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A Designed Fluorescent Method by Using PbS with Gelatin via Quantum Dots for the Determination of Phenylpropanolamine Drug in Human Fluid Samples

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Abstract

By increasing fluorescence emission and absorption or by shutting down, fluorescent chemical sensors to detect drugs have been considered and used due to their non-destructiveness, and their ability to show decomposed concentrations, fast response, and high accuracy. In this research, a chemical sensor was synthesized by using PbS functionalized with gelatin quantum dots for Phenylpropanolamine (PPA) drug. The calibration curve was linear in the range of (0.05 to 10.0 μgL^{-1}). The standard deviation of less than 2.0 %, and detection limits of 3S/m of the method (0.05 μgL^{-1}) in time 60 s, 335 nm were obtained for the sensor level response of PbS Quantum Dot–Gelatin nanocomposites sensor with evaluated 99% confidence interval. The observed outcomes confirmed the suitability recovery and a very low detection limit for measuring the Phenylpropanolamine drug. The fluorometric method was introduced to measure Phenylpropanolamine in real samples such as urine and blood which can be used for other drugs and hospital samples. The chemical PbS Quantum Dot–Gelatin nanocomposites sensor made it possible as an excellent sensor with good reproducibility.

Keywords: Phenylpropanolamine (PPA) drug, Fluorescence, PbS with Gelatin Synthesis, Quantum Dots.

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Introduction

Drug delivery systems have been created for improving therapeutic properties of the drugs and are often in form of a drug-containing capsule. Such systems release the drugs at a specific amount in a specific site; therefore, they affect drugs pharmacokinetics and distribution. Nanoparticles have been widely applied in drug delivery [1]. Determining the amount of drug in the biological samples is very important to determine its effect in the body system. Accordingly, different methods with high sensitivity, selectivity and efficiency, as well appropriate analysis for the determination, extraction and measurement are presented for drugs in real samples [2].

One of the biggest problems in the decomposition of biological samples is the existence of different species and their effects on the decomposition process of the drug. For this reason, many drug measurement methods are based on separation techniques such as gas chromatography and high-performance liquid chromatography that are very time-consuming methods with difficult working conditions [3].

Phenylpropanolamine hydrochloride (PPA) is a nasal decongestant mainly used in combinations for relief of cold symptoms as it has indirect sympathomimetic activity [4]. PPA is also known as β-hydroxyl amphetamine, and is a member of the phenyl ethylamine and amphetamine chemical classes [5]. Pharmaceutical drug preparations of PPA have changed in their stereoisomer composition in different countries, which may explain differences in misuse and side effect profiles [6]. Analogues of PPA include ephedrine, pseudoephedrine, amphetamine, methamphetamine [7]. Its chemical name is (1RS, 2SR) -2-amino -1-phenyl propanol.

The BP described non-aqueous potentiometric titration for PPA [4]. The USP suggested non-aqueous titration method using glacial acetic acid for PPA pure form and HPLC method for its capsules, extended released capsules, tablets, extended released tablets and oral solutions [8]. For that reason, precise and reliable calculation of (PPA) in real samples is crucial for guaranteeing consumers' health. Diverse quantitative analytical method including Flow injection [9], capillary gas chromatography [10], and liquid chromatography [11]. There are different methods used for PPA determination spectrophotometry [12]. Recently, noble metal nanoparticles-based UV–visible spectrometric and fluorometrically methods have drawn special attention for selective and sensitive reorganization of target species (inorganic, organic and biomolecules) in various complex matrices [13].

Fluorometrically techniques exhibit an advantage over the aforementioned techniques as being low-cost apparatus, fast and simple utilized for determining (PPA) drug in different matrices. Attention has newly been drawn to noble metal nanoparticles-based UV–visible spectrophotometric and fluorometrically methods for the selective and delicate reorganization of target species (inorganic,

organic, and biomolecules) in different complex matrices [14]. Accordingly, developing a simple, selective, and delicate method like the fluorescence emission intensity measurement in determining toxic samples and biomolecules was highlighted [15,16]. In this method sensing toxic samples was done with high sensitivity and excellent selectivity for the discerning and accurate reorganization of species (1-inorganic 2- organic and 3- biomolecules) in different intricate matrices, attention has been drawn to noble metal nanoparticles-based with the help of the quenching properties of quantum dots method [17,18].

Recently attention has been directed to fluorescent sensors in tracing toxins owing to their outstanding properties like simplicity in operation, great selectivity, high-sensitivity, and real-time monitoring [19]. Numerous fluorescence probes, in the past few decades, have been announced for recognition of biomolecules (organic and inorganic) [20], and quantum dots (QDs) [21]. Therefore, the necessity of developing alternative and eco-friendly materials became apparent [22]. Identical to the electronic Fermi wavelength, the nature of molecules in fluorescent sensors like 1-discrete energy level, 2-good light stability, 3-strong light luminescence, 4-biocompatibility, and other exclusive physiochemical characteristics make them extremely potential in the domain of sensing and imaging [23]. However, single-component quantum dots are easy to reunite because of surface defect. Core-shell quantum dot composites depending on selecting the core-shell materials can improve this phenomenon and endow some new properties [20-23].

Quantum dots (QDs) are small semiconductors less than 10 nanometers in size and have electronic properties that differ from larger particles due to quantum mechanics. They are a major issue for nanotechnology. When quantum dots are illuminated by ultraviolet light, an electron at the quantum dot can be excited at a higher energy state. In the case of the quantum dot, this process involves the transfer of an electron from the capacitance band to the conduction band. The excited electron can return to the capacitance band and release its energy by emitting light. The color of that light depends on the energy difference between the conduction band and the capacitance band [18, 20, 24].

Quantum dots have intermediate properties between bulk semiconductors and discrete atoms or molecules. Their selective properties change as a function of size and shape. There are many methods for producing different semiconductors. Typical points are made of binary compounds such as (PbS, CdS, PbSe, CdSe, CdTe, InAs, and InP). Different points may also be made from triple compounds. In addition, recent advances have been made that could provide the synthesis of colloidal percent quantum dots [24, 25]. PbS nano-composites can by various methods such as the application of stabilizing and reducing chemicals of glutaraldehyde, reduction prepared [26].

Gelatin as a natural, completely non-toxic, and biocompatible polymer derived from collagen, is a very suitable option for coating nanoparticles of lead sulfide quantum dots. Because it can be made into fine and stable particles and at the same time it can be used as a transfer agent which creates significant stability in the form of cross-linking in these materials. More importantly, its by-products are absorbable in the body to be destroyed or decomposed [27].

In the present article, an uncomplicated facile strategy was employed in preparing water-soluble, stable PbS with gelatin by utilizing glutaraldehyde as a stabilizer. As it is shown in Figure 1. The existence of (PPA) drug provokes the aggregation of nano-clusters with the improvement of fluorescence intensity. In addition, the successful application of nano-probes in detecting (PPA) drug in different real samples along with their significant efficiency and perfect recovery prove their great potentialities in practical application. In the present work, a fluorometric method was designed for determining (PPA) drug. The extreme sensitivity, selectivity, and simplicity of the proposed method led to the absolute superiority of this method over other aforementioned ones. The method was effectively applied in determining (PPA) drug in blood and urine samples.

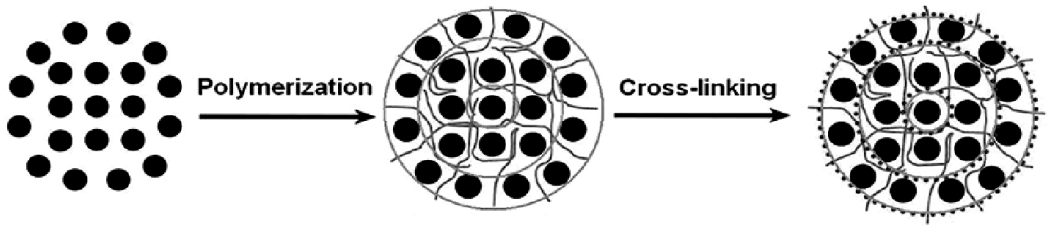

Figure 1. Schematic illustration of the PbS quantum dots sensor functionalized with gelatin synthesis.

Experimental

Reagents and materials

All chemicals of lead nitrate $Pb(NO_3)_2$ (99%), sodium sulfide (Na_2S) (99.0 %), gelatin, and glutaraldehyde were bought from Merck Company. Phenylpropanolamine (PPA) drug (98.0 %), purchased from India Company). For pH < 7.0, as buffer solutions were prepared from 1 ml of boric acid/acetic acid/phosphoric acid (1.0 M), and for pH >7.0 was adjusted by addition of 0.2M sodium hydroxide, DD H_2O (Double distilled water) was used in the preparation of the solutions.

Instruments

All the recordings were done at room temperature, measurements Phenylpropanolamine (PPA) drug were done using a Horiba JY Fluorolog-3 molecule fluorometer (Paris Company, France), and spectrophotometer model 1601 PC (Shimadzu Company, Japan). Time-resolved luminescence intensity decay was registered, and by using a 335 nm laser light source, samples were excited.

Fourier transform infrared (FT-IR) spectra were registered on a PerkinElmer (FT-IR spectrum BX, Germany). The structure and phase evaluation of prepared samples was carried out by using Philips X pert MPD, X-ray diffract meter with CuKα radiation at beam acceleration conditions of 40 kV/35 mA. For the measurement of pH, the pH/Ion meter (model-728, Metrohm Firm, Switzerland, Swiss) was employed.

Pretreatment of real samples

In a 100 mL beaker, the treatment of a 50 mL portion of a urine or blood samples (or a spiked human fluid samples) in the hospital (Ahvaz) was done using 2 mL of concentrated HNO_3 (63%) and an $HClO_4$ (70%) mixture of 2:1 and then covered with a watch glass for 10 min and then with the help of a 100 mL volumetric flask. 5 mL of the obtained clear solution was picked up and the analysis of Phenylpropanolamine (PPA) drug was found by the standard addition method procedure [28].

Synthesis of PbS Quantum Dot–Gelatin Nanocomposites Sensor

The nanoparticle PbS was synthesized in reactive solution prepared using lead nitrate $Pb(NO_3)_2$ and sulfide sodium (Na_2S) with concentration of (0.1 M and 0.1 M). The Gelatin pellets were used as a base medium and its concentration was set to (0.1 M). 20 mL of all the above solutions were prepared separately, using distilled water as a solvent and mixed in a beaker. 2 ml of glutaraldehyde (25%) was added into the solution as a complexing agent, which can easily bind the metal ions. The reactive vessel with solution was immersed into 20 ml acetone maintained at 40^oC and pressure of 10^{-5} mbar. A thermometer was placed in the vessel to measure the temperature of the bath solution and a temperature sensor and dimer with temperature controller were attached to maintain the constant temperature. The solution was stirred well with the help of magnetic stirrer to maintain the homogeneous mixture. The prepared solution was colorless and turned yellowish after 30 min and suddenly changed into gray color; these indicate the chemical reactions and confirm the formation of PbS. The reactive solution was continuously stirred for 2 h. The powder was collected and dried in a hot air oven at (57^oC) [29].

Mechanism of Phenylpropanolamine (PPA) drug

The mechanism of (PPA) drug can be defined as the process shown in Figure 2. Meanwhile, two (PPA) drug molecules were simultaneously involved in the process, an electron was separated from the nitrogen atom in their ring, and radical cations were formed. The radical molecules then were converted into their resonant form and then immediately dimerized with each other (dimerization is

a common process for unstable cationic radicals). The result of the process was loss than four electrons and two protons with the participation of two molecules of (PPA) drug. It should be noted that due to the large surface area and high electron transfer ability of the modifiers, the steps in the process, including two phases of electron loss, occurred simultaneously and were not separable in the figures, so only one peak was observed in the fluorometric of (PPA) drug.

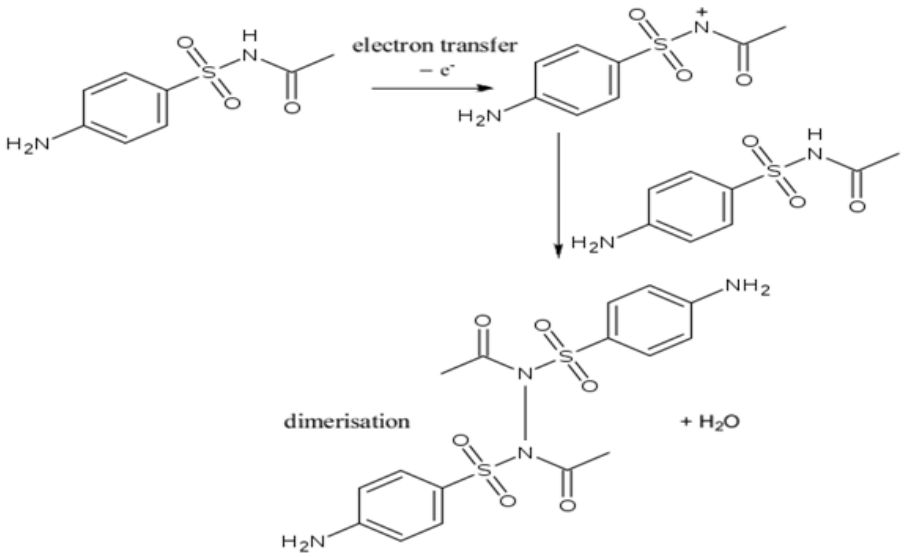

Figure 2. The mechanism of phenylpropanolamine (PPA) medicament.

Procedure Fluorescent Detection measurements

In this procedure, PbS Quantum Dot–Gelatin nanocomposites (2.5×10^{-2} mol L^{-1}), then 2 ml of glutaraldehyde (25%), 1 mL of acetate buffer (pH 4.0), and different concentrations of (PPA) drug (10.0 µg L^{-1}) were added to 10 mL volumetric flasks and diluted with double distilled water. The difference between the quantities of the increasing fluorescence emission in a wavelength equal to (335 nm) in a time interval equal to (40-60 s), was estimated which can be seen in Figure 3.

By adding PPA drug to the solution, it was observed that the fluorescence emission intensity of the ethanol solution of PbS quantum dot–gelatin nanocomposites at the wavelength of (335 nm) was dropped. All reaction steps were repeated by increasing the concentration (0.2 µg L^{-1}) of the PPA drug every 10 s in the fluorometric of PPA drug (ΔI b) and ultimately (ΔI) I_0 blank-I sample. There was a sharp change in the fluorescence emission of the sensor in the 335 nm region, a continuous increase of PPA drug at intervals of (10 s) in solution and changes in the fluorescence emission intensity of the sensor, peak fluorescence emission during 325 nm, with an increase in increasing fluorescence emission, which all can be seen in Figure 3.

All these steps would be repeated for a reaction without the presence of PPA drug (AAb). Finally (AA) AAblank-AAsample was calculated. The spectrum changes were due to the addition of PPA

drug in the range of (0.1 to 1.1 µg L^{-1}) and the formation of a complex. As it can be seen, the complex (PPA drug-sensor) has two absorption peaks, the first at a wavelength of 335 nm and the second at a peak appears at a wavelength of 385 nm (Figure 4) [30,31].

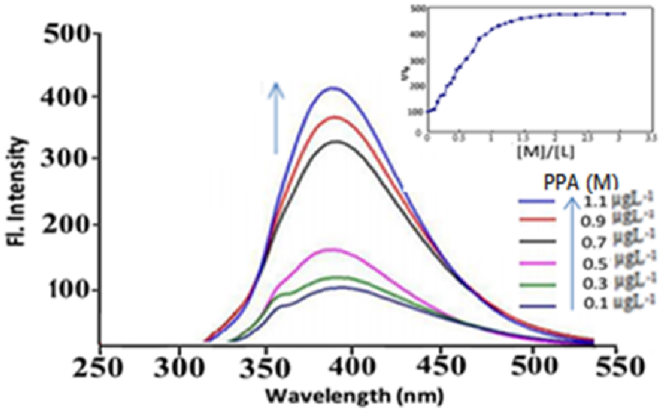

Figure 3. The Fluorescent Detection of the (PPA) medicament by PbS Quantum Dots–Gelatin nanocomposites in 335 nm; and added solution increasing of the (PPA) medicament (0.2 µg L^{-1}) in time 10 s. (2.5×10^{-2} mol L^{-1} of PbS Quantum Dots–Gelatin nanocomposites, pH 4.0, acetate buffer solution).

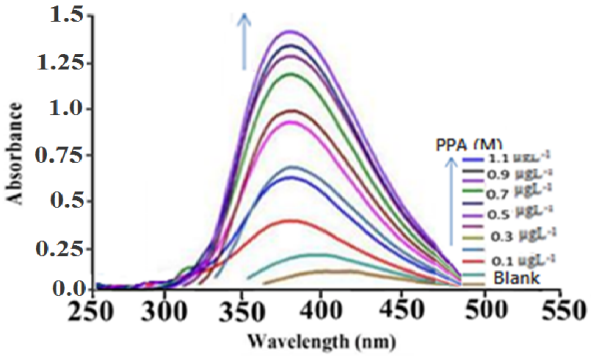

Figure 4. The absorption spectra of the (PPA) medicament by PbS Quantum Dots–Gelatin nanocomposites added solution increasing of the (PPA) medicament solution (0.2 µg L^{-1}) in time 10 s. (2.5×10^{-2} mol L^{-1} of PbS Quantum Dots–Gelatin nanocomposites, pH 4.0, acetate buffer solution).

Results and discussion

Characterization of PbS Quantum Dot–Gelatin nanocomposites Synthesis

FTIR spectra for PbS Quantum Dot–Gelatin nanocomposites Synthesis are shown in Figure 5a. The vibrational frequencies for stretching bonds in PbS molecule could not be detected by FTIR analysis. It confirms that PbS does not show any definite absorption peaks in the range 400 - 4000 cm^{-1} The vibration modes located at 3423 cm^{-1} can be assigned to the O–H broad absorption mode due to the hydroxyl group in the compound. The absorption band at 2928 cm^{-1} corresponds to the C-H stretching vibration mode. The broad absorption near 1300 - 1000 cm^{-1} confirms the presence of the C–O bond. The absorption band at 1637 cm^{-1} is due to the O–H bending vibration from the water molecules adsorbed into the surface.

A further subtle point existed that no significant difference between the FTIR spectra of PbS quantum dots with gelatin Synthesis nanoparticles was observed [32]. The XRD pattern of the PbS Quantum Dot–Gelatin nanocomposites is shown in Figure 5b. The synthesized nano powders were found to be polycrystalline in nature. All detectable peaks corresponding to (111), (420), (331), (400), (222), (311), (220), (200) and (422) planes belonged to the pure cubic phase of PbS (JCPDS no. 78–1901) [33].

Figure 5c shows the morphological features and particle size distribution of the PbS Quantum Dot–Gelatin anocomposites using the SEM micrograph. It is seen that the particles were mostly spherical with a various size distribution as they formed agglomerates. From the particle size distribution, we obtained the average particle size in the range of 37-44 nm very close to those determined by XRD analysis [34]. As shown in Figure 5d, which deals with the thermal gravimetric analysis (TGA) of gelatin-coated lead sulfide nanoparticles, we see a 98% weight reduction at temperatures below 650°C for gelatin. While under the same conditions for lead sulfide nanoparticles coated with a high molecular weight polymer, we see only 28% weight loss [34].

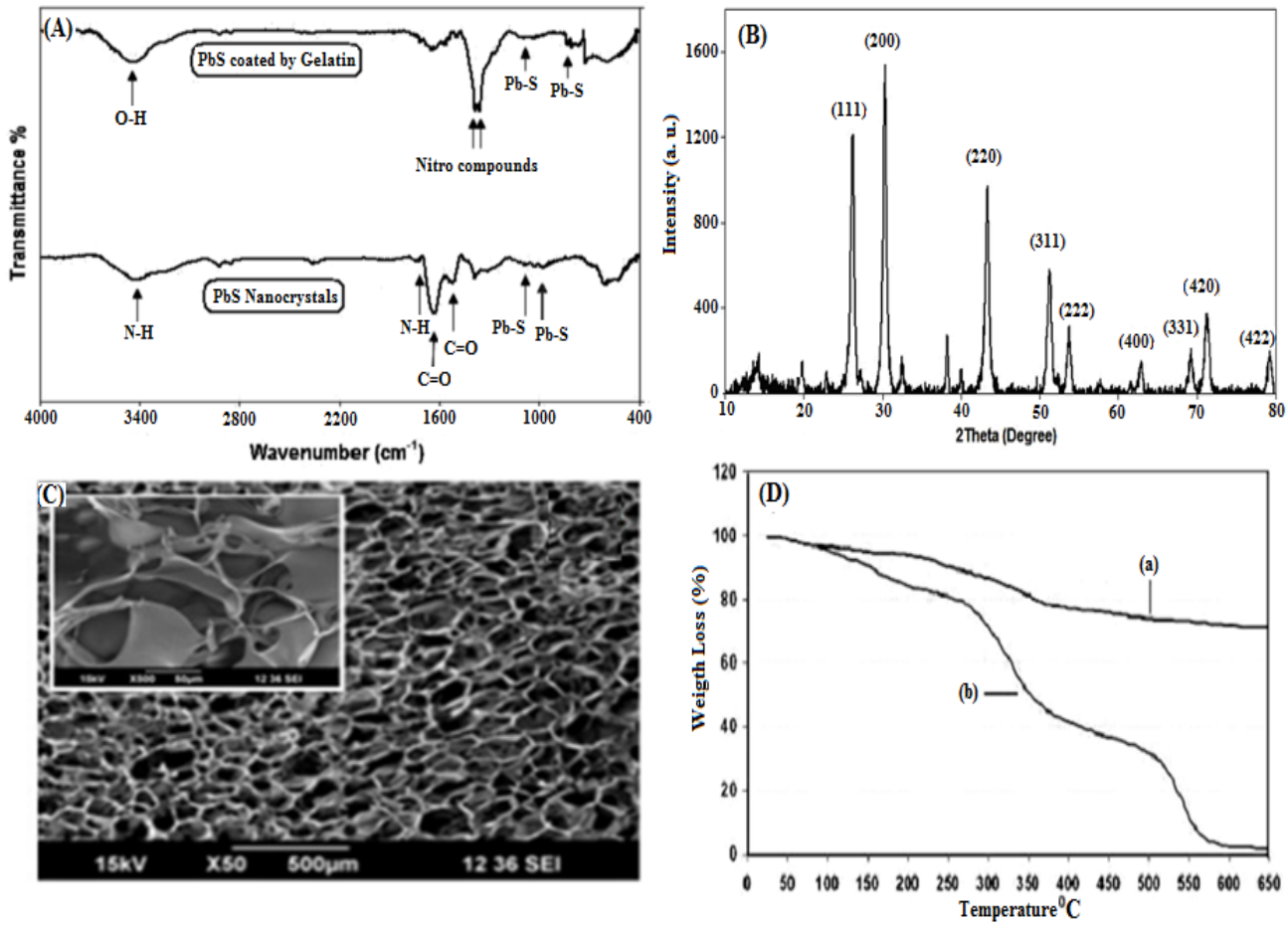

Figure. 5. The (A) FT-IR transmittance spectrum image (B) XRD of the preparation of synthesized PbS Quantum Dot–Gelatin nanocomposites (C) SEM image of synthesized PbS Quantum Dot–Gelatin nanocomposites and (D) Thermal gravimetric analysis (TGA) of gelatin-coated lead sulfide nanoparticles.

Optimization of Sensing Conditions

It is interesting that the fluorescence intensity of the as-prepared PbS Quantum Dot–Gelatin nanocomposites was significantly enhanced in the presence of (PPA) drugs. In order to obtain a highly sensitive response for the detection of (PPA) drugs the optimization of pH values, PbS Quantum Dot–Gelatin nanocomposites and incubation time was carried out systematically.

The pH value of the reaction solution could greatly influence the interaction between PbS Quantum Dot–Gelatin nanocomposites and (PPA) drugs. To inspect the effect of PbS Quantum Dot–Gelatin nanocomposites on the reaction rate, 1 ml (PPA) drugs 10.0 μg L^{-1} solution, PbS Quantum Dot–Gelatin nanocomposites, 2.0×10^{-2} mol L^{-1} and 2 ml glutaraldehyde (25%) were added to the volumetric flask 10 ml and by adding distilled water and the fluorescence intensity of solution was measured. The fluctuating pH values in the range of 2–9 of the (PPA) drug-PbS Quantum Dot–Gelatin nanocomposites complex at 385 nm were investigated.

As displayed in Figure 6A. The fluorescence intensity significantly increased with the increasing solution pH, and reached its maximum when pH reached 4.0. A possible explanation as the pH influenced the (PPA) drug speciation in solution [35, 36]. Therefore, pH 4.0 was selected as the optimum pH value for (PPA) drug detection. Meanwhile, to inspect the effect of PbS Quantum Dot–Gelatin nanocomposites on the reaction rate, 1 ml (PPA) drugs 10.0 μg L^{-1} solution, 2 ml glutaraldehyde (25%) and 1 ml, PbS Quantum Dot–Gelatin nanocomposites, 0.5×10^{-3} to 4.0×10^{-2} mol L^{-1} are added to the volumetric flask 10 ml and by adding distilled water. The fluorescence intensity of solution was measured. The above-mentioned operation was repeated for blank solution (the solution without (PPA) drug). Illustrated in Figure 6B, 2.5×10^{-2} mol L^{-1} was selected as the desired concentration. In addition, the effect of reaction time on the fluorescence intensity was also studied. It can be seen from (Figure 6C) that the fluorescence intensity increased rapidly, and reached its maximum at around 60 sec, after which it remained relatively stable. Therefore, a reaction time of 60 sec was chosen in this experiment [19, 37].

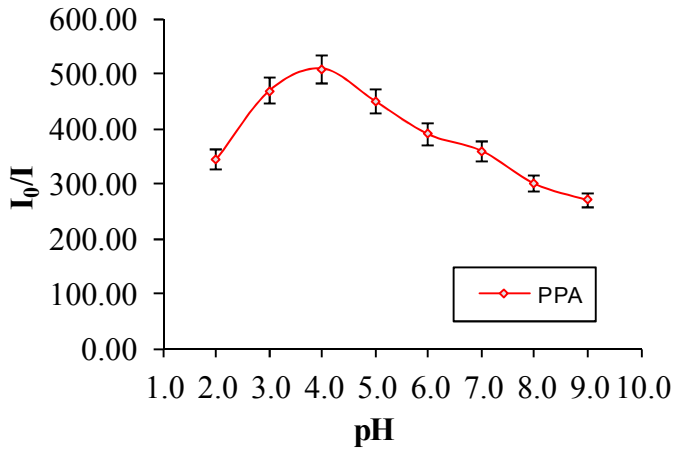

Figure 6A. The impact of pH in the fluorescence intensity rate, PbS Quantum Dot–Gelatin nanocomposites, 2.5×10^{-2} mol L^{-1}, glutaraldehyde (25%), time 60 s, 335 nm).

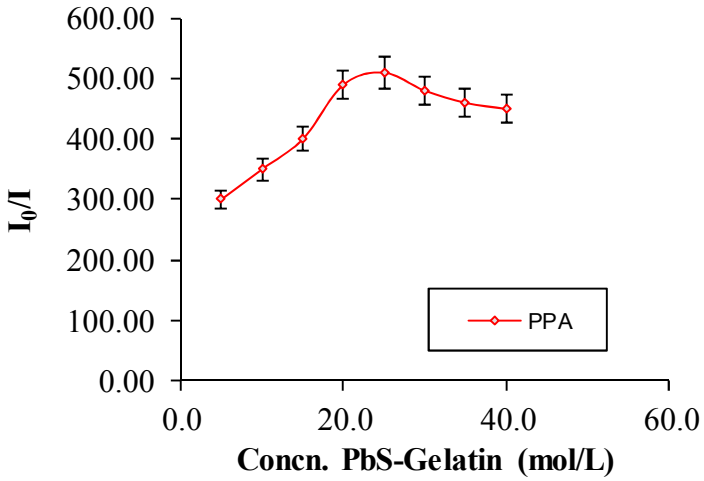

Figure. 6B. The impact of PbS Quantum Dot–Gelatin nanocomposites in the fluorescence intensity rate. glutaraldehyde (25%), pH 4, time 60 s, 335 nm).

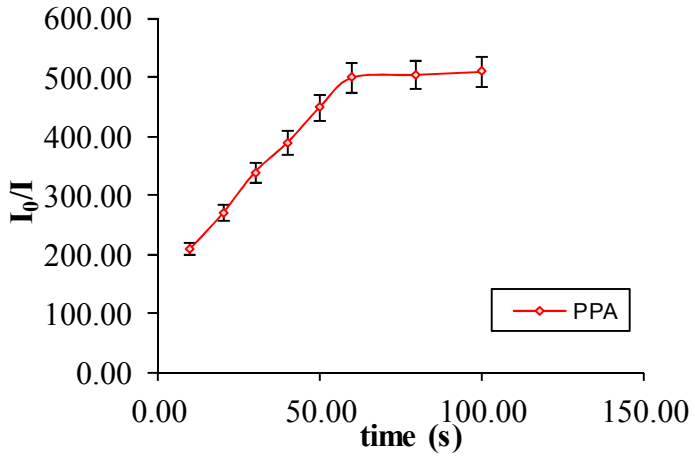

Figure. 6C. The impact of time in the fluorescence intensity rate. PbS Quantum Dot–Gelatin nanocomposites, 2.5×10^{-2} mol L^{-1}, glutaraldehyde (25%), pH 4, 335 nm).

Calibration curve

The excellent catalyst activity of the PbS quantum dots–gelatin nanocomposite, which was examined in the previous sections, made it possible to measure (PPA) drug at low concentrations. For this purpose and for the analysis of solutions, it was necessary to prepare a calibration curve to use to measure the concentration of unknown samples [13,19]. To prepare the calibration curve, the solutions with different concentrations of (PPA) drug (from 0.05 to 10.0 µg L^{-1}) were prepared and their fluorescence intensity technique, which is shown in Figure 7. It can be seen that when the concentration of (PPA) drug gradually increased, its peak oxidation current also increased and there was a direct and linear relationship between the concentration and the peak oxidation current, as the (PPA) drug calibration equation was shown in Figure 7. The precision of the method was evaluated by performing (n=10) repeated measurements of (PPA) drug solutions. The Relative Standard Deviations (RSD) for these determinations were (2.0 %) and limit of detection (LOD) (0.05 µgL^{-1}) respectively [37,38].

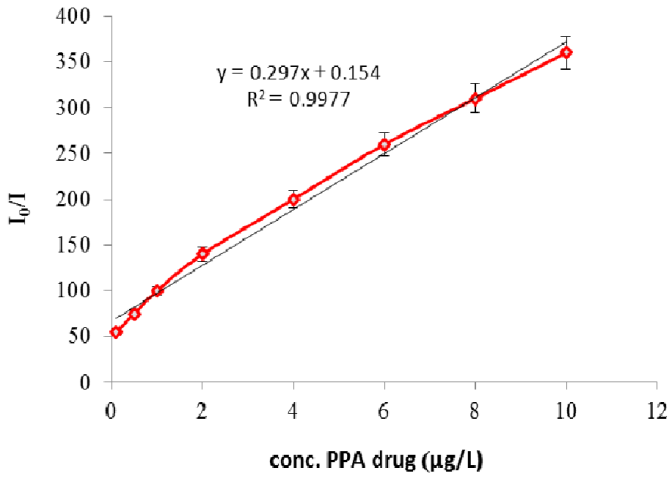

Figure 7. Calibration graph from 0.05 to 10.0 µg L^{-1} of phenylpropanolamine (PPA) medicament.

Optimum values of parameters

The optimum values of parameters are demonstrated in Table1. The method can be used as an alternative method for (PPA) medicament measurement owing to advantages like excellent selectivity and sensitivity, low cost, simplicity, low detection limit and no need in utilizing organic harmful solvent.

Table. 1. Investigation of method repeatability at conditions.

Parameter	Optimum Value for (PPA) drug (M)
Phenylpropanolamine (PPA) drug (M)	(10.0 μgL^{-1})
PbS Quantum Dot–Gelatin nano composites (M)	(2.5×10^{-2} $molL^{-1}$)
pH	4.0
Equilibration time (s)	(60 s)
Linear range (LDR)	(0.05 – 10.0 μgL^{-1})
Detection limit (LOD)	(0.05 μgL^{-1})
Relative Standard Deviations (RSD)	Less than (2.0 %)
Advantages	High repeatability, sensitivity, selectivity, wide linear range and no need to organic solvent

Interference Studies

After establishing the measurement method, to evaluate the selectivity of the prepared PbS Quantum Dot–Gelatin nanocomposites sensor for determining the (PPA) drug the effect of various substances on the determination of (PPA) drug (10.0 μgL^{-1}) for method respectively was tested under optimum conditions. Several representative potential interferences such as inorganic cations, anions, molecular species and dyes were investigated individually for their effect on (PPA) drug recovery. As exhibited in Table 2, the tolerance limit was determined as the maximum concentration of the interfering substance which resulted in an error less than (±5%) for measuring (PPA) drug in real samples [19,39]. In addition, it confirms the importance of the sensor in terms of cost effectiveness.

Table 2. Impacts of the matrix medicaments on the retrieving of the examined (PPA) drug (n=5).

Foreign species	**Tolerance limit ($\mu g\ L^{-1}$)**
Amoxicillin, Ampicilline, Acetominophene, Cortisone, Cyclosporine	800
Tramadol, Methadone	750
NH_4^+, Mg^{2+}, F^-, K^+, Cu^{2+}, Fe^{3+}, Ca^{2+}, Cl^-, I^-	500
Naratriptan, Rizatriptan, Sumatriptan, Zolmitriptan, Megestrol, Tamoxifen	100
Epinephrine, Sulfacetamide	50

Application of the real sample

In order to evaluate the efficiency of fluorescence intensity method for trace analysis of (PPA) drug existing in real samples, the results were compared by standard spectrophotometric methods, and the total amount of the (PPA) drug was estimated (n = 3) (Table. 3). Accordingly, the prepared

fluorescence intensity had a very good performance for determining the (PPA) drug in urine and blood samples [37, 40]. Therefore, determining (PPA) drug in samples done by standard addition method was estimated to be below the detection limit of the related element. Based on the outcomes of replicating analyses for each sample, it was shown that the (PPA) drug retrievals were mainly quantitative with a low RSD. The potentiality of the recommended method for the determination of trace quantities of these elements in distinct samples was proven [40].

Table 3. Recovery of trace (PPA) drug from urine and blood sample after employing presented procedure (n=3).

Samples	Added (µg L^{-1})	Founded (µg L^{-1})	RSD %	Recovery %
Urine hospital Golestan Ahvaz	0.0	0.30	2.6	----
	0.5	0.79	1.5	98.0
Blood hospital Golestan Ahvaz	0.0	0.32	3.6	----
	0.5	0.84	2.3	104.0
Urine hospital Razi Ahvaz	0.0	0.49	2.9	----
	0.5	0.97	1.8	96.0
Blood hospital Razi Ahvaz	0.0	0.74	1.1	----
	0.5	1.25	1.2	102.0

Conclusion

The article focused on measuring the amount of trace (PPA) drug utilizing PbS quantum dots–gelatin nanocomposites sensor, by utilizing glutaraldehyde as a stabilizer sensor. A successful analytical method for measuring (PPA) drug was prosperously developed via a sensitized fluorescence emission with the help of PbS quantum dots–gelatin nanocomposites. The method can be used as an alternative method for (PPA) drug measurement owing to such advantages as excellent selectivity and sensitivity, low cost, simplicity, low detection limit and no need to utilizing organic harmful solvent or extraction. The lowest determining error (PPA) drug could be obtained in a short time, which strongly confirms the greater contribution for the deletion of (PPA) drug by PbS quantum dots–gelatin nanocomposites sensor. On the other hand, some of advantages for this work are listed below:

(I) Fast and clean synthesis without the use of hazardous, toxic and dangerous compounds or surfactants as a highly stable and reusable ecofriendly catalyst under solvent-free condition.

(II) PbS quantum dots–gelatin nanocomposites sensor provides several advantages such as simple, mild condition, easy workup, and excellent yield in a short time.

All these characteristics make PbS quantum dots–gelatin nanocomposites sensor a potential biosensor for drug measurement when juxtaposed against other commercial materials.

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