**Sensitivity fluorescence detection of heparin based on self-assembly of mesoporous silica nanoparticle–gold nanoclusters with emission enhancement characteristics**

Lin Ma, Mengyue Zhang, Aijun Yang, Qin Wang, Fei Qu, Fengli Qu and Rong-Mei Kong

Heparin (Hep) is widely used as a major anticoagulant in surgery. Simple and sensitive methods capable of quantitative detection of Hep are desired for better regulating its clinical use. Herein, a novel nano-assembly of amino-functionalized mesoporous silica nanoparticle–gold nanoclusters (MSN–AuNCs) with remarkable emission enhancement characteristics for sensitive fluorescence detection of Hep is developed. The electrostatic interaction between the positively charged amino-functionalized MSNs and the AuNC-stabilizing surface ligands triggers the self-assembly of MSN–AuNC nanocomposites which exhibit more than 5-fold fluorescence emission enhancement. However, the presence of negatively charged Hep inhibits the emission enhancement phenomenon due to the effective wrapping of Hep on the surface of MSNs, which blocks the interaction between AuNCs and MSNs. Benefitting from the remarkable emission enhancement and the competing binding of Hep, facile and ultrasensitive detection of Hep can be realized with a detection limit as low as 2 nM. Moreover, the successful application of the proposed method for detection of Hep in human serum samples shows promise for clinical applications.

**1. Introduction**

It is of great significance for both pharmaceutical analysis and clinical therapy to quantitatively monitor biomolecules with clinical medicinal values in living systems. Heparin (Hep) is the highest negatively charged polysaccharide in biological systems. Through electrostatic interactions with cationic proteins, Hep can regulate various physiological processes. As a naturally existing biomolecule, Hep exhibits an excellent anticoagulant effect both in vitro and in vivo, which is mainly used for the clinical purpose of prevention and treatment of thrombotic diseases. However, an overdose and long-term use of heparin could induce many life-threatening adverse effects such as thrombocytopenia, hemorrhage, hyperkalemia and osteoporosis. To minimize the risks of these complications, precisely controlling the dose of Hep during surgery or anticoagulant therapy is of great importance, and requires a facile and sensitive method for the accurate determination of Hep concentration. Current clinical methods for detecting Hep levels rely on an activated clotting time assay (ACT), activated partial thromboplastin time assay (aPTT), and antifactor Xa which are indirect and plagued with some limitations such as being time consuming, high cost and insufficiently reliable. Therefore, developing facile and reliable methods for selective and sensitive detection of Hep is still highly desirable.

Considerable efforts have been devoted to the development of Hep detection methods, such as colorimetric assays, resorcinol–light scattering assays, electrochemical methods, and fluorescence approaches. Among them, the fluorescence method seems to be a promising alternative for fast and visual analysis owing to its convenient operation, high sensitivity and selectivity, and direct monitoring of target analytes in live cells, tissues, and even animals. Many fluorescence methods have been developed recently for the detection of Hep using small cationic molecules, supramolecules, conjugated polymers, fluorophore labelled biomolecules, and aggregation-induced emission (AIE) fluorogens. Although these fluorescence methods display good performance for the determination of Hep, most of these methods involve laborious multistep organic synthesis, or the probes used in these methods suffer from poor solubility in water. As one of the most promising fluorescent nanomaterials, gold nanoclusters (AuNCs) have attracted extensive research interest.
due to their remarkable properties, such as favorable biocompatibility, good water-solubility, excellent photostability, molecular-like luminescence, long-life time fluorescence in the red-near-infrared region, and large two-photon excitation.

Therefore, AuNCs have been widely used in biosensing, bioimaging, and therapy. Therefore, designing a novel facile and reliable fluorescence method based on AuNCs for sensitive and selective detection of Hep could be considered as a very effective strategy.

Nevertheless, the environmental stability and luminescence properties of AuNCs are highly dependent on the cores of the clusters, the surface ligands used to functionalize/stabilize them, and the dispersion media. Therefore, many efforts have been devoted to improving the environmental stability and luminescence performances of AuNCs, such as exploring various ligands or using the method of metal doping. Although extensive research studies have been carried out on the syntheses, there has only been limited progress in improving the luminescence performances of AuNCs. Recently, research on the improvement of metal nanocluster fluorescence based on AIE principles has aroused great interest, mostly in the aggregation of thiol-capped metal nanoclusters. For instance, Yahia-Ammar et al. reported a versatile method to prepare monodisperse and stable self-assembled particles with 4-fold AIE enhancement properties using a cationic polymer to cross-link AuNCs. However, the non-uniform size and distribution of the cationic polymer based AIE particles can limit their AIE enhancement properties. Lin et al. reported the AIE enhancement of glutathione (GSH) capped copper nanoclusters (GSH-CuNCs) by the chelation of zinc ions and applied this phenomenon to photo-luminescence light-up detection of zinc ions and imaging in living cells. Huang et al. reported that the aggregation of GSH-CuNCs in organic solvents showed bright luminescence which could be effectively quenched by the introduction of a small amount of water. However, this AIE based fluorescence enhancement of metal nanoclusters is mainly induced by the organic solvent, cation and pH values, which may restrict the application of the fluorescence enhancement phenomenon of metal nanoclusters to particular environments. Therefore, it is of great importance to develop new emission enhancement inducers for metal nanoclusters that can be used in biosensing and bioimaging under physiological conditions.

As a promising nanomaterial with high colloidal stability, mesoporous silica nanoparticles (MSNs) have intensively received research attention in the field of drug delivery platforms because of their versatility and low cytotoxic features in biological systems. Compared with other nanomaterials, MSNs possess remarkable properties, such as uniform and controllable mesoporous structure, high specific surface area, easy surface functionalization, and excellent cellular membrane-penetrating capacity, enabling MSNs to load various functional reagents such as anticarcinogens and transport them to the designated location. In addition, the synthesis of MSNs is simple, economical and controllable. Especially, amino-functionalized MSNs with a high density of positive charges can be expected to improve the loading of negatively charged cargos through electrostatic adsorption. Therefore, amino-functionalized MSNs will be a favourable candidate for inducing the self-assembly of metal nanoclusters via electrostatic adsorption.

Herein, based on the competing electrostatic interaction strategy, we have developed a novel amino-functionalized MSN–AuNC nanocomposite with emission enhancement characteristics for fluorescence detection of Hep with high sensitivity for the first time (Scheme 1). The GSH-capped AuNCs are first loaded into the pores and onto the surfaces of MSNs due to the electrostatic interactions between the positively charged amino-groups of MSNs and the AuNC-stabilizing surface ligands. Greatly improved fluorescence emission of MSN–AuNC nanocomposites is observed with an enhancement of more than 5-fold. In the MSN–AuNC nanocomposites, the amino-functionalized MSNs play the role of an attractive anchor to collect and immobilize the AuNCs, thus restricting the AuNC motion and occurrence of the emission enhancement phenomenon. However, in the presence of Hep, the high density of their negative charges induces stronger interactions between Hep and MSNs. Thus, the self-assembly process of MSN–AuNC nanocomposites is hindered and the emission enhancement phenomenon is broken due to the effective wrapping of Hep on the surface of amino-functionalized MSNs. Therefore, the as-prepared nanocomposites exhibit a highly sensitive response to Hep with a rational decrease in fluorescence. The linear response range of Hep is from 5 to 150 nM with a detection limit of as low as 2 nM. Moreover, the proposed method is successfully applied for the detection of Hep in human serum samples with satisfactory results.

2. Experimental section

2.1 Reagents and apparatus

GSH, chloroauric acid (HAuCl₄), heparin (Hep, 185 U mg⁻¹), the molecular weight of 644.2 g mol⁻¹ was determined by disaccharide), ascorbic acid (AA), chondroitin 4-sulfate (ChS), hyaluronic acid (HA), human serum albumin (HSA), bovine serum albumin (BSA), adenosine triphosphate (ATP), cysteine
(Cys), glycine (Gly), lysine (L-Lys), phenylalanine (L-Phe), tyrosine (Tys), glucose (Glul), galactose (Gal), and all the inorganic salts were purchased from Aladdin (Shanghai, China). Tetraethyl orthosilicate (TEOS), (3-aminopropyl) triethoxysilane (APTES) and hexadecyl trimethylammonium bromide (CTAB) were purchased from Sigma-Aldrich Co. LLC. (St Louis, USA). Aqueous ammonia solution (NH₃·H₂O, 28%), methanol and sodium hydroxide (NaOH) were purchased from Sinopharm Chemical Reagent Beijing Co. Ltd. The buffer used in this work was 10 mM Tris-HCl (pH 7.0, 1 mM KCl, 5 mM MgCl₂). The pH was measured on a Mettler-Toledo Delta 320 pH meter. All the reagents were of analytical grade and used without further purification. All aqueous solutions were prepared with deionized water (resistivity >18 MΩ cm) produced by a Millipore system.

All the fluorescence spectra were recorded by using a F-7000 spectrometer (Hitachi, Japan) with excitation wavelength at 365 nm using a 5 nm/5 nm slit width and 700 V PMT detector voltage. UV-vis spectra were recorded by using a Varian Cary-300 UV-vis spectrophotometer. Morphological characterization of the nanomaterials was carried out using a JEM-2100PLUS transmission electron microscope (TEM, Japan). The zeta potential was measured by using a Malvern Zetasizer Nano Instrument (Malvern Ltd, Malvern, UK) at room temperature. The photographs were obtained by using a ZF-1B box-like ultraviolet analyzer (Shanghai, China).

2.2 Synthesis of AuNCs

The GSH-capped AuNCs were prepared by following the protocol reported by Xie’s Group.34 Typically, HAuCl₄ aqueous solution (1%, 0.84 mL) and GSH (100 mM, 0.3 mL) were mixed with 8.86 mL of ultrapure water at room temperature and then heated to 70 °C under gentle stirring (500 rpm) for 22 h. Afterwards, a light yellow aqueous solution with strong orange-red emission was obtained. The formed AuNC solution was stored in a refrigerator at 4 °C for further use.

2.3 Synthesis of amino-functionalized MSNs

The amino-functionalized MSNs were synthesized by a co-condensation method in basic solution to obtain a uniform distribution of the functional groups both inside the mesoporous and on the nanoparticle surface.41 Typically, CTAB (0.5 g) was initially dissolved in 200 mL of distilled water. Then, NaOH aqueous solution (1.75 mL, 2 M) was slowly dropwise added into the CTAB solution under vigorous stirring for 20 min at 80 °C. When the temperature was stabilized, TEOS (2.5 mL) was slowly dropwise added into the above solution and vigorously stirred for 15 min. After that, APTES (0.5 mL) was added dropwise and vigorously stirred for another 2 h at 80 °C. Finally, the obtained white precipitates were centrifuged at 8000 rpm for 10 min and washed three times with methanol and distilled water. The excess CTAB was removed by refluxing the amino-functionalized MSNs at 80 °C for 10 h in the mixture solution of HCl (9 mL, 37%) and methanol (150 mL). Subsequently, the product was washed thoroughly with distilled methanol and deionized water. The collected amino-functionalized MSNs were dried under vacuum for 50 °C overnight.

2.4 Fluorescence detection of Hep

Fluorescence detection of Hep was conducted in 500 μL Eppendorf tubes. Typically, 60 μL of MSN solution (2 mg mL⁻¹) and 165 μL Tris-HCl buffer were mixed with 60 μL of Hep solution at different concentrations and incubated at 37 °C for 15 min. Then, 15 μL of AuNC solution was added into the as-mentioned solution and gently shaken on a thermostatic oscillator at 25 °C for 30 min. Finally, the fluorescence spectra were recorded with an excitation wavelength of 365 nm. The practicality investigation of the fluorescence method for Hep detection was conducted in diluted human serum samples. Serum sample experiments were performed according to the Guidelines for Ethical Committee, Qufu Normal University. All studies were approved by the Ethical Committee, Qufu Normal University. Informed consent was obtained from human participants of this study.

3. Results and discussion

3.1 Characterization of the synthesized nanomaterials

The size and morphology of the synthesized AuNCs and MSNs were first characterized by TEM. It is found that the AuNCs present a uniform monodispersion in water (Fig. 1A). Fig. 1B shows the particle size distribution histograms of the AuNCs, indicating that the diameters of these AuNCs range from 1.4 to 2.5 nm with an average size of about 1.9 nm. Fig. 1C shows a typical TEM image of the as-synthesized amino-functionalized MSNs, indicating that the MSNs are nearly spherical and uniform with an average diameter of about 80 nm. Moreover, plenty of pores with a pore diameter larger than that of AuNCs can be observed on the silica nanoparticles (the inset of Fig. 1C). Therefore, MSN–AuNC nanocomposites can be yielded by loading AuNCs into the pores and onto the surfaces.
of MSNs through the electrostatic interactions between the positively charged amino-groups of MSNs and the AuNC-stabilizing surface ligands (Scheme 1A). The formation of MSN–AuNC nanocomposites was also confirmed by TEM (Fig. 1D), which clearly shows that the AuNCs are effectively loaded into the pores and onto the surfaces of MSNs.

The fluorescence spectra were recorded to investigate the fluorescence properties of AuNC and MSN–AuNC nanocomposites. As shown in Fig. 2A, for both AuNC and MSN–AuNC nanocomposite samples, the emission bands are centered around 570 nm and the excitation peaks are located at 365 nm. Upon the addition of 60 μL MSN solution (2 mg mL⁻¹) into 15 μL as-synthesized AuNC solution in 225 μL Tris-HCl buffer, the fluorescence intensity of the AuNCs exhibits more than 5-fold enhancement. The remarkable emission enhancement may be due to the fact that the self-assembly of the MSN–AuNC nanocomposites results in the restriction of AuNC motion, thus reducing the dynamic quenching probability of the AuNCs. The inset of Fig. 2A shows the photograph of AuNCs and MSN–AuNCs under the excitation of a 365 nm ultraviolet lamp. It can be clearly seen that the MSN–AuNC nanocomposites exhibit a brighter orange red emission.

UV-vis absorbance spectra were also recorded to verify the successful preparation of the AuNCs, MSNs and MSN–AuNCs (Fig. 2B). As shown in the spectra, the AuNCs exhibit an absorption peak at 375 nm in the UV-vis region (curve a). The absorbance spectrum of amino-functionalized MSNs exhibits no obvious absorbance peaks (curve b), which is identical to those reported in the literature.¹¹ After the formation of MSN–AuNC composites, an absorption peak located at 375 nm appeared (curve c), which is attributed to the electrostatic absorption of AuNCs into the pores and onto the surfaces of MSNs.

3.2. Feasibility for Hep detection

The proposed fluorescence assay for Hep detection is mainly based on the competing electrostatic interaction strategy. Herein, the electrostatic interactions between Hep, AuNCs and amino-functionalized MSNs were first characterized by the zeta potential measurements. As shown in Fig. 3A, the GSH-capped AuNCs exhibit a negative zeta potential at about −18.2 mV, while the Hep exhibits a lower negative zeta potential at about −32.1 mV, revealing the higher density of negative charges of Hep than that of AuNCs. The amino-functionalized MSNs have a distinct positive zeta potential at about 29.8 mV. The MSN–AuNC nanocomposites exhibit a very small positive zeta potential due to the electrostatic interactions between AuNCs and amino-functionalized MSNs. The mixture of Hep and MSNs shows a negative zeta potential at about −12.4 mV, indicating that there is a strong electrostatic interaction between Hep and amino-functionalized MSNs and the positive charges of MSNs are occupied by Hep completely. Therefore, the zeta potential results indicate that the interaction of MSNs towards Hep is stronger than that of MSNs towards AuNCs, revealing the theoretical feasibility of the competing electrostatic interaction strategy.

The feasibility of the proposed method for fluorescence detection of Hep was then verified by fluorescence experiments under different conditions. As shown in Fig. 3B, the individual AuNCs exhibit weak fluorescence in the Tris-HCl buffer system (curve a), and the mixture of AuNCs and Hep induces almost no fluorescence signal changes (curve b), indicating that the Hep has no effect on the fluorescence intensities of AuNCs. Excitingly, a fluorescence enhancement of more than 5-fold at 570 nm compared with that of AuNCs can be observed from the addition of MSNs into AuNC solution to form MSN–AuNC nanocomposites (curve c). The great improvement of fluorescence intensity is mainly attributed to the strong electrostatic interactions between AuNCs and amino-functionalized MSNs and the high loading capacity of MSNs, which result in the emission enhancement phenomenon of AuNCs. However, after the introduction of Hep into the amino-functionalized MSN solution, the addition of AuNCs induce only very little enhancement of fluorescence (curve d), indicating the effective wrapping of Hep and blocking of the positive charges on the MSN.

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**Fig. 2** (A) The fluorescence excitation and emission spectra of AuNCs and MSN–AuNCs. (B) UV–vis spectra of (a) AuNCs, (b) MSNs and (c) MSN–AuNCs.

**Fig. 3** (A) Zeta potential of (a) AuNCs, (b) Hep, (c) MSNs, (d) MSN–AuNCs, and (e) MSNs + Hep. (B) Fluorescence emission spectra of (a) AuNCs, (b) AuNCs + Hep, (c) MSN–AuNCs, and (d) MSNs + Hep + AuNCs; [AuNCs] = 15 μL, [Hep] = 200 nM, [MSNs] = 0.4 mg mL⁻¹.
surface. Therefore, the stronger electrostatic interactions between Hep and amino-functionalized MSNs can hinder the interaction between AuNCs and amino-functionalized MSNs, thus no emission enhancement of AuNCs can occur. These results indicate that the MSN–AuNC nanocomposite based method holds promise for label-free fluorescence detection of Hep.

3.3. Optimization of assay conditions

To obtain a high fluorescence sensing performance of the proposed method for Hep detection, the detection parameters were optimized including the amino-functionalized MSN concentrations, pH values, and reaction time (Fig. S1–S4†). Since the fluorescence signal is offered by the AuNCs aggregated in the pores and on the surfaces of amino-functionalized MSNs, the amount of MSNs used in the assay was first optimized by varying the concentration of MSNs and fixing the volume of the AuNC solution at 15 μL in Tris-HCl buffer. As shown in Fig. S1† the fluorescence intensity increases obviously with the addition of increasing MSN concentration until it reaches 0.4 mg mL\(^{-1}\), indicating the saturated loading of AuNCs by MSNs. The fluorescence intensities decrease slightly when the concentration of MSNs is further increased, which may be due to the dilution effect on the aggregation of AuNCs induced by the excessive amount of MSNs. Therefore, 0.4 mg mL\(^{-1}\) amino-functionalized MSNs are used for the following experiments. The pH values of the buffer involved in the fluorescence assay were investigated since the pH can affect the charges of each substance. The pH value investigation was conducted by varying the detection pH at fixed concentrations of 0.4 mg mL\(^{-1}\) MSNs and 200 nM Hep and a fixed volume of 15 μL of the AuNC solution in Tris-HCl buffer. As shown in Fig. S2,† the fluorescence intensity decreases sharply in the pH range of 6.0 to 7.0, and then increases gradually with the increase of pH. The weak acid solution may affect the negative charges of Hep and thus affect the wrapping and blocking efficiency for amino-functionalized MSNs, resulting in only a slight aggregation of AuNCs and a weak fluorescence enhancement. However, the high pH can affect the positive charges of MSNs because of the deprotonation of their amino-groups. Therefore, it can be explained by the fact that pH 7.0 can result in a stronger electrostatic interaction between Hep and MSNs, and thus a best response can be obtained. Moreover, the reaction time investigation results indicate that the self-assembly of MSN–AuNC nanocomposites through electrostatic interactions can be completed within 30 min (Fig. S3†), and the sensitive response to Hep can be achieved in 15 min (Fig. S4†), suggesting that a fast detection of Hep can be expected.

3.4. Analytical performance for the detection of Hep

The developed fluorescence method based on MSN–AuNC nanocomposites was applied for the quantitative detection of Hep under optimum conditions. As shown in Fig. 4A, it is clearly seen that with the increase of Hep concentrations, the fluorescence intensities of the MSN–AuNCs system decrease gradually, suggesting that the proposed method is suitable for fluorescence detection of Hep. Fig. 4B shows the linear relationship between the Hep concentrations ranging from 5 to 150 nM and the quenching efficiencies of MSN–AuNCs. The limit of detection that can be achieved is as low as 2 nM, estimated by the 3σ rule. In addition, the analysis performances of the developed fluorescence method were compared with those of other fluorescence detection methods previously reported for Hep. As shown in Table S1,‡ in comparison with most of other fluorescence methods, better detection sensitivity can be achieved by the current method. Moreover, the developed fluorescence method is simple and fast. The high sensitivity indicates the success of the novel MSN–AuNC sensing design for label-free fluorescence detection of Hep.

In addition to sensitivity, high selectivity is another essential parameter for a new designed sensing system with potential applications in biological media. In this work, Chs, HA, BSA, HSA, ATP, GSH, Cys, Gly, L-Lys, L-Phe, Tys, Glu, Gal, and some common metal ions (Na\(^{+}\), K\(^{+}\), Mg\(^{2+}\), Ca\(^{2+}\), Fe\(^{3+}\), Al\(^{3+}\), Cl\(^{-}\), NO\(_3^{-}\), CO\(_3^{2-}\), PO\(_4^{3-}\), HPO\(_4^{2-}\), and H\(_2\)PO\(_4^{-}\)) were chosen as the interfering substances to investigate the selectivity. Fig. 5 shows the variation of fluorescence intensities at 570 nm in the presence of Hep and other interfering substances at different concentrations. Compared with the obvious fluorescence decrease caused by Hep, most of these interferents cannot trigger apparent fluorescence changes. It is worth men-

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Fig. 4 Sensitivity of the sensing system for the detection of Hep. (A) Fluorescence emission response to Hep at increasing concentrations. (B) Plot of fluorescence decrease intensities (ΔF = F₀ − F) versus concentrations of Hep. F₀ and F are the fluorescence intensities at a peak value of 570 nm in the absence and presence of Hep, respectively. Inset: Plot of the linear region from 5 to 150 nM. Error bars were estimated from three replicate measurements.
 sécurized interactions. The self-assembly of the MSN–AuNC nanocomposites with remarkable emission enhancement characteristics can avoid the sophisticated fluorophore labeling process of fluorescent probes. The Hep played the role of a positive charge protector of amino-functionalized MSNs, hindering the interactions between AuNCs and MSNs, and thus quenched the fluorescence emission enhancement of AuNCs. The simple and facile method exhibits high sensitivity with a low detection limit of 2 nM and high selectivity toward Hep. Moreover, satisfactory results of the further application in human serum samples for the detection of Hep were achieved by using the proposed method, demonstrating its promising application in practical biological samples. The simplicity and convenience in preparation and operation of this method make it a practical candidate for widespread fluorescence applications.

Table 1 Recovery of Hep from human serum samples using the standard addition method

<table>
<thead>
<tr>
<th>Sample</th>
<th>Found (nM)</th>
<th>Added (nM)</th>
<th>Total (nM)</th>
<th>Recovery (%)</th>
<th>RSD (n = 3, %)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>40.5</td>
<td>96.5</td>
<td>4.6</td>
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<td></td>
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<td>73.6</td>
<td>104.8</td>
<td>3.9</td>
<td></td>
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<tr>
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<td>120.6</td>
<td>99.4</td>
<td>3.8</td>
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<tr>
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<td>46.8</td>
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<td></td>
<td>100.0</td>
<td>129.4</td>
<td>103.5</td>
<td>2.3</td>
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</tbody>
</table>

3.5. Detection of Hep in human serum samples

In order to demonstrate the practicality of the MSN–AuNC nanocomposite based fluorescence method, the detection of Hep was performed in diluted human serum samples. As shown in Table 1, the original Hep concentrations in the two human serum samples (1%) are 21.2 and 25.9 nM, respectively, which are all in the normal range of 1.2–1.8 mg L$^{-1}$ without dilution (equal to 1.86–2.79 μM). Moreover, the recoveries of the spiked amounts of Hep in the above two human serum samples ranging from 96.5% to 104.8% are satisfactory and acceptable, suggesting that this method holds promise for potential application in human serum sample analysis and requires only small amounts of sample.

4. Conclusions

In summary, we have developed an MSN–AuNC nanocomposite based label-free fluorescence assay for the detection of Hep through the competing electrostatic interactions. The self-assembly of the MSN–AuNC nanocomposites with remarkable emission enhancement characteristics can avoid the sophisticated fluorophore labeling process of fluorescent probes. The Hep played the role of a positive charge protector of amino-functionalized MSNs, hindering the interactions between AuNCs and MSNs, and thus quenched the fluorescence emission enhancement of AuNCs. The simple and facile method exhibits high sensitivity with a low detection limit of 2 nM and high selectivity toward Hep. Moreover, satisfactory results of the further application in human serum samples for the detection of Hep were achieved by using the proposed method, demonstrating its promising application in practical biological samples. The simplicity and convenience in preparation and operation of this method make it a practical candidate for widespread fluorescence applications.

Conflicts of interest

There are no conflicts of interest to declare.

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Notes and references


