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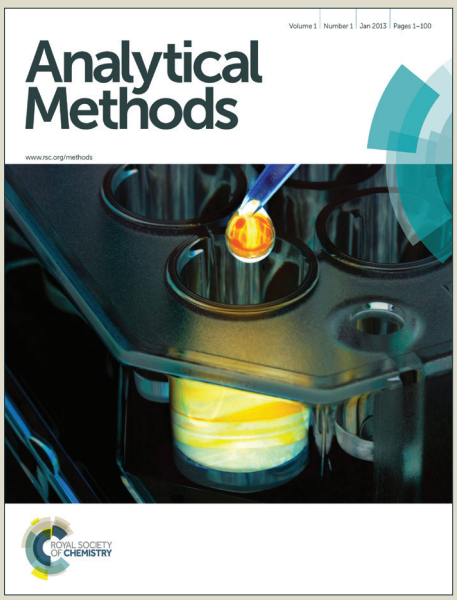

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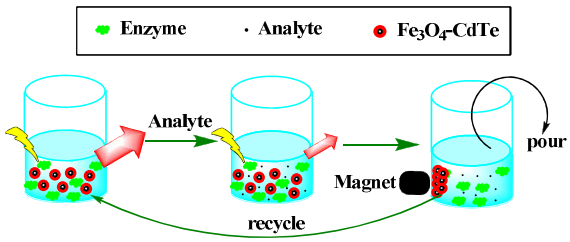
A reusable fluorescence method is developed to detect hydrogen peroxide and glucose with high sensitivity based on the Fe_3O_4@CdTe nanocomposites.



Journal Name

RSCPublishing

ARTICLE

Magnetic–fluorescent nanocomposites as reusable fluorescence probes for sensitive detection of hydrogen peroxide and glucose †

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2014,
Accepted 00th January 2014

DOI: 10.1039/x0xx00000x

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Hao Zheng,[a] Rongxin Su,[*a,b] Zhao Gao,[a] Wei Qi,[a,b] Renliang Huang,[c] Libing Wang,[a] and Zhimin He[a]

Multifunctional nanoprobe with excellent reusable capability for practical detection can not only increase resource utilization rate, but also reduce discharge of toxic nanoparticles into the environment. In this paper, a novel magnetic–fluorescent nanocomposites (Fe_3O_4@CdTe) had been successfully fabricated through layer-by-layer (LBL) self-assembly. The particles were used to develop a reusable fluorescence method to detect hydrogen peroxide and glucose with high sensitivity. The obtained core-shell Fe_3O_4@CdTe nanocomposites were characterized by transmission electron microscopy and fluorescence spectroscopy. The results indicated the successful formation of a CdTe shell on the surface of the magnetic Fe_3O_4 core. Its sensing performance towards H_2O_2 and glucose was then discussed in detail. The emission of the nanocomposites gradually reduced with the increasing analyte concentration. High sensitivity and good selectivity were observed from the composites. More importantly, these composites can be easily recovered and reused for several cycles due to their magnetism and high stability. Furthermore, we demonstrated this fluorescent sensor can be used for glucose detection in human urine samples. As a multifunctional nanoplatform, the present nanoprobe holds genuine potential in future biosensing applications.

Introduction

Luminescent quantum dots (QDs) have been investigated in recent years as target-specific probes to develop various sensors and biosensors. The high photobleaching threshold, photostability, chemical stability, and the photoluminescence-tuning ability by controlling particle size yields superior performance of QDs in many applications [1-3]. However, the separation and recovery of toxic QDs is difficult in practical applications, which poses a big issue in sensor and biotechnological applications. Fe_3O_4 is a magnetic nanomaterial that possesses excellent superparamagnetism, and this material can be easily surface modified and separated from the nonmagnetic materials in magnetic field [4-8]. The combination of magnetic and fluorescent properties in nanocomposites is beneficial for nano- and biotechnology. It enables the engineering of uniquely targeted, nanoscale photonic devices that could be manipulated by an external magnetic field. Several works have focused on fabrication of magnetic–fluorescent nanocomposites. Layer-by-layer (LBL) self-assembly is an effective approach to construct well-defined nanostructures with functional hybrid nanoshells [9-12]. LBL deposition is based on alternating adsorption of oppositely charged species, by which electrostatic forces and hydrogen-bonding interactions hold the assembly of nanostructures together [10, 13, 14].

Glucose is a major component of animal and plant carbohydrates in biological systems. This monosaccharide is a source of energy for living cells and a metabolic intermediate during synthesis of complex molecules. Maintenance of glucose levels is important to slow the progression of long-term complications associated with diabetes. Therefore, determining the glucose concentration is necessary for clinical diagnosis and bioengineering. Various analytical methods for detection of glucose have been reported. Among these, the methods based on fluorophotometry possessed many advantages such as operational simplicity and high sensitivity [15-18].

Herein, we achieved the assembly of the Fe_3O_4@CdTe nanocomposites based on LBL method (Fig. 1). The resulting microspheres are utilized as highly sensitive and separable chemosensors to detect hydrogen peroxide and glucose. Fe_3O_4@CdTe core–shell composites are highly sensitive chemosensors for glucose. More importantly, they can be easily separated by an external magnetic field using a small magnet. Furthermore, we can reuse these microspheres in another detection (Fig. 1).

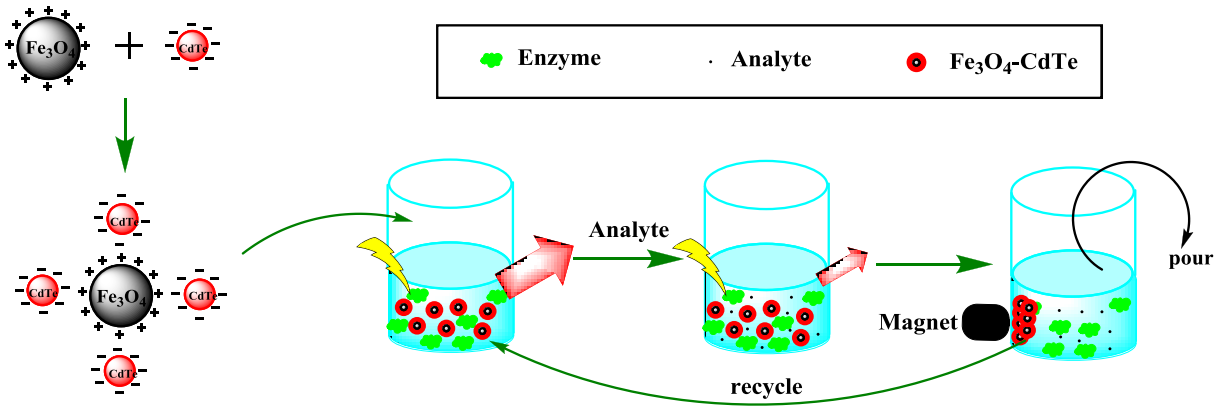

Fig. 1 Schematic of the preparation of Fe_3O_4@CdTe composites together with their sensing process and recycling

Materials and methods

Materials

3-Mercaptopropionic acid (MPA), sodium borohydride, tellurium powder, glucose oxidase enzyme (GOx, EC 1.1.3.4, 125 U/mg) and D-(+)-glucose were purchased from Sigma–Aldrich Chemical Co. (USA). $CdCl_2 \cdot 2.5H_2O$ was obtained from the Peking Chemical Plant. Ferric chloride and ferrous chloride were from Tianjin Bodi Chemicals Co. Ltd. Hydrogen peroxide (H_2O_2, 30% in water) was purchased from Tianjin Guangfu Chemicals Co. Ltd. All other chemicals were of analytical reagent grade and used as received. Ultrapure water from a Milli-Q ultrapure water purification system (Millipore, Billerica, USA) was used throughout the experiments.

Preparation of CdTe

The reaction system was deaerated and protected under nitrogen environment. CdTe QDs were prepared as previously described [19]. NaHTe was prepared by adding 40 mg of $NaBH_4$ to a tube containing 15 mg of Te powder and 0.2 mL of ultrapure water. The reaction was continued for several hours until all of the Te powder was dissolved; the reaction yielded a white crystalline. Subsequently, 86.5 mg of $CdCl_2$ was dissolved in 295 mL of ultrapure water; 79.22 μL of MPA was injected, and the pH was adjusted to 9.1 with 1 mol L^{-1} NaOH. The mixture was stirred for 20 min; freshly prepared NaHTe solution was quickly added into the mixture with vigorous stirring [$n(Cd^{2+}):n(Te^{2-}):n$(MPA) = 1:0.2:2.4]. The mixture was refluxed for hours until CdTe colloids were obtained in the desired period.

Preparation of Fe_3O_4 nanoparticles

Nano-sized magnetic Fe_3O_4 was prepared by reacting a mixture of 5 mL each of 0.15 mol L^{-1} $FeCl_2$ and 0.3 mol L^{-1} $FeCl_3$ [$n(Fe^{2+}):n(Fe^{3+})$ = 1:2] in aqueous phase with 15 mL of 0.5 mol L^{-1} NaOH as precipitator at 50 ℃ for 1 h.

Preparation of Fe_3O_4@CdTe nanocomposites

The prepared magnetic Fe_3O_4 nanoparticles were diluted by addition of 100 mL ultrapure water and surface modified by addition of 5 mL of 0.05 mol L^{-1} 1,6-hexylenediamime (pH 5.0, solution A). Subsequently, 45 mL of prepared CdTe was subjected to 5 mL of solution A [$n(Fe_3O_4):n$(CdTe) = 1:3]. The resulting solution was refluxed at pH 6.0 and 30 ℃ for 1 h. The procedure yielded the core–shell magnetic QDs (i.e., Fe_3O_4@CdTe composites). Fe_3O_4@CdTe composites were separated from the resultant solution using a common magnet. With the upper fluid removed in a beaker, the Fe_3O_4@CdTe precipitate was collected and ultrasonically cleaned with ethanol; the procedure was repeated thrice. The final product was vacuum-dried in an oven at 50 ℃. The powder products were preserved or re-dispersed in water.

Fluorescence measurements

The detection of H_2O_2 was conducted by adding 0.1 mL of the prepared solution of Fe_3O_4@CdTe composites in a cuvette [20]. Subsequently, various concentrations of 2 mL of H_2O_2 solution were added. Fluorescence emission spectra of the nanoparticles were recorded by a Cary Eclipse spectrofluorophotometer (Agilent Technologies, Inc., USA). Ex/Em of the slits was 5.0/10.0 nm, and the PMT voltage was 700 V. The emission spectra were recorded from 550 nm to 800 nm upon excitation at 450 nm.

To detect glucose, the mixture containing various concentrations of 2 mL of glucose and 0.1 mL of 1.0 mg mL^{-1} GOx was first incubated at 37 ℃ for 15 min. Following the incubation, 0.1 mL of the multifunctional Fe_3O_4@CdTe nanoparticle solution was added to the mixture for 15 min. Fluorescence intensities were recorded from 550 nm to 800 nm. All of the fluorescence detections were under the same conditions.

An aqueous solution mixed with variety of carbohydrates and inorganic ions was prepared. Then, glucose of certain concentration was added into the mixture. Three human urine samples were provided by the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, including one from a volunteer (5-fold diluted) and others after 50 g oral glucose tolerant test (OGTT, 10-fold diluted). The samples are diluted directly without any pretreatment. The glucose analysis had been done as described above. According to the standard curve, the glucose concentration in the mixture was obtained.

Recycling of Fe_3O_4@CdTe nanocomposites

Two milliliters of glucose was mixed with 0.1 mL of 1.0 mg mL^{-1} GOx; 0.1 mL of Fe_3O_4@CdTe composite solution was added into the mixture. Following the reaction, a magnet was used to separate the composite; the nanoparticles were then reused twice under the same conditions.

Results and discussion

Characterization of Fe_3O_4@CdTe nanocomposites

The as-prepared Fe_3O_4@CdTe composites were characterized by fluorescence spectroscopy (Fig. 2) and transmission electron microscopy (TEM; Fig. 3). The inset in Fig. 2 shows that the formed solution of nanoparticles was black under visible light (photograph A), whereas the same solution emitted a red fluorescence under UV light (photograph B) because of the size of CdTe [21, 22]. Figure 2 reveals that the multifunctional Fe_3O_4@CdTe nanoparticles exhibit a maximum emission wavelength (MEW) at 651 nm; in contrast to the MEW of CdTe QDs, about 14 nm redshift was detected because of the increase in size of Fe_3O_4@CdTe. The luminescence intensity of Fe_3O_4@CdTe was lower than that of CdTe QDs; the decreased luminescence intensity was attributed to the quenching of the fluorescent entity by the magnetic core [23].

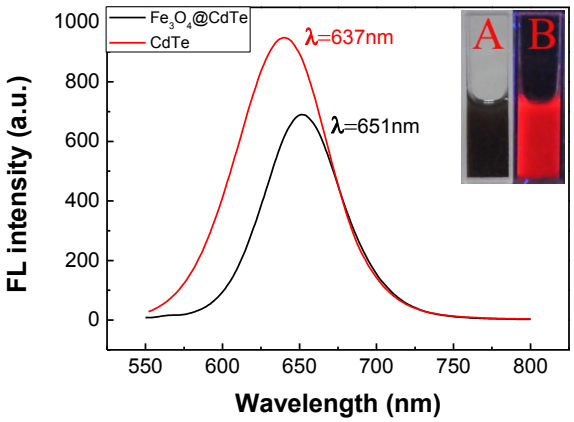

Fig. 2 Fluorescence Emission spectra of the as-prepared Fe_3O_4@CdTe nanocomposites (black) and CdTe (red). The inset displays the nanoparticle solution under visible light (photograph A) and UV irradiation by a handheld UV lamp with excitation wavelength of 365 nm (photograph B).

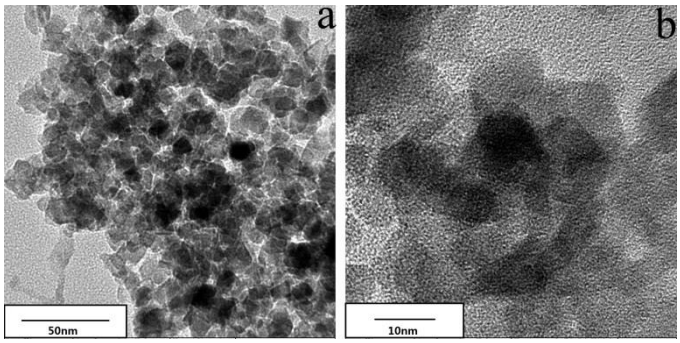

Fig. 3 (a) A TEM image of Fe_3O_4@CdTe nanocomposites. (b) A high-resolution TEM image of a single Fe_3O_4@CdTe nanocomposite.

The spectral characteristics suggested the successful preparation of multifunctional Fe_3O_4@CdTe nanoparticles. TEM (JEM-2100F, Japan) images were obtained to further confirm the formation of the nanoparticles. Figure 3 illustrates the typical TEM images of Fe_3O_4 particles dispersed in an aqueous solution. The data indicated that the size of a multifunctional Fe_3O_4@CdTe nanoparticle was about 30 nm. A relatively light agglomeration was observed in the samples because of the magnetism of Fe_3O_4. Moreover, the high-resolution TEM allowed visualization of the CdTe QDs with lower contrast adsorbed on the surface of a magnetite nanoparticle.

Separation of Fe_3O_4@CdTe nanocomposites

The black Fe_3O_4@CdTe nanocomposites can be easily separated (Fig. 4A and 4B) from the reaction with a common magnet. And the separation was attributed to the excellent magnetic properties of Fe_3O_4. Precipitation and separation of multifunctional Fe_3O_4@CdTe nanoparticles only took several seconds under magnetic field. The separated nanoparticles displayed a strong red fluorescence under UV lamp (Fig. 4C and 4D).

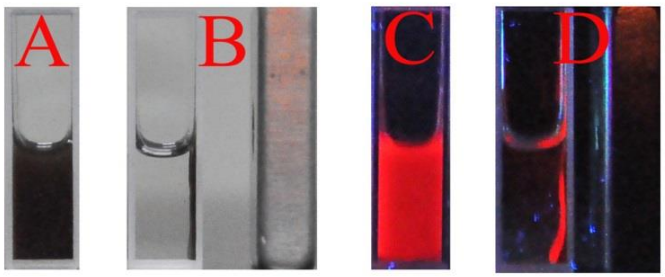

Fig. 4 The Fe_3O_4@CdTe nanocomposites before (A) or after (B) magnet separation under visible light; and those before (C) or after (D) magnet separation under UV irradiation

Fluorescence quenching of Fe_3O_4@CdTe nanocomposites by H_2O_2

The fluorescence responses of Fe_3O_4@CdTe composites to H_2O_2 were analyzed. We used the probe to detect various H_2O_2 concentrations in the solution. The fluorescence intensity of multifunctional Fe_3O_4@CdTe nanoparticles decreased with increasing H_2O_2 concentration (Fig. 5). The inset in Fig. 5 reveals a good linear correlation (R = 0.9971) between ($F_0 - F$) and H_2O_2 concentration from 0.1 mM to 1 mM; the best-fit equation is given as:

$$(F_0 - F) = 384.1342C + 1.1108 \ (R = 0.9971)$$

where F_0 and F are the fluorescence intensity of multifunctional Fe_3O_4@CdTe nanoparticles in the absence and presence of H_2O_2; C represents the H_2O_2 concentration. The fluorescence response of the nanoparticles to H_2O_2 was sensitive; the detection limit was 3.5×10^{-5} M (S/N = 3). Although the calculated detection limit was slightly higher than those from previous reports on H_2O_2 detection by fluorescence method, the multifunctional Fe_3O_4@CdTe nanoparticles could be recycled by application of external magnetic field [17, 18].

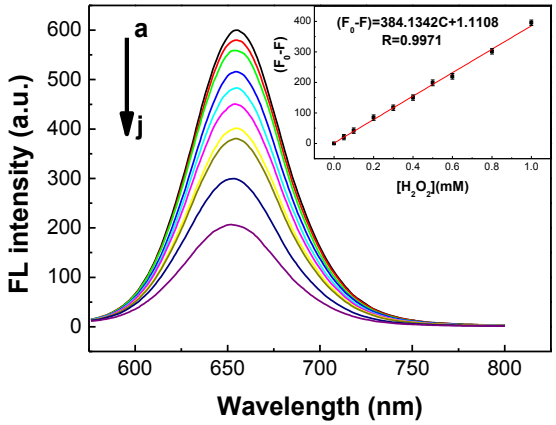

Fig. 5 Fluorescence responses of Fe_3O_4@CdTe nanocomposites after the addition of H_2O_2; H_2O_2 concentrations (from a to j, mM): 0, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, and 1.0. Inset: Relative fluorescence intensity of multifunctional Fe_3O_4@CdTe nanoparticles against H_2O_2 concentration (0.05–1.0 mM); F_0 and F are the fluorescence intensities in the absence and presence of H_2O_2, respectively

Detection of glucose based on Fe_3O_4@CdTe nanocomposites

The Fe_3O_4@CdTe composites can be used as a versatile platform to develop biosensors for various analytes; different enzymes can catalyze the production of substrates that influence the fluorescence of QDs in the nanoparticles. In a previous study [17], CdTe QDs were chosen as a sensitive probe for H_2O_2; the particles were further used to detect glucose with glucose oxidase as the catalyst and produce H_2O_2. We also chose glucose oxidase to prove the applicability of multifunctional Fe_3O_4@CdTe nanoparticles for biosensor development. Figure 6 reveals that the fluorescence intensity gradually reduced with increased glucose concentration. A good linear correlation (R = 0.99871) was observed between ($F_0 - F$) and the glucose concentration from 0.5 mM to 10 mM (Fig. 6)

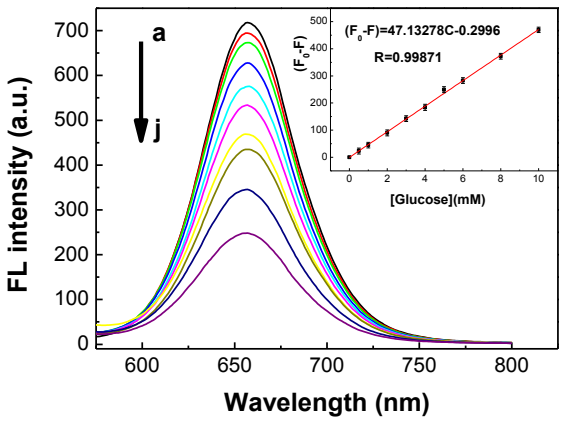

Fig. 6 (A) Fluorescence spectra representing the quenching effect of glucose–GOx system with different glucose concentrations on the fluorescence of Fe_3O_4@CdTe nanocomposites. Glucose concentrations (from a to j, mM): 0, 0.5, 1, 2, 3, 4, 5, 6, 8, and 10. Inset: The relationship between ($F_0 - F$) and the concentration of glucose; F_0 and F are the fluorescence intensities in the absence and presence of glucose, respectively

The equation was given as:

$$(F_0 - F) = 47.13278C - 0.2996 \ (R = 0.99871)$$

where F_0 and F are the fluorescence intensities of multifunctional Fe_3O_4@CdTe nanoparticles in the absence and presence of glucose, respectively; C represents the glucose concentration. The detection limit for glucose was 4.0×10^{-4} M (S/N = 3), which was similar to those obtained using previously reported methods [15, 24-26]. In some previous reports, Fe_3O_4 nanoparticles or gold nanoparticles have been used as peroxidase mimetics or enzyme catalyst to provide a colorimetric assay for glucose detection[27-29]. But in our work, Fe_3O_4 nanoparticles exhibit excellent properties in magnetism and have little impact for the fluorescence detection. Compared with complicated analytical procedures and expensive reagents of their methods, our fluorescence methods offer many advantages such as simple instrumentation, easy operation, low-cost and the ability of multiple measurement. Based on the combination of magnetism and fluorescence in Fe_3O_4@CdTe nanoparticles, the particles were used to develop a reusable fluorescence method to detect glucose with high sensitivity.

Mechanism of fluorescence quenching

By LBL self-assembly, the distance between the Fe_3O_4 nanoparticles and the CdTe QDs on the surface of the nanocomposites is relatively long. Therefore, in the core-shell system, Fe_3O_4 nanoparticles have little impact on the fluorescence signal from the surface CdTe QDs. After GOx is added into the solution, glucose is oxidated to produce H_2O_2. Subsequently, H_2O_2 chemically etches the surface CdTe QDs to generate many surface defects, leading to the quenching of QD photoluminescence. By monitoring the change in the FL intensity, we can then calculate the glucose concentration in the samples.

Selectivity for glucose detection

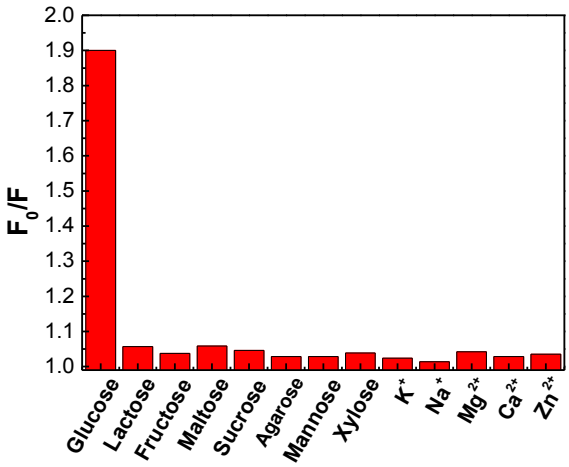

Fig. 7 Relative fluorescence intensities of Fe_3O_4@CdTe composites in the presence of glucose as well as other carbohydrates and metal ions

Figure 7 shows that the changes in the relative fluorescence intensity (F_0/F) of Fe_3O_4@CdTe nanocomposites obtained after

separate addition of glucose (1 mM) as well as other carbohydrates and metal ions under the same conditions. Addition of glucose to the nanoparticles significantly changed the value of (F_0/F) because of the high substrate specificity of GOx. On the other hand, other carbohydrates and metal ions yielded little effects under similar conditions. Therefore, the multifunctional Fe_3O_4@CdTe nanoparticles can be used as sensitive and selective glucose biosensors.

Detection of glucose in mixture and human urine samples

In order to evaluate the feasibility of the proposed method, the developed fluorometric method was applied to the detection of glucose in three mixtures and human urine samples. Urine 1 are donated by a volunteer. Urine 2-3 are obtained from individuals after taking 50 g oral glucose tolerant test. As shown in Table 1 and Table 2, the results obtained by Fe_3O_4 nanocomposites based fluorometric method were similar to the actual concentrations or reported concentrations. It demonstrates that Fe_3O_4 nanocomposites have the potential in practical sample analysis.

Table 1 Detection of glucose concentration in the mixture by using Fe_3O_4@CdTe nanocomposites

Mixture	Concentration determined by Proposed method (mM)	Actual concentration (mM)	RSD (%)
Mixture 1	7.103	7.00	1.41
Mixture 2	5.536	5.50	1.03
Mixture 3	4.077	4.00	1.89

Table 2 Detection of glucose concentration in the human urine samples by using Fe_3O_4@CdTe nanocomposites

Urine	Concentration determined by Proposed method (mM)	Reported concentration (mM) [a]	RSD (%)
Urine 1	0.856	0.91	2.52
Urine 2	2.745	2.80	2.37
Urine 3	3.693	3.65	2.69

[a] The results were reported by a clinic laboratory.

Reuse of Fe_3O_4@CdTe nanocomposite for detection

To make full use of the Fe_3O_4@CdTe nanocomposite, they should be recycled and reused after detection. We used 1 mM and 3mM glucose to test the repeated use of the nanoparticles. Following the completion of glucose detection on the first time, we used a magnet to separate the composite nanoparticles from the detection system. The composite nanoparticles were washed thrice by water. We then used the composite nanoparticles to detect glucose for another time. Using this method, we successfully recycled the Fe_3O_4@CdTe nanocomposites.

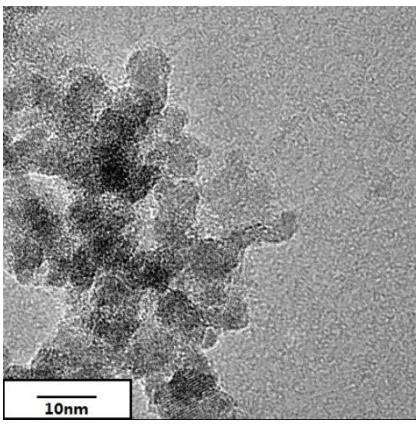

Fig. 8 A high-resolution TEM image of the recycled Fe_3O_4@CdTe nanocomposites.

Figure 8 shows that there is no significant change in the core-shell structure of the Fe_3O_4@CdTe composites after recycle. It means that the Fe_3O_4@CdTe composites were structurally stable during the process of detection, which laid a good foundation for reuse.

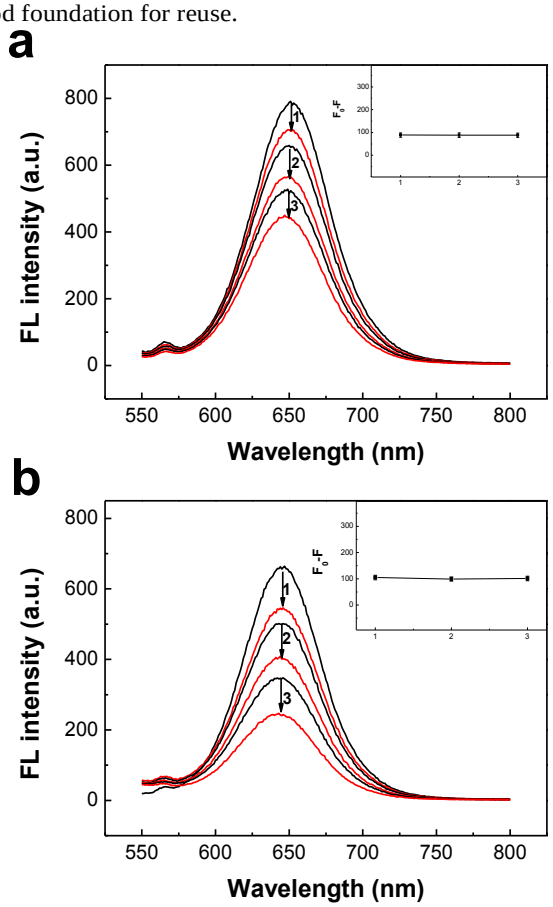

Fig. 9 Fluorescence responses of the recycled Fe_3O_4@CdTe nanocomposites with different glucose concentrations. (a) 1mM (b) 3mM. Inset: The relationship between ($F_0 - F$) and recycle number of the composite nanoparticles; F_0 and F are the fluorescence intensities in the absence and presence of glucose, respectively.

The fluorescence slightly decreased after washing by water (Fig. 9), which was attributed to the residual mixture of the

detection system. Figure 9 reveals that multiple detections under different times exhibited the same degree of nanoparticle quenching. And the nanocomposites can be well applied to detect glucose with different concentrations. The equivalent fluorescence quenching degree implies that recycling and reusing the nanoparticles are realizable.

Conclusions

In summary, we demonstrated the preparation of a novel functional composite that comprised CdTe immobilized on Fe_3O_4 via strong electrostatic attractions. The Fe_3O_4@CdTe composite exhibited excellent fluorescence emissions and high stabilities. The composites are the potential candidates for bioapplications, such as biolabeling, biosensors, drug delivery, and bioseparation. The sensing system of Fe_3O_4@CdTe composites exhibited high sensitivity toward glucose in aqueous solution, and good selectivity over the other carbohydrates. This study can also be extended to detect other substrates using the corresponding enzymes. Therefore, this study presents a new design mode of the fluorescence biosensor and provides an approach to detect numerous substrates. Furthermore, we can recycle the nanoparticles from the reaction system and reuse them, which indicate that the nanoparticles are environmentally friendly. In addition, we also found this method can be used in glucose detection in human urine samples. The advantages of Fe_3O_4@CdTe composites create opportunities to analyze various biological systems.

Acknowledgement

This work was supported by the Ministry of Science and Technology of China (Nos. 2012AA06A303, 2012YQ090194, and 2012BAD29B05), the Natural Science Foundation of China (No. 21276192, 51173128 and 31071509), and the Ministry of Education (No. B06006 and NCET-11-0372).

Notes and references

[a] *State Key Laboratory of Chemical Engineering, Tianjin Key Laboratory of Membrane Science and Desalination Technology, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, P. R. China. Fax: (86)022-27407599; Tel: (86)022-27407599; E-mail: surx@tju.edu.cn*
[b] *Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300072, China*
[c] *School of Environmental Science and Engineering, Tianjin University, Tianjin 300072, PR China*
[†] *Electronic supplementary information (ESI) available.*

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