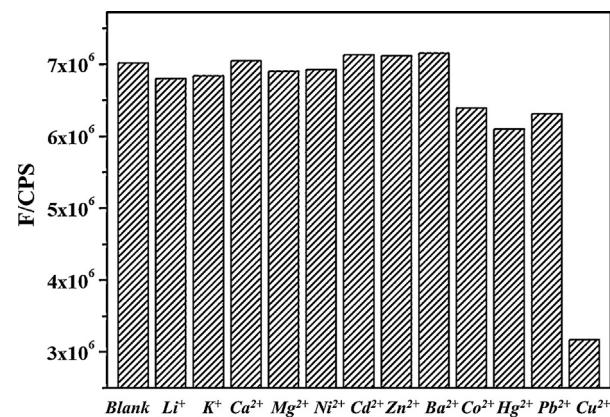


Fig. 2. The value of F in the presence of 20.0 nM Cu^{2+} or 10.0 μM Li^+ , K^+ , Ca^{2+} , Mg^{2+} , Ba^{2+} , Zn^{2+} , Fe^{3+} , Cd^{2+} , Mn^{2+} , 1.0 μM Pb^{2+} , Ni^{2+} , 100 nM Ag^+ , Hg^{2+} , where F indicated the fluorescence intensities at 514 nm.

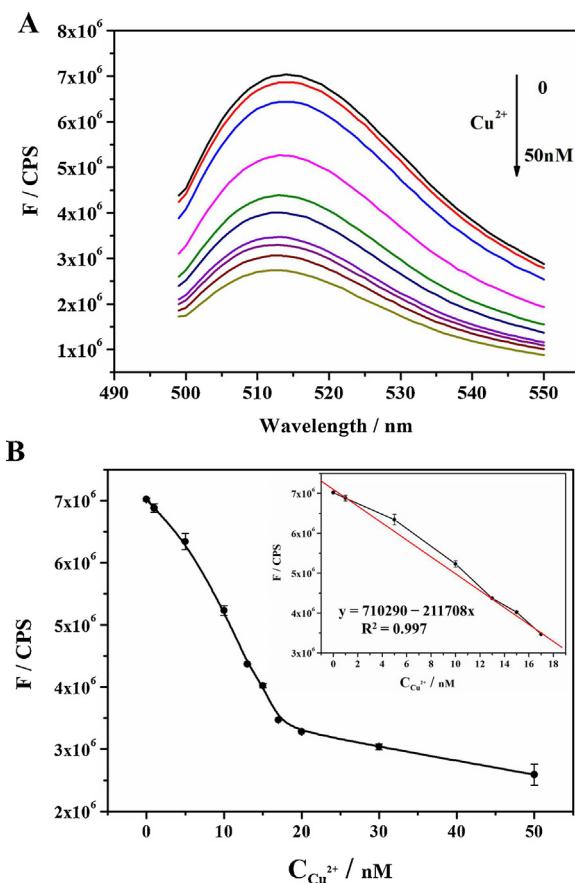


Fig. 3. (A) Fluorescence spectra of reaction solution upon the addition of Cu²⁺ with different concentrations. (B) A plot of $F - F_{\text{blank}}$ versus different concentrations of Cu²⁺. Inset shows a linear relationship in the range of 1.0–17.0 nM. The error bars represent standard deviations obtained from three parallel experiments.

concentrations of Cu²⁺ were recorded. As shown in Fig. 3A, with the increasing concentrations of Cu²⁺, there was a gradual decrease in the fluorescence intensity at 514 nm. For the sake of quantitative analysis of Cu²⁺, the value of fluorescence intensity at 514 nm was utilized. A good linear relationship was found in the range from 1.0 nM to 17.0 nM, and the detection limit was 0.37 nM calculated by $3\sigma/S$ (Fig. 3B). Therefore, our developed approach was demonstrated sensitively for the detection of Cu²⁺. The comparison of

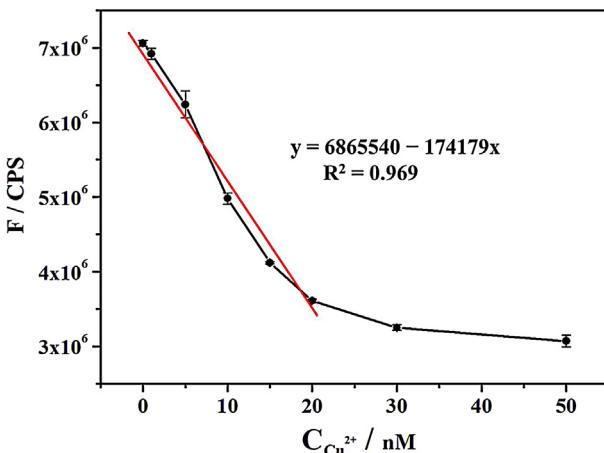


Fig. 4. A plot of $F - F_{\text{blank}}$ versus different concentrations of Cu²⁺ in drinking water samples. The error bars represent standard deviations obtained from three parallel experiments.

analytical performances between our developed method and some reported colorimetric and fluorescent methods for Cu²⁺ detection was shown in Table S1.

3.5. Detection of Cu²⁺ in real samples

To evaluate the practical utilization of the developed fluorescence detection of Cu²⁺ in real samples, barreled mineral water was spiked with Cu²⁺ and measured in the assay. As shown in Fig. 4, the values of fluorescence intensity were found to be dependent on the concentration of Cu²⁺. A linear decrease of fluorescence intensity versus the concentration of Cu²⁺ over the range from 1.0 nM to 20.0 nM was observed with the detection limit of 0.64 nM based on $3\sigma/S$. Hence, these results suggested that this proposed method was suitable for determination of Cu²⁺ in real samples.

4. Conclusion

In summary, we reported a highly sensitive fluorescent sensor for the detection of Cu²⁺ based on the catalytic oxidation of cysteine by Cu²⁺ and cysteine-induced increase in fluorescence intensity of FITC-AuNPs. This assay exhibited excellent selectivity toward Cu²⁺ over other metal ions. And our sensing system successfully avoided complicated synthetic procedures and poor water solubility relative to other fluorescent methods. What's more, the experimental results provided a great potential application of the proposed method in real samples, thus paving the way for wide use of AuNPs in design of optical sensors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.colsurfa.2014.12.050>.

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