

Cd-Cysteine Nanorods as a Fluorescence Sensor for Determination of Fe (III) in Real Samples

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Abstract A new Cd-Cysteine complex nanorods (Cd-Cys NRs) were synthesized in one step at room temperature, and its morphology, structure and spectral properties were characterized by transmission electron microscopy (TEM), elemental analysis (EA), X-Ray diffraction (XRD), solid state and normal UV-Vis, Fourier transform infrared (FTIR) and spectrofluorometry. The developed Cd-Cys NRs were used as a fluorescence sensor for detection of Fe (III) in different aqueous matrices. The selectivity and sensitivity of the fabricated nano-sensor based on its fluorescence quenching in the presence of Fe (III) were probed according to the Stern-Volmer equation. The detection limit of the method was in micromolar per liter range. Cd-Cys NRs response tested in different complex samples such as Rosemary plant leaves, exhibited a well-defined response. Anticoagulation measurements were performed to evaluate their blood biocompatibility.

Keywords Biosensor · Fluorescent probe · Cd-Cys nanorods · Fe(III) determination · Heavy metal ions · Hemocompatibility

Introduction

Fluorescence sensing is a rapidly developing field of research and technology. Designing and synthesizing a selective and

sensitive metal ion fluorescent sensor has attracted attention of chemists in the past two decades. Many attempts have been made to develop fluorescent probes for a variety of analytes due to fluorometric advantages such as ultimate sensitivity, specificity, simplicity, versatility, and high temporal and spatial resolution [1–7].

Iron ions can be found in almost everything around us, in water, soil, plants, foods, medicines, cells and so on [8–14]. Two physiochemical form of iron are well known, Fe (II) and Fe (III) which could be converted to each other through their environments like oxidation-reduction or pH changes. In the human body, Fe(II) is the form which utilizes in cell for oxygen storage and Fe(III) acts as active center of many enzymes [15]. Also Fe(II) can affect wine oxidation and its aging whereas Fe(III) capable of promoting precipitation in wine which is an example of the importance of measuring iron in industry [16].

Many techniques for the detection iron metal ions have been reported including electrochemical methods like voltammetry [17], and spectroscopic methods such as flame atomic absorption spectrometry (FAAS) [18], inductively coupled plasma mass spectrometry [19], inductively coupled plasma-atomic emission spectrometry (ICP-AES) [20] and spectrophotometric methods. Reported spectrophotometric methods usually suffer from several problems like working just in high acidic or basic solutions [21], long sensor synthesizing processes [22] or high cost of reagents [23].

Due to the uniqueness structure of biomolecules, the biomolecule-assisted methods in synthesizing of nanomaterials are promising and growing field of study [24–26]. Biological thiols, such as cysteine (Cys) and homocysteine (Hcy), play essential role in human physiology. Cys is a source of sulfide in iron sulfur clusters [27, 28]. Cys with -SH, -NH₂, and -COOH functional

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groups has a strong tendency to coordinate with metal ions [24]. Positive effect of the capping of the luminescent CdS quantum dots (QDs) with Cys has been investigated with spectrofluorometric methods by Rosenzweig and Chen; capped QDs showed quenching in presence of Cu(II) and Fe(III) metal ions and enhanced by Zn(II) ions in water [29].

Moreover, one-dimensional semiconductor nanostructures such as nanorods (NRs) and nanowires (NWs) due to their special structures, unique electrical and optical properties have found their ways to analytical chemistry [30–33]. Many types of NRs or NR-based materials have been used as sensors, including metal oxide NRs such as ZnO and W_2O_3 , polymer NRs and metal NRs such as Au nano-sensor [34]. In this research, Cd-Cys NRs, which were not reported before, were successfully synthesized with a convenient, one step method at room temperature. In presence of Fe (III), in aqueous solutions, synthesized NRs showed a significant fluorescence quenching at 363 nm ($\lambda_{ex} = 316$ nm).

Experimental

Reagents

All chemicals were purchased from E. Merck, Darmstadt, Germany, and were of analytical reagent grade. Distilled deionized water (DDW) were used for preparing all of the solutions. The metal ions stock solutions of 1.0×10^{-2} M were made up of their nitrate and chloride salts. The Hg (II) ions stock solutions of 1.0×10^{-2} M were made up of their acetate salt.

Instrumentation

Photoluminescence (PL) spectra were obtained using a Shimadzu RF-5301PC spectrofluorometer (Japan) in room temperature (298 ± 2 K). FTIR spectra were obtained by Thermo Nicolet Nexus 670 (USA). Absorption spectra were measured on double beam Analytik Jena Specord Plus spectrophotometer and solid phase UV-Visible spectra were acquired with Analytik Jena Specord S600 spectrophotometer. The morphology of the synthesized nanomaterials was probed by CM-philips10 transmission electron microscopy (TEM). PANalytical model X'Pert Pro MPD was used for acquiring XRD patterns. Gallenkamp muffle furnace (England) was employed for turning the plant leaves into ashes. Elementar model Vario EL III (Germany) used for Elemental Analysis. AA-6300 Shimadzu (Japan) atomic absorption spectrometer (AAS) was utilized for measuring the amount of iron in the complex matrixes. Euronda

sonicator model 4D (Italy) was used for dispersing the NRs in the water. For centrifugation, Hettich zentrifuge model D-78, 532 tuttlingen were utilized. All pH measurements were made with a Istek pH-220 L model equipped with a Istek USA built electrode. Wisettir model MSH-20D used for magnetic stirring of the solutions.

Software

Drawing all of the chemical reactions and purposed three dimensional molecular structures was performed by using Chem & Bio 3D Ultra version 11.0 and Chem & BioDraw Ultra version 11.0 of CambridgeSoft products.

Preparation of Complex Samples

Feroglobin Medicine Tonic

Feroglobin medicine made in Alborz Darou Company of Iran under the license of Vitobiotics Company of England used for this experiment. 1 mL of the tonic was diluted in a 1 L volumetric flask and was assayed by AAS. The amount of each ingredients has been taken from its bottle label and placed in Table 1.

Synthesis of Cd-Cys NRs

0.090 g of L-Cysteine and 0.230 g of $CdCl_2 \cdot H_2O$ were placed in 1 L beaker which contained 650 mL DDW and

Table 1 Feroglobin medicine continents

NO.	Nutrition information	Av. Per 5 mL	%RDA
1	Thiamin HCL (Vitamin B1)	5 mg	286
2	Vitamin B2	1 mg	63
3	Vitamin B6	1 mg	100
4	Vitamin B12 (Cyanocobalamin)	5 µg	500
5	Folic Acid	50 µg	75
6	Dexpanthenol	2 mg	–
7	Calcium Glycerophosphate	10 mg	–
8	Nicotinamide (Vitamin B3)	10 mg	44
9	Iron (Elemental)	10 mg	50
10	Zinc (Elemental)	3 mg	33
11	Vitamin C	32 mg	–
12	Copper	0.2 mg	–
13	Manganese	0.25 mg	–
14	Lysine HCl	20 mg	–
15	Honey	100 mg	–
16	Malt Extract	500 mg	–

RDA recommended daily allowance

dissolved while it stirred with a magnetic stirrer and a glassy solution appeared. Then 4 mL of ethanolamine was added to the solution, the light cloudy solution was kept under stirring for 6 h using the speed of about 830 rounds per minute (RPM) at room temperature. The obtained white Cd-Cys NR_s sediment separated from the solution by centrifugation, washed with absolute ethanol three times and dried at room temperature (Fig. 1). The synthesizing process was repeated for several times and the sediments were characterize each time with FTIR, UV-Vis and spectrofluorometer to make sure of the Cd-Cys NRs synthesizing process. The yield was about 88 %.

Fluorescence Measurements

0.080 g of the synthesized Cd-Cys NRs was dispersed in DDW by sonication, then transferred to 100 mL volumetric flask and diluted to the mark. Its fluorescence intensity was measured at 363 nm ($\lambda_{\text{ex}} = 316 \text{ nm}$) with 1- cm sample cell and slit width of 5.0 nm in fast scan mode. In further studies regarding fluorescence response of the Cd-Cys NRs, metal ion solutions or complex sample solutions was mixed equally with the 0.80 g/L Cd-Cys NRs solution. The Cd-Cys NRs fluorescence response was examined using the well-known Stern-Volmer equation (Eq. 1) and their corresponding plots.

$$\frac{F_0}{F} = 1 + K_{SV}\{Q\} \quad (1)$$

Where F_0 and F are Fluorescence intensity in the absence and presence of the quencher, K_{SV} is the Stern–Volmer quenching constant, and Q is the concentration of the quencher.

Results and Discussion

Characterization of NRs

TEM Image

Figure 2 illustrates TEM images of the Cd-Cys NRs complex in 200 nm scale. As shown in the images the diameter range of Cd-Cys NRs are from 46 to 76 nm, their length is from 380 to 580 nm. The length is proportional to the diameter and thicker NRs are longer.

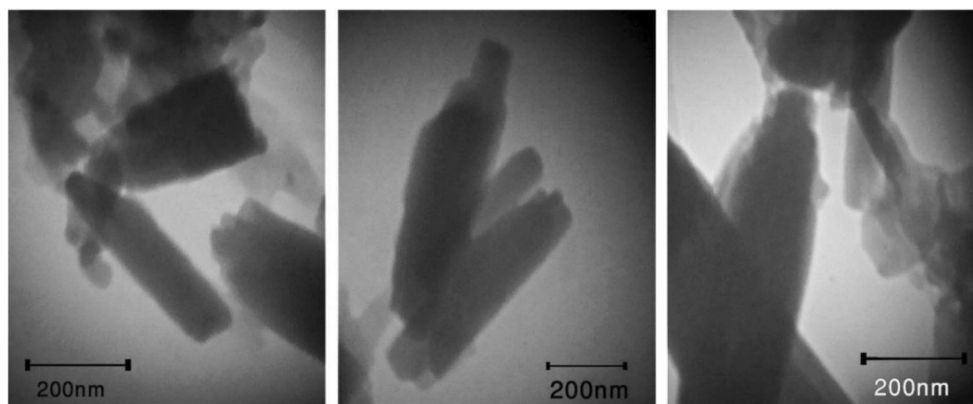
XRD Pattern

To find out crystalline or amorphous nature of the Cd-Cys NRs, a XRD pattern was acquired. The Cu anode was employed with scan speed of 2° per minute from 0 to 80° . As it is obvious from Fig. 3, unlike the amorphous form of Cd-Cys NWs [36], sharp and clear peaks proved its crystalline form. By comparing the Cd-Cys NRs XRD pattern with cysteine chloride which was reported by Jason G. Parsons et al. [37], the appearance of Cys peaks at 19° , 21° , 22° and 25° in the

Fig. 1 Schematic procedure of synthesizing NRs



Fig. 2 TEM images of Cd-Cys NRs



XRD patterns of Cd-Cys NRs, indicates the incorporation of Cys in the nanocomplex.

Using Scherrer equation (Eq. 2), the nano crystalline size (D) was calculated by the information on the XRD patterns.

$$D = \frac{K\lambda}{\beta \cos \theta} \quad (2)$$

Where λ is radiation wavelength, β is full-width at half maximum, K is shape factor. Assuming the $K = 0.90$, the approximate diameter of the Cd-Cys NRs found to be 98.93 nm which is close enough to TEM results. The discrepancy between the theoretical value of NRs diameter and the measured diameter using TEM, comes from some inaccuracy in the Eq. 2 formula [38].

FTIR Spectra

A KBr pellet of Cys was prepared, and its FTIR spectrum was acquired. Characteristic vibrational frequencies of Cys were assigned in Fig. 4. Cys has three susceptible functional groups able to bind to cadmium ion.

Figure 5 is the FTIR spectra of Cd-Cys NRs, demonstrating the existence of two peaks at 3327 and 3255 cm^{-1} which belong to primary amines, indicating the presence of N-H bond. The assumption that cadmium binds to COO^- group has been ruled out due to the presence of a strong peak at 1596 cm^{-1} . The absence of S-H peak from 2540 to 2600 cm^{-1} shows that the binding between Cd and Cys has been occurred via -SH group of Cys.

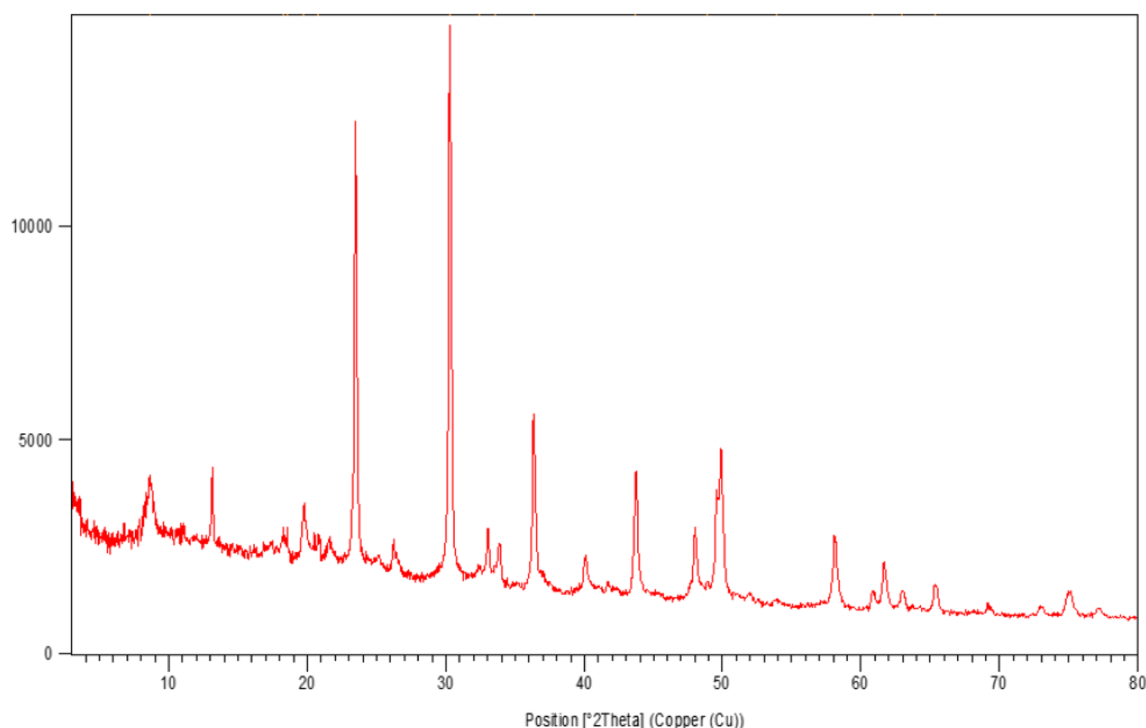


Fig. 3 XRD pattern of Cd-Cys NRs

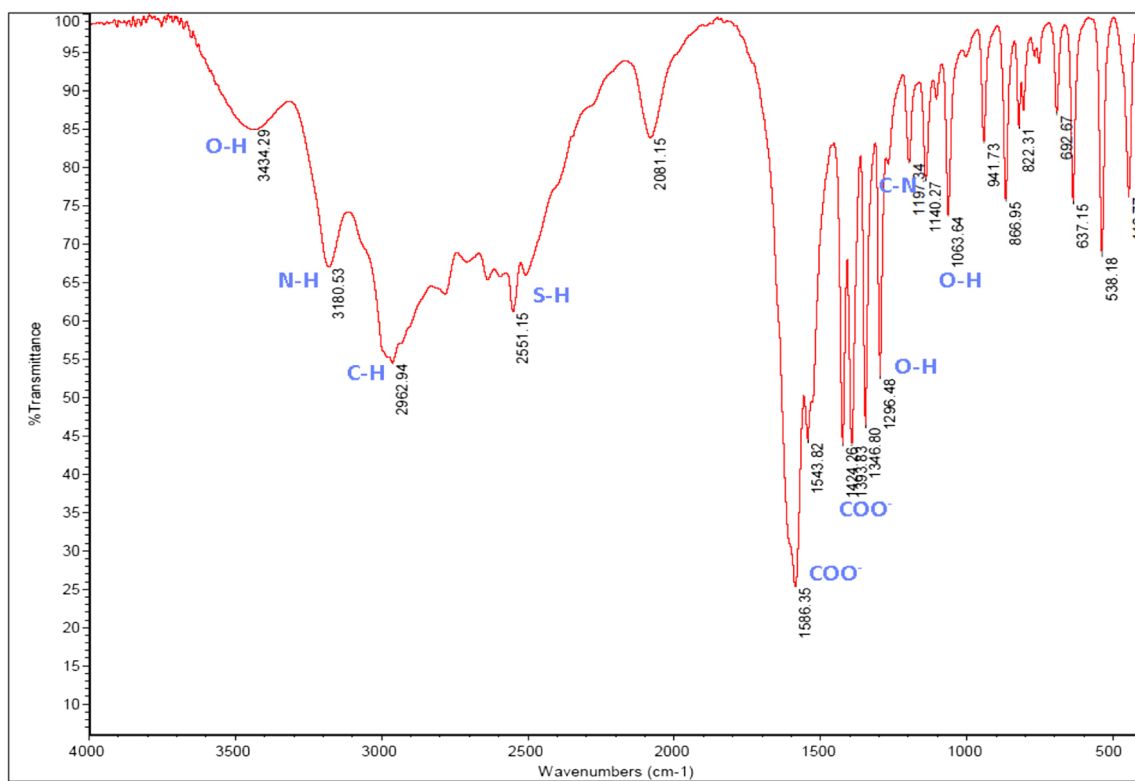


Fig. 4 FTIR spectrum of L-Cysteine

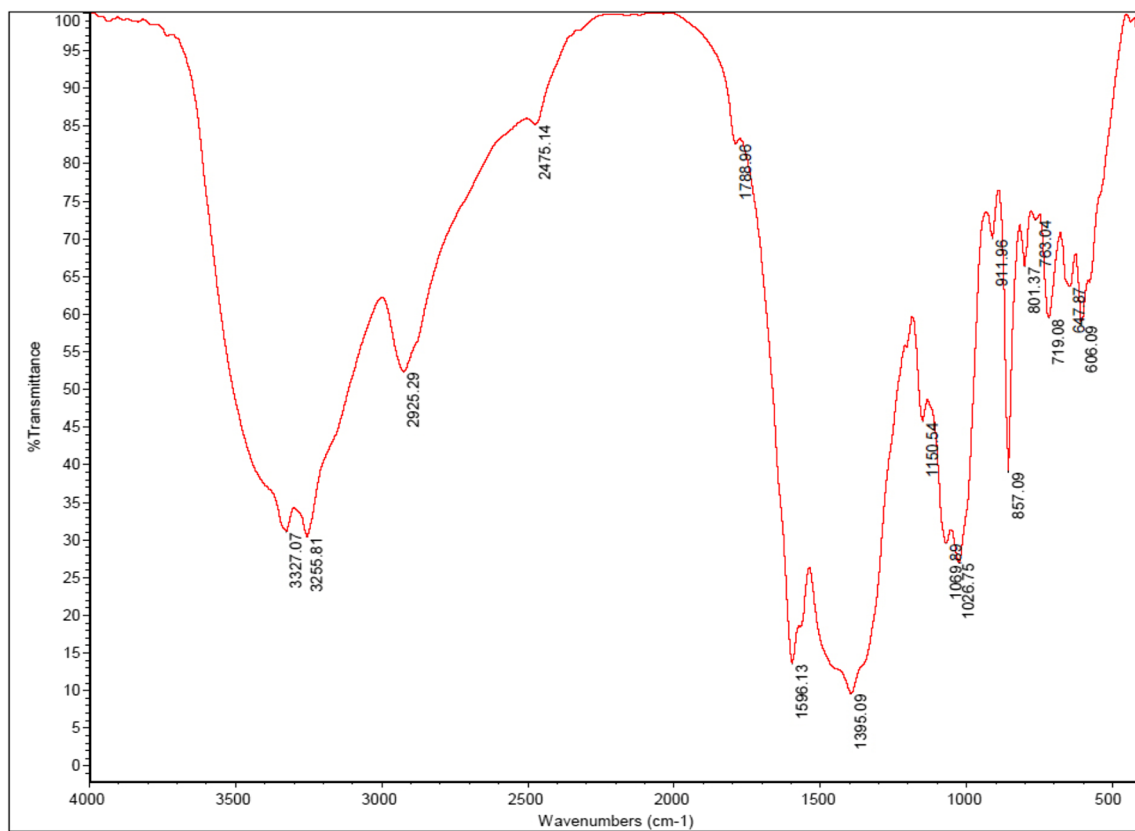


Fig. 5 FTIR spectrum of NRs

Normal UV-Vis Spectra

Substantial information can be obtained by UV-Visible especially about molecular structure and identification [39]. Spectrophotometric technique could be used for molecular spectral characterization as well [40]. Three 10^{-4} mol/L solutions of Cd(II), Fe(III), Cys and a 0.8 g/L solution of Cd-Cys NRs were prepared in DDW and scanned through wavelengths range of 190 to 1000 nm. Little absorption in UV range was observed for Cd-Cys NRs (Fig. 6).

Elemental Analysis

By comparing to the other reports regarding similar structures for rod-like nanoparticles, $\text{HOOCCH}(\text{NH}_2)\text{CH}_2\text{S}-\text{Cd}-\text{OH}$ molecular structure was purposed [24, 36, 41], which later was confirmed by elemental analysis as shown in Table 2.

On the basis of experimental results and possible Cd-Cys complexes structure [37], the purposed formation mechanism of Cd-Cys NRs is shown in Fig. 7. First Cys molecules have tendency to be attracted to the Cd^{2+} ions by their $-\text{SH}$ and $-\text{NH}_2$ groups which leads to the formation of Cd-S bond causing a primary complex of Cd-Cys comes to exist in water. After addition of ethanolamine which creates a weakly basic environment, metal-Cys NRs complex produces. The coordination reaction happening between Cd metal ions and $-\text{SH}$

Table 2 Elemental analysis of Cd-Cysteine complex nanorods

	Content %		
	N	C	H
Experimental	4.197	15.49	3.14
Calculated	5.60	14.44	2.83

group of Cys causes uniform distribution of inorganic ions in the matrix.

Effect of Temperature and NRs Concentration on the Fluorescence Emission

Monitoring Cd-Cys NRs fluorescence emission intensity in temperature range of 10–65 °C (283–338 K) did not show any measurable changes (Figure S1) indicating insensitivity of the nano-sensor towards temperature fluctuations. Varying the Cd-Cys NRs concentration affected the intensity of the peaks, by increasing the concentration of Cd-Cys NRs from 5.00×10^{-4} g/L to 1.10 g/L a remarkable rise in intensity of the fluorescence peak was observed (Fig. 8).

Effect of pH on NRs Fluorescence Emission

Very small amount of Cd-Cys NRs were taken for pH testing (about 0.05 g/L). Increasing the pH to 10 caused an increase in Cd-Cys NRs fluorescence emission, further increase did not

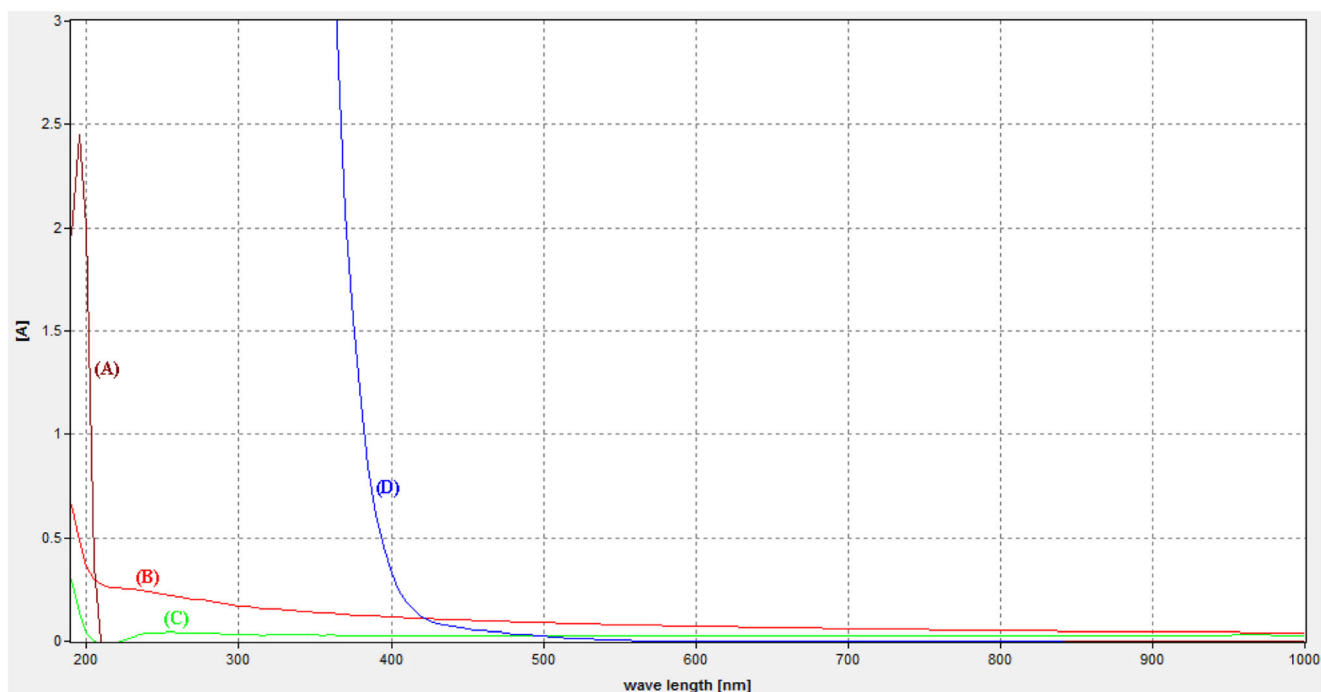


Fig. 6 UV-Vis spectra: (A) is Cd^{2+} solution, (B) is nanorods, (C) is L-Cysteine and (D) is stand for Fe(III) solution

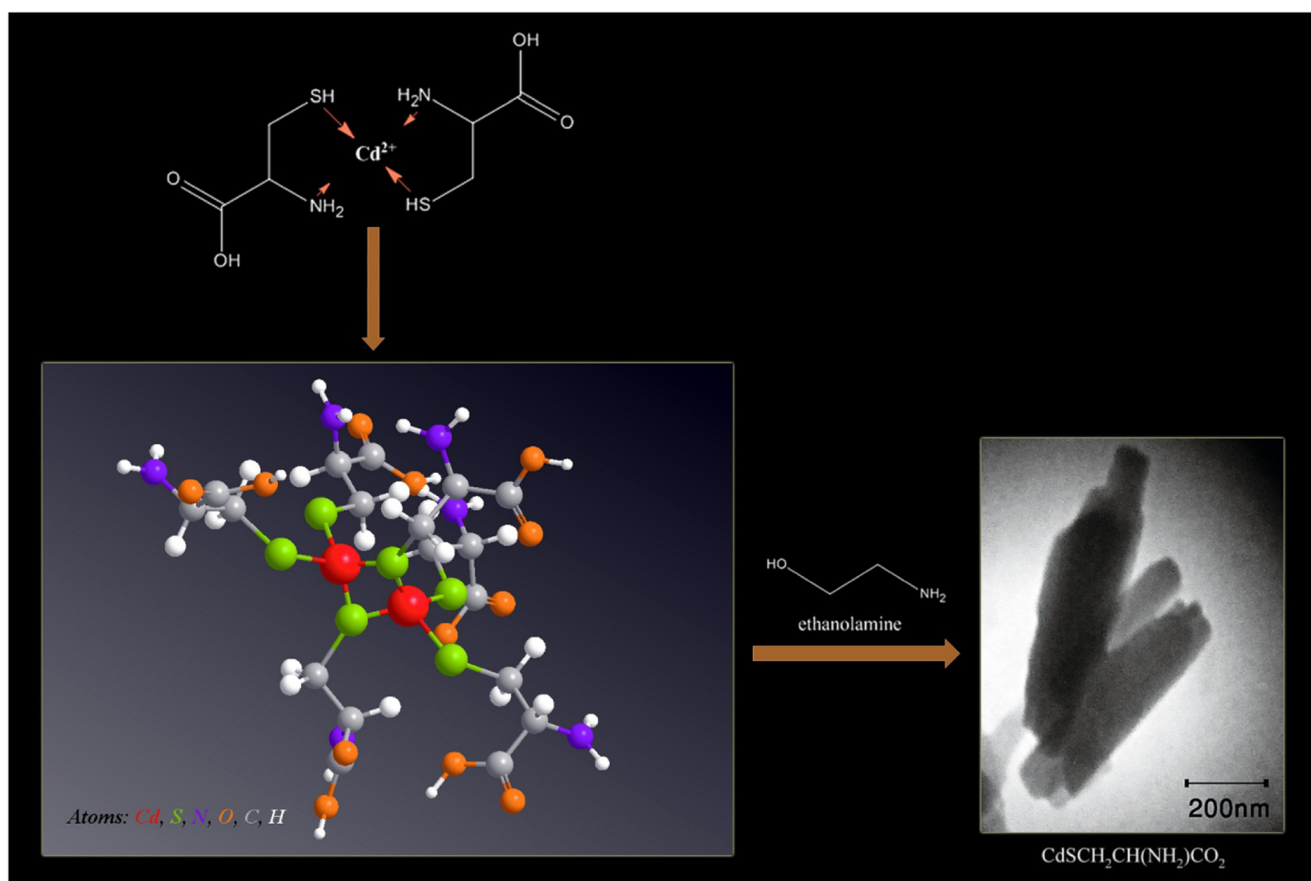


Fig. 7 The scheme for the formation of Cd-Cys nanorods

lead to meaningful changes in the intensity of the peaks (Fig. 9). For choosing optimum pH, two more important

points besides the peak intensity of Cd-Cys NRs in DDW should be considered. i) Further investigation shows that

Fig. 8 Effect of NRs concentration on the fluorescence peak

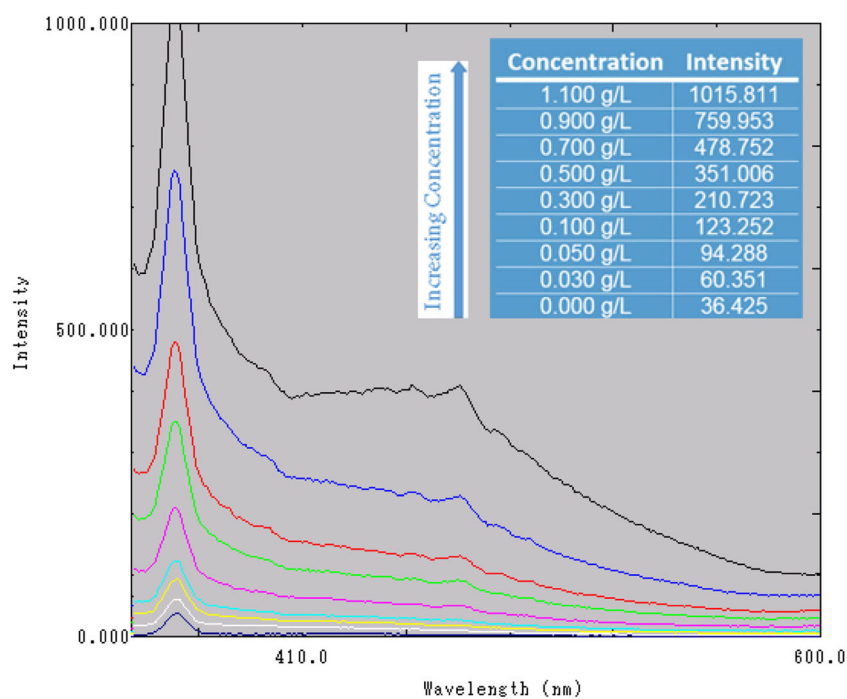
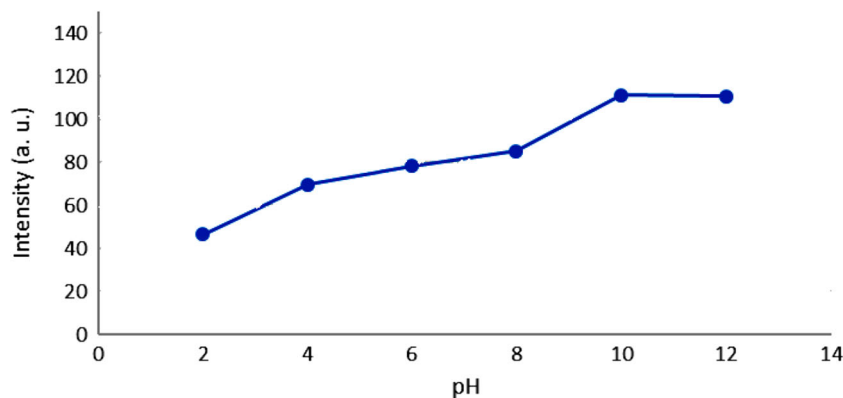


Fig. 9 Effect of pH on solo NRs emission in DDW

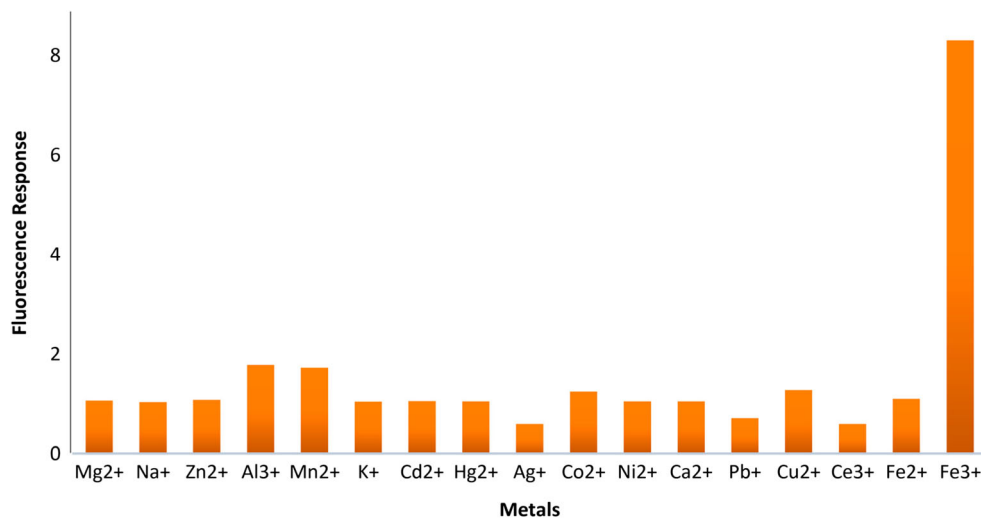


increasing the pH to higher than 6.5 causes a decrease in the selectivity of Cd-Cys NRs in complex samples. ii) The changes in the degree of formation of different metal complexes in higher pHs could lead to co-precipitation of NRs with insoluble complexes or low soluble metal complexes, so pH of 6.5 was chosen as optimum pH.

Effect of Different Metal Ions on NRs Fluorescence Emission

Two important parameters in chemical analysis, i.e. selectivity and sensitivity, of Cd-Cys NRs were investigated. Effects of 17 different metal ions (Mg^{2+} , Na^+ , Zn^{2+} , Al^{3+} , Mn^{2+} , K^+ , Cd^{2+} , Hg^{2+} , Ag^+ , Co^{2+} , Ni^{2+} , Ca^{2+} , Pb^{2+} , Cu^{2+} , Ce^{3+} , Fe^{2+} , Fe^{3+}) on NRs fluorescence emission intensity were probed. The response of the Cd-Cys NRs toward Fe (III) ions was significantly more intense than the other metal ions showing a good selectivity. In fact there was no obvious change in fluorescence response for the other metal ions, except for Cu^{2+} , Mn^{2+} and Al^{3+} which is still so much weaker than response of the Cd-Cys NRs to the Fe(III) ions even at higher concentrations (Fig. 10).

Fig. 10 Fluorescence Response of Cd-Cys NRs to different metal ions. All metals have concentration of 1.00×10^{-3} mol/L (pH = 6.5)



Increasing the Fe(III) ions concentration in Cd-Cys NRs solution from 1.00×10^{-8} mol/L to 1.00×10^{-2} mol/L range caused the fluorescence emission intensity to quench (Fig. 11). There is a correlation between the ratios of fluorescence intensity versus concentration of Fe(III) over a wide range from 1.00×10^{-7} mol/L to 5.00×10^{-4} mol/L (Figure S2). The detection limit (DL) of the sensor could be calculated from the following equation:

$$DL = \frac{3S_b}{m}$$

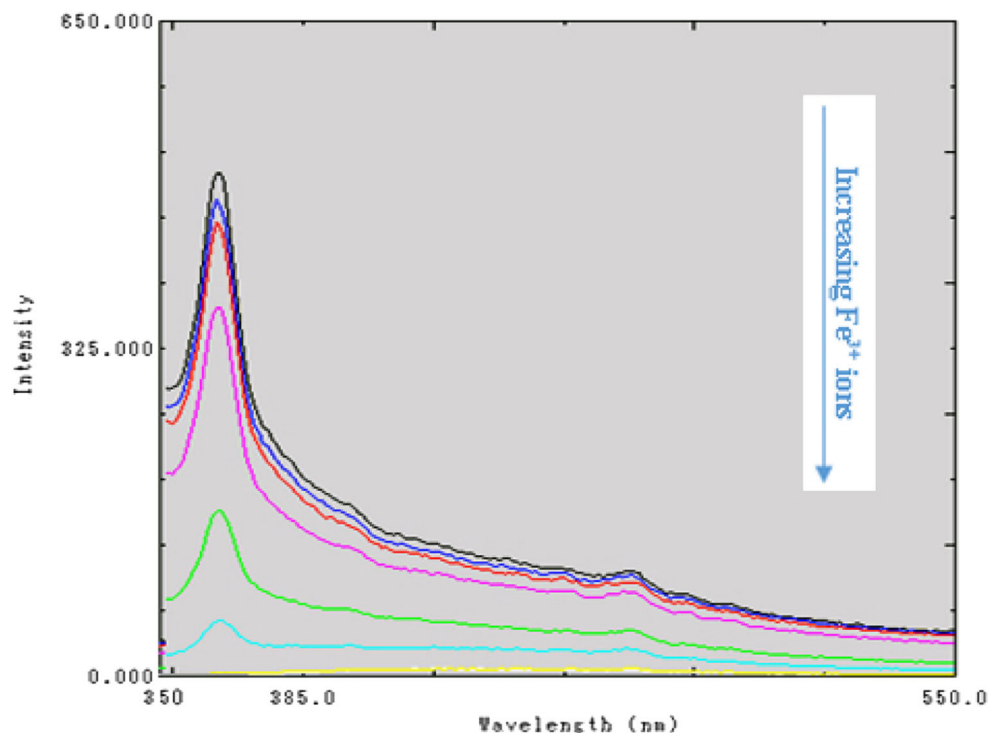
Where S_b is standard deviation and m is the slope of the curve. The detection limit was found to be 2.69×10^{-7} mol/L.

Mechanism of Quenching and Reaction Between NRs and Fe (III) Ions

Solid Phase UV-Vis Spectra

As mentioned before, structural differences between the compounds can be characterized by UV-Visible spectroscopy.

Fig. 11 Effect of increasing Fe(III) ions on the NRs fluorescence emission intensity



About 10 mL of solution containing 0.5 g/L of Cd-Cys NRs in the presence of 10^{-4} mol/L of Fe (III) solution was prepared, dried and stored. A thin layer of Cd-Cys NRs solid and a thin layer of dried solid Cd-Cys-Fe complex placed in the cells respectively for taking their solid state UV-Vis spectrum from 200 to 1000 nm to compare their structures. As shown in the Fig. 12 there is a significant differences between the absorbance of the solo-nanorods (A) and nanorods in the presence of Fe (III) in the solution (B) proving structural changes and creation of a new complex.

Normal UV-Visible Spectra

As Doak et al. showed for gold nanoparticles [42], larger absorbance is related to larger particles in size distribution. The increase in absorbance of Cd-Cys NRs in the presence of 10^{-4} mol/L Fe (III) as shown in Fig. 13 is an evidence for creation of larger particles.

FTIR Spectra

Figure 14 exhibits the FTIR spectrum of Cd-Cys NRs reacted with Fe(III). Stored dried Cd-Cys-Fe complex used for acquiring the spectrum. Peaks at 3430 and 1034 cm^{-1} belong to O-H. Peaks at 1596 and 1402 cm^{-1} prove the presence of free COO^- in the structure. Lack of the $-\text{SH}$ group peak is due to bond formation between the Cd and Cys as Cd-S-R, but the

absence of any peak for $-\text{NH}_2$ group shows that Fe(III) binds to the NRs structure making Fe-N-R bond.

The coordination bond between $-\text{SH}$ and Cd(II) leads to the ligand to metal charge transfer. In the presence of Fe (III) metal ions, Fe (III) binds to $-\text{NH}_2$ groups of Cys. The intrinsic paramagnetism of Fe (III) metal ions is responsible for fluorescence quenching [42–46]. One of the possible reactions between NRs and Fe (III) is formation of a dative bond between non-bonding orbital electrons of nitrogen and empty orbital of Fe (III).

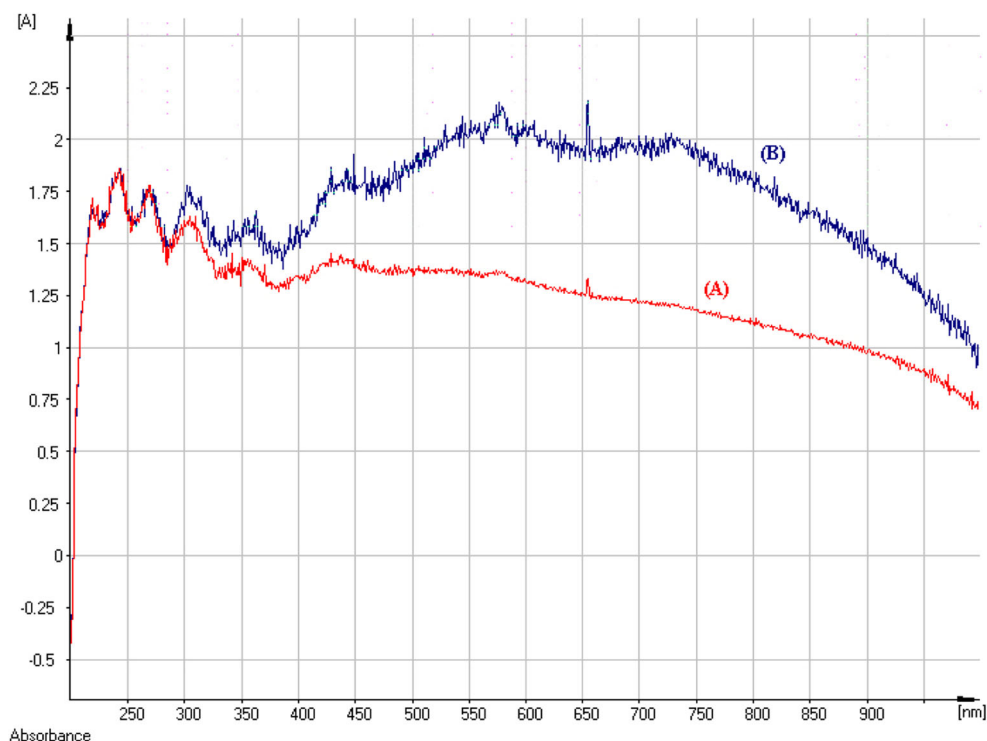
Complex Matrix Samples

For testing the ability of the purposed nano-sensor in measuring the amount of analyte in real samples, three different industrial, biological and medicinal samples have been studied. AAS was chosen in two of real samples to compare our purposed fluorometric method precision with other spectroscopic methods.

Artificial Wastewater

Fe (III) ions have been used in wastewater treatment in co-precipitation process. $\text{Ni}(\text{II})$, $\text{Zn}(\text{II})$, $\text{Cu}(\text{II})$, $\text{Pb}(\text{II})$, $\text{Cd}(\text{II})$ are the common metals which could be removed from wastewater by Fe(III) salts like FeCl_3 [43, 44]. For studying the effect of these metal ions and their co-precipitation with Fe(III) on nano-sensor response an experiment was designed. A

Fig. 12 Solid state UV-visible spectra of (A): solo-nanorods and (B): nanoroads in the presence of Fe(III)



250 mL solution which contained 5.00×10^{-5} mol/L of the above mentioned ions and 1.00×10^{-4} mol/L of Fe (III) was made. NRs fluorescence response showed the concentration of 9.51×10^{-5} mol/L (5 % error). The response of the detector indicated that Fe (III) ions had a priority for reaching the nano-sensor in comparison with the other metal ions.

Rosmarinus officinalis Plant

Different plants and herbs have been used and studied for long time as a flavor in foods or their healing abilities. Rosemary (*Rosmarinus officinalis*) is one of the well-known herbs with pharmacological and antimicrobial properties [45, 46]. In an

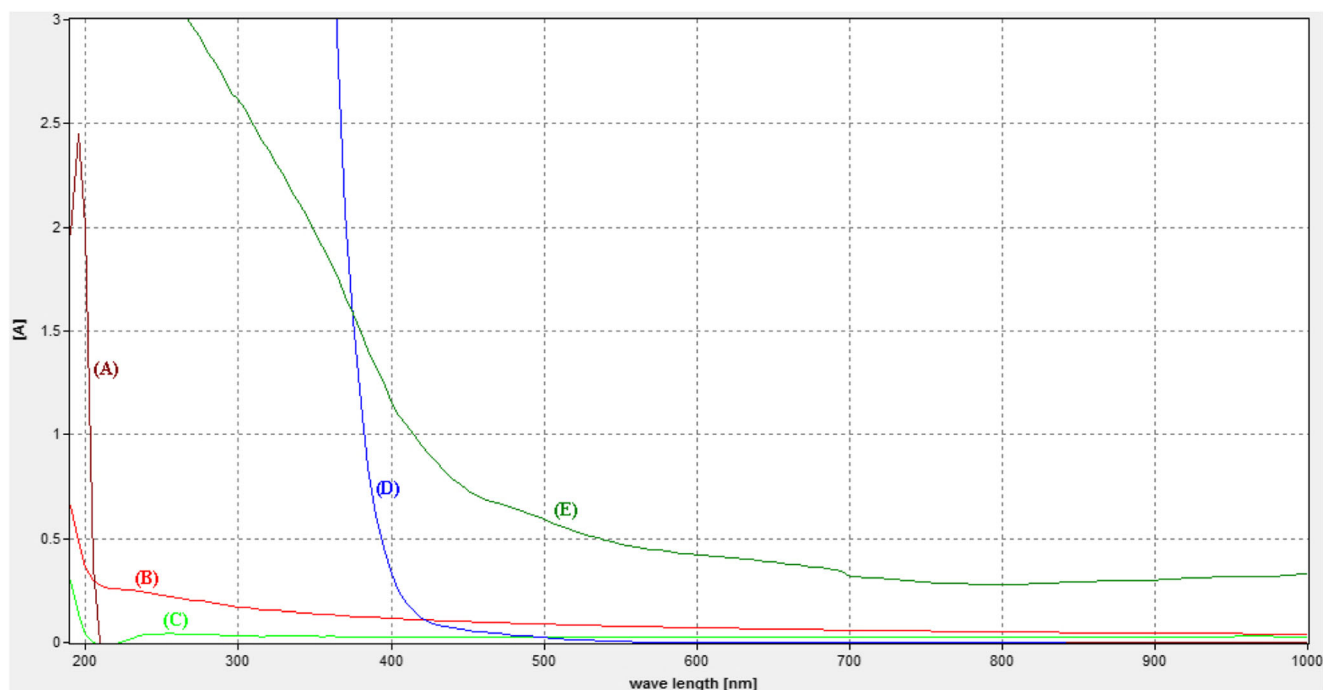


Fig. 13 UV-visible spectras: (A) is Cd^{2+} solution, (B) is nanorods, (C) is L-Cysteine, (D) is Fe(III) solution and (E) is blog to Cd-Cys-Fe complex

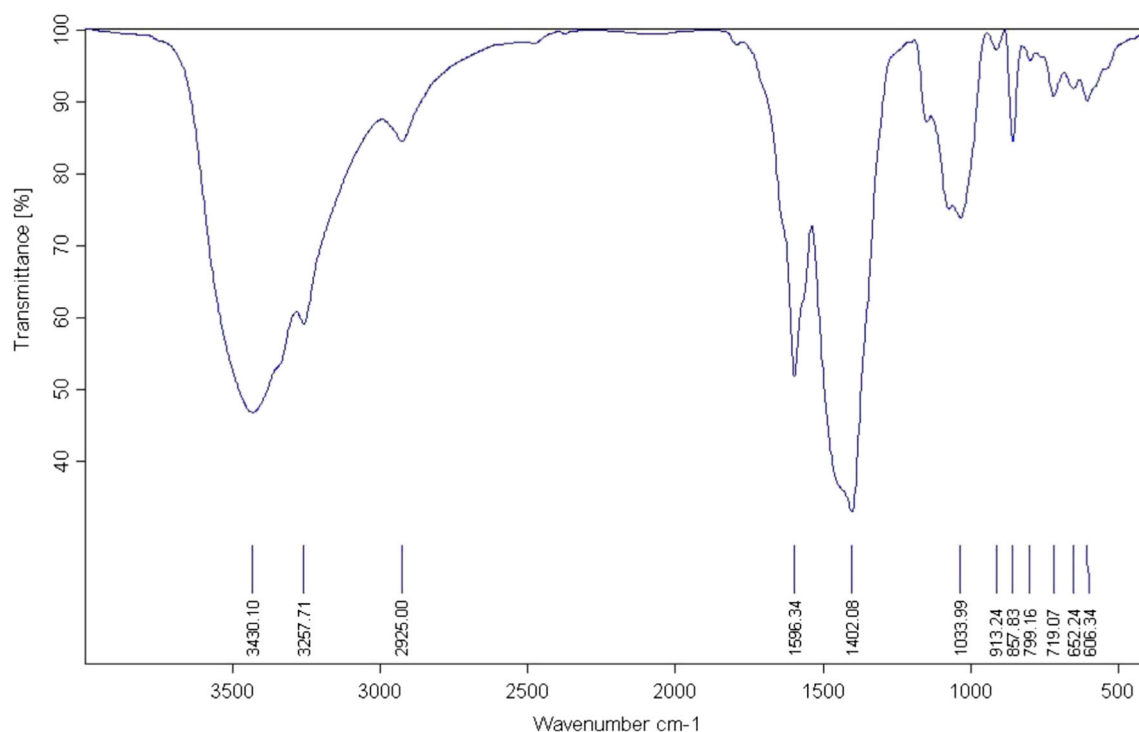
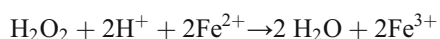


Fig. 14 FTIR spectrum of Cd-Cys NRs reacted with Fe(III)

experiment the amount of iron was measured by the Cd-Cys nano-sensor. The leaves solution contains various different mineral metals plus iron, with different unknown concentrations. First the total amount of iron in the main solution was measured with AAS and found to be 1.35×10^{-1} mol/L in the main solution. For setting the concentration on the linear range of the detector and testing its ability in measuring low amounts of analyte, 1 mL of the leaves solution was diluted in a 1 L volumetric flask to obtain 1.35×10^{-4} mol/L concentration. The fluorescence response of the Cd-Cys NRs showed the concentration of Fe(III) in the solution was 7.1×10^{-6} mol/L. Then one drop of H_2O_2 was added to the fluorescence cuvette containing the solution and the response of the Cd-Cys NRs gave Fe(III) concentration of 1.23×10^{-4} mol/L (which has about 8 % error comparing to AAS response). This concentration will be the total amount of the iron in the solution because all of the Fe(II) was converted to Fe(III) according to the following equation:



By subtraction of first response of the Cd-Cys NRs from the second one, we were able to measure the amount of the Fe^{2+} in the solution which was 1.159×10^{-4} mol/L.

Feroglobin Medicine

A Feroglobin medicine tonic known as specific blood building nutrient, contains ferrous sulfate in a complex with B

vitamins, folic acid, minerals such as zinc which are also important in blood formation and other nutritional supplements. Here the amount of iron in this tonic was measured by Cd-Cys NRs fluorescence response. First the total amount of iron was determined with AAS and found to be 1.86×10^{-1} mol/L in the main solution. For setting the concentration on the linear range of the detector, 1 mL of the main solution was diluted in a 1 L volumetric flask to obtain 1.86×10^{-4} mol/L solution. The fluorescence response of the Cd-Cys NRs gave the value of Fe(III) 6.74×10^{-6} mol/L; this amount of Fe(III) in the solution is near detection limit of the detector. Then one drop of H_2O_2 (35 %) was added to the cuvette. The concentration of Fe(III) was determined spectrofluorometrically and found to be 1.73×10^{-4} mol/L (almost 6 % error with respect to AAS response). The second reading was the total concentration of iron in the solution because all of Fe(II) was converted to Fe(III). By subtracting the first response from the second, the amount of the Fe(II) found to be 1.66×10^{-4} mol/L.

Table 3 The APTT, PT, TT data

	PT	APTT	TT
Plasma	15.4	45	18.9
NRs	39.8	135.3	20.4

Reported PT, APTT and TT times are the average datum of the 10 times repeating the same testing

Hemocompatibility Tests

High selectivity of the sensor makes it suitable candidate for biological and biochemical studies, such as measuring the amount of an analyte in blood, but selectivity itself is not enough; Hemocompatibility is a key property of biomaterials that comes in contact with blood [47]. Even in vitro blood analyses, sensor should not cause coagulation of the blood samples.

The in vitro anticoagulation activity of the Cd-Cys NRs was evaluated by prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT). The PT is corresponding to the extrinsic pathway of the blood-clotting system, APTT detects the intrinsic coagulation, and TT is the assay for the last step of coagulation, are well-known methods to determine the biocompatibility of the material [35, 48, 49]. All assays were conducted using citrated human plasma from a healthy donor. The results was shown in Table 3. Both the PT and APTT values are remarkably prolonged for Cd-Cys NRs with respect to plasma, indicating their significance in vivo anticoagulation activity. Clot time of APTT is considerably above the maximal values, almost three times greater compared to 45 s for plasma. A small increase is also detected for the TT value. The data in Table 3 exhibited a good blood compatibility of Cd-Cys complex NRs.

Conclusion

We successfully synthesized and characterized new Cd-Cys NRs in one step at room temperature. Cd-Cys NRs which were utilized as a fluorescence nano-sensor complied with the most important characteristics of a favorable sensors that is stability, selectivity, sensitivity by measuring micro-molar per liter Fe (III) concentrations. The structure of the Cd-Cys NRs in the absence and presence of Fe (III) was examined. The hemocompatibility tested by anticoagulation measurements showed the biocompatibility of synthesized nano-sensors. The ability and response of the nano-sensor tested in different real samples with complex matrices and the results exhibited the usability of this method in pharmacological, phytochemical and industrial researches.

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