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Designed a Spectrophotometric Method for the Determination of Acetaminophen Drug Residual after Consumption in Human Fluid Samples by Using Chitosan-Capped Gold Nanoparticles

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Abstract
In this study, we used a prepared from chitosan-capped AuNPs for the determination of trace amount acetaminophen drug in various matrices such human fluids by kinetic spectrophotometric method. The calibration curve was linear in the range of (0.05 to 10.0 µg L^{-1}). The standard deviation of (1.9%), and detection limit of the method (0.05 µg L^{-1} in time 6 min, 325 nm) were obtained for Sensor level response chitosan-capped AuNPs with (95%) confidence evaluated. Observed outcomes confirmed the suitability recovery, and a very low detection limit for measuring the acetaminophen drug. The method introduced to measure acetaminophen drug in real samples such as urine, and blood can be used for other drugs, and hospital samples.

Keywords
Acetaminophen, Chitosan, Human Fluids, Kinetic Spectrophotometric.

1. INTRODUCTION

Determining the amount of drug used in the biological sample is very important to follow the amount of 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 of drugs in real samples [1,2]. Acetaminophen (AP) is a common analgesic, and antipyretic drug purchased for the relief of minor pain such as fever, and headaches. AP has no toxic effect in normal therapeutic doses while large doses particularly with simultaneous consumption of alcohol or other drugs can cause nephrotoxicity, skin rashes, inflammation of the pancreas, and liver disorders [3-5]. In that respect, for tracing one medicament in pharmaceutical, and biological samples, for discerning, and accurate reorganization of species (1-inorganic 2-organic and 3-biomolecules) in different intricate matrices, and determining environmental pollution caused by drugs in pharmaceutical and biological samples attention has been using of spectrometric method, and by sensors metal nanoparticles sensor [6-9].

Due to the profitable application of metal nanoparticles, technologies has taken advantage of nanoscale materials in a variety of fields from chemistry to medicine [10,11]. Recovery of nanoparticles from plant tissue is tedious, expensive, and requires enzymes to destroy plant cellulose tissue. Therefore, used the Small molecular polymer substrates in low processing, and large scale to prepare various metal nanoparticles. In recent years, the use of plant extracts for the preparation of metal nanoparticles has been proposed as an easy and suitable alternative to chemical, and physical methods [12,13]. The forms, sizes, and structures of metallic materials which are extensively linked to their chemical, physical, and optical characteristics, set the ground for successful use of them in technologies. In this respect, the exceptional physical, chemical, and biological properties of AuNPs have been confirmed. This exceptionality arises from the size, form, composition, crystallinity, and structure of AuNPs in comparison with its bulk form [14-16]. The exclusive properties of AuNPs have application in the fields of sensing, medicine, pharmacy, and biomedical engineering varying sizes, and shapes have been utilized in a broad range of applications, and medical equipment, such as electronic devices, paints, coatings, soaps, detergents [17,18].

Herein, chitosan-capped AuNPs with were first synthesized successfully, and utilized for the fabrication of sensitive and specific sensor toward (AP) drug activity with the help $NaBH_4$ as an economic, and effective reducing, and stabilizing

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determining for (AP) drug by sensors operate based on the induced color change from the aggregation of Au nanoparticles after the formation of complex. As shown in (Scheme. 1), AuNPs nanoparticles led to the formation of chitosan-capped AuNPs - (AP) drug assembly in the presence of sodium borohydride. The sensitivity of the chitosan-capped AuNPs platform was significantly enhanced owing to the high absorbing efficiency of chitosan to (AP) drug. Meanwhile, with the combination of the high affinity of (AP) drug with Au as well as the huge specific area of the Chitosan scaffold, the fabricated chitosan-capped AuNPs can reversibly enrich ~95.0% of (AP) drug in real samples [19,20].

This study aimed to find a simple, fast and very sensitive method for identifying and measuring the (AP) drug by chitosan-capped AuNPs sensor. With an initial isolation method to measure this drug, various effective factors such as (pH, (AP) drug concentration, chitosan-capped AuNPs concentration, time Reaction, etc.) on the response of the method, and obtaining the optimal test values, and obtaining the linear range, detection and accuracy of the method presented in the measurement of (AP) drug as well as comparing the performance of the method with routine clinical techniques, and checking the accuracy of the method, and the identification and measurement of (AP) drug by a kinetic spectrophotometric new method in real samples (blood serum). The chemical chitosan-capped AuNPs sensor made it possible as an excellent sensor with reproducibility, good recovery and a very low detection limit for measuring (AP) drug. The method by kinetic spectrophotometric introduced to measure (AP) drug in real samples such as urine, and blood can be used for hospital samples.

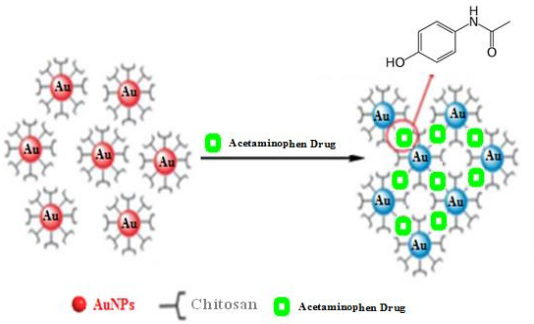

Fig 1. Schematic Illustration of the reaction between (AP) drug and chitosan-capped AuNPs.

2. EXPERIMENTAL

2.1. Reagents and materials

All chemicals including ($HAuCl_4$) (98%), Sodium borohydride ($NaBH_4$) (99%), Chitosan (99%), were provided from Merck Company while acetaminophen (AP) drug (98.0%) from (Razi Company, Iran). Buffer solutions with pH < 7.0 were prepared using 1 mL of boric acid−acetic acid−phosphoric acid (1.0 M), and pH > 7.0 was adjusted by the addition of 0.2 M sodium hydroxide. Double distilled water in the preparation of the solutions.

2.2. Instruments

UV–visible spectra, drugs concentrations were determined and their measurements were done using a Maya Pro 180 spectrophotometer (Shimadzu Company, Japan). Fourier transform infrared spectra (FT-IR) were obtained on a (PerkinElmer FT-IR spectrum BX, Germany). X-ray diffractometer 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.

2.3. Pretreatment of real samples

In a 100 mL beaker, treatment of a 50 mL portion of a human fluids (urine or blood) samples (or a spiked human fluids samples) in hospitals Ahvaz were 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, desired. 5 mL of the obtained clear solution was picked, and the analysis acetaminophen drug by standard addition method procedure [19].

2.4. Synthesis of Chitosan-capped AuNPs

In this regard, the following details of the materials are important to consider in their synthesis: surface property, size distribution, apparent morphology, particle composition, dissolution chitosan-capped AuNPs were Prepared by the Reduction of $HAuCl_4$ with $NaBH_4$ as a modifier according to the method in the literature [29]. Briefly, 10.0 mL Chitosan (2.0 mM) solution was added into the reaction flask that contained 1.0 mL of $HAuCl_4$ (2.0 mM) under vigorous stirring. After 15 min, 1.0 mL of $NaBH_4$ (2.0 mM) added into the above solution at room temperature and stirred for 1 h. UV–Visible spectrum of chitosan-capped AuNPs. The inset picture shows chitosan-capped AuNPs. The dark colloidal solution color was changed to bright yellow, confirming that the formation of chitosan-capped AuNPs. The chitosan-capped AuNPs solution was stored in the dark at 4.0 ± 2.0°C to remain stable for several weeks (Fig. 2).

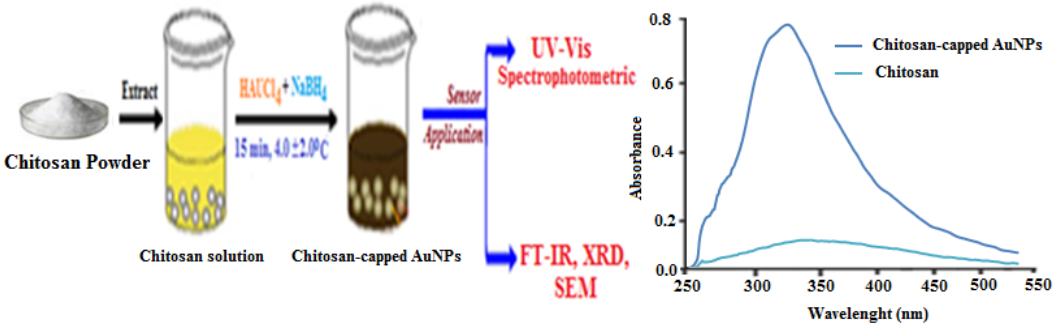

Fig 2. Synthesis of chitosan-capped AuNPs.

2.5. Procedure kinetic Spectrophotometric Detection measurements

The ensuing steps have been considered for a kinetic spectrophotometric method experiment in the current study, at the initial step: Some of the sample solution containing 1 ml of (AP) drug (10.0 µg L^{-1}) was added to a 10 ml volumetric balloon. Then 1 ml of utilizing sodium borohydride as a stabilizer for sensor (2.0×10-2 mol L^{-1}) was added to the flask. By increasing the first drop of 1 ml of chitosan-capped AuNPs solution (2.0×10^{-2} $molL^{-1}$) into a balloon, the reaction start time is recorded by a timer, after 5 seconds from the start of the reaction the solution is stirred for 30 seconds, Subsequently, an adequate amount of the solution was added to a 1 cm cell. Finally through using of UV–visible spectrum (AAb), the measurement of the difference between the quantities of the absorption in wavelength equal to (325 nm) in a time interval (1.0 -6.0 min).

By adding (AP) drug to the solution, it was observed that absorbance kinetic spectrophotometric of the chitosan-capped AuNPs at the wavelength of (325 nm) dropped. At the same time, with the help of spectrophotometry and UV–visible spectrum (AAb), the apparent spectral evolution including the formation of a well-defined isosbestic point at around (325 nm) was estimated. All reaction steps were repeated by increasing the concentration (0.2 µg L^{-1}) of the (AP) drug every 30 seconds. Moreover, the mentioned steps were repeated for a reaction in the absence of (AP) drug (Abs b). Eventually, (Abs a) Abs blank – Abs sample was calculated. The reaction of the (AP) drug by chitosan-capped AuNPs was detected in the acidic medium in its wavelength (325 nm, Fig. 3), demonstrate the absorption spectra in an aqueous solution [21,22].

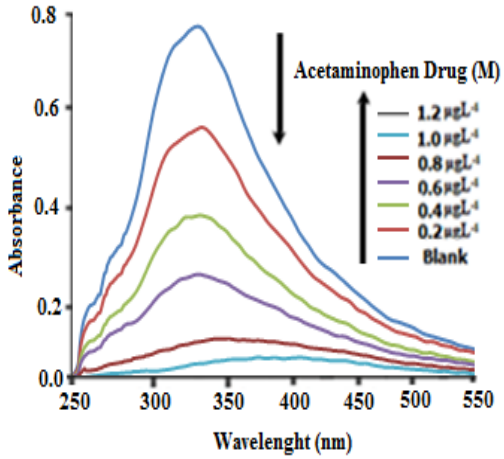

Fig 3. The absorbance chitosan-capped AuNPs by addition of the (AP) drug solution (0.2 µg L^{-1}) at intervals time 30 s.

3. RESULT AND DISCUSSION

3.1. Characterization of sensor

In Fig.4a, the FTIR spectrum of activated carbon prepared from chitosan-capped AuNPs is shown. Additionally, the observed absorption signal at 3451 cm^{-1} points to O-H groups' presence because of the alcoholic or phenolic functional groups. Also, the presence of C-H groups is well proven by the signal observed at 2930 cm^{-1}. Correspondingly, the C=C active group's presence is confirmed by the signal observed 1568 cm^{-1}, the signal at 776.8 cm^{-1} is relevant to the Au-O group of the chitosan-capped AuNPs [23]. Different X-ray emission peaks are chitosan-capped AuNPs shown in (Fig. 4b). The signals at 38.5 (122), 45.0 (111), 52.2 (200), 54.4 (231), and 72.7 (220) are ascribable to diffractions and reflections from the carbon atoms [24]. The perfect crystalline nature of the material was proven after functionalizing with chitosan-capped AuNPs. However, the great intensity of the signal at 45.0 (111) confirmed that there has been a slight amount of material in an amorphous state. The morphological properties of the samples scrutinized by SEM are exhibited. By looking at (Fig. 4c). After surface modification, the chitosan-capped AuNPs became uneven, larger, and bundled [24,25]. EDX (energy-dispersive X-ray spectroscopy) spectrum of the EDX spectrum recorded from a film, after formation of chitosan-capped AuNPs shown in (Fig. 4d) [25].

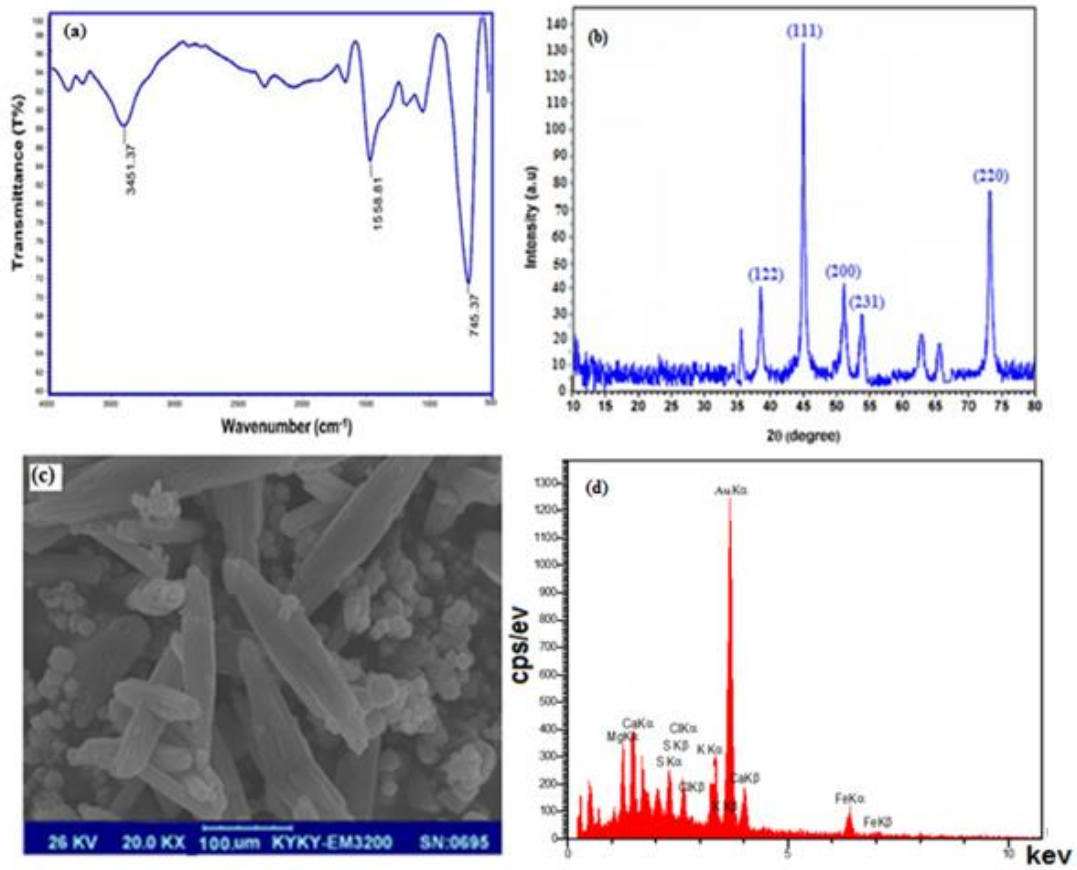

Fig 4. (a) FT-IR transmittance spectrum (b) Different X-ray emission peaks (c) The (SEM) image of the prepared (d) EDX transmittance spectrum are Chitosan-capped AuNPs.

3.2. Optimization of decomposition

It would be interesting to know that in the presence of (AP) drug, there observed a considerable improvement in the effectual colorimetric sensing, and absorbance kinetic spectrophotometric method of the as-prepared chitosan-capped AuNPs. Obtaining an exceptionally sensitive response in detecting (AP) drug rests upon the systematic optimization of pH, chitosan-capped AuNPs, and incubation time.

In this section, the best type of buffer and its volume for maximum absorption (AP) drug with chitosan-capped AuNPs sensor are investigated. To this step, the procedure is as follows: In 10 ml balloons, separately 1 ml of (AP) drug (10.0 µg L^{-1}) and a volume of each type of acetic acid / boric acid / phosphoric acid buffer and then 1 ml of 1 chitosan-capped AuNPs sensor (2.0×10^{-2} mol L^{-1}), 1 ml of utilizing sodium borohydride as a stabilizer for sensor (2.0×10^{-3} mol L^{-1}), to the solution inside the balloon, after (6 minutes), the adsorption reaction of the solutions by the device read a spectrophotometry and UV–Visible spectrum. 1 ml of acetic acid buffer shows the highest percentage for the determination of (AP) drug, so acetic acid / tri chloric acetate buffer (1.0 M) to adjust the pH solution as the optimal buffer.

After measuring the absorbance intensity of the solution, a thorough investigation was carried out on the absorbance pH values in the range of (2-9) for the (AP) drug - chitosan-capped AuNPs complex at (325 nm). A s evident in (Fig. 5a), absorbance kinetic spectrophotometric rapidly on changing the pH from 1.0 to 5.0, while it decreased at pH values higher than 5.0. This phenomenon might be because of the weak complexion at lower pH values (pH <5.0). On the other hand, the reduced response of the proposed chitosan-capped AuNPs sensor for the determining (AP) drug at pH > 5.0 could be due to a possible formation of the hydroxide of (AP) drug in solution. Thus, pH 5.0 was selected as a favorable pH for all subsequent experiments. Concurrently, 1 ml (AP) drug (10.0 µg L^{-1}) solution, 1 ml sodium borohydride (2.0×10^{-3} $molL^{-1}$), and 1ml Chitosan-Capped AuNPs (0.5×10^{-3} to 4.0×10^{-2} mol L^{-1}), were mixed in a volumetric flask 10 ml using distilled water to find out about the impact of chitosan-capped AuNPs sensor on the reaction rate. Again absorbance intensity of solution. The previously mentioned operation has been replicated for blank solution (the solution in the absence of (AP) drug).

The findings are exhibited in (Fig. 5b). Consequently (2.5×10^{-2} mol L^{-1}) based on those findings was determined as the perfect concentration [26,27].

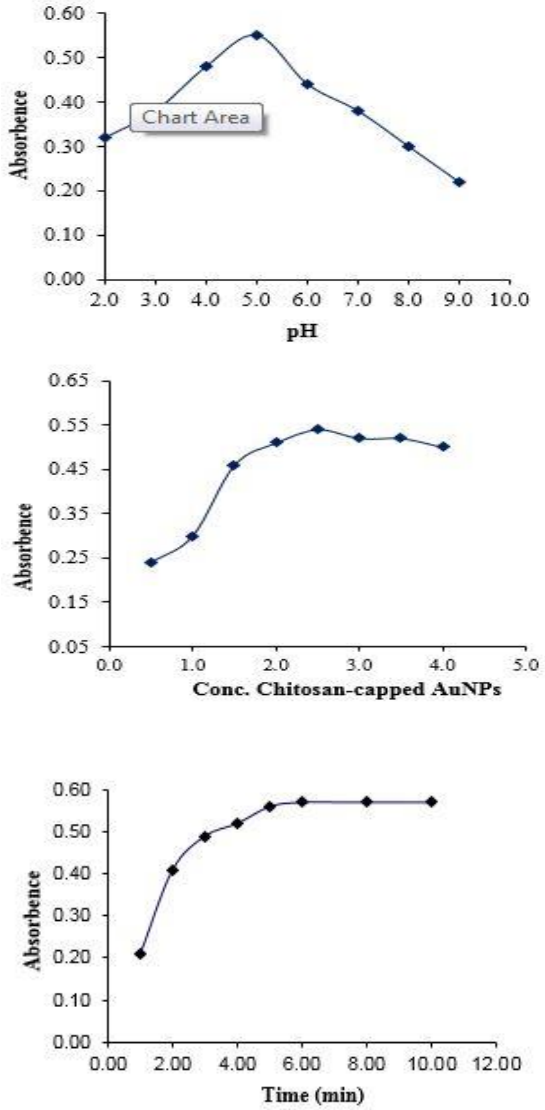

Fig 5. (a) The Effect of pH on the absorbance. (Sample volume, 10 mL: Chitosan-capped AuNPs, 2.0×10^{-2} M, sodium borohydride, 2.0×10^{-3} M, (AP) drug = 10.0 µg L^{-1}, time 6 min, 325 nm) (b) The Effect of chitosan-capped AuNPs concentration on the absorbance. (Sample volume, 10 mL: sodium borohydride, 2.0×10^{-3} M, pH =5, (AP) drug = 10.0 µg L^{-1}, time 6 min, 325 nm) (c) The Effect of time on the absorbance. (Sample volume, 10 mL: Chitosan-capped AuNPs, 2.5×10^{-2} M, sodium borohydride, 2.0×10^{-3} M, pH =5, (AP) drug = 10.0 µg L^{-1}, 325 nm).

To look over the efficacy of sodium borohydride concentration, with a help of volumetric flask 10 ml firstly 1 ml (AP) drug (10.0 µg L^{-1}) solution, 1 ml sodium borohydride with different concentration (0.05 to 3.0×10^{-3}mol L^{-1}), and 1 ml chitosan-capped AuNPs, (2.0×10^{-2}mol L^{-1}) Again after (6.0 min). The decision on desired concentration for sodium borohydride at based on the results to be (2.0×10^{-3} mol L^{-1}). Also, the impact of reaction time on the absorbance spectrum was investigated. Based on (Fig. 5c), it has become apparent that the absorbance intensity enhanced expeditiously, and reached its peak at around 6 min. After 6 min, a relative stability was spotted in the absorbance intensity. Thus, 8 min was determined as the perfect reaction time in this experiment [28,29].

3.3. Measurement of (AP) drug in standard solutions and calibration.

Analytical performance of chitosan-capped AuNPs sensor for determination of (AP) drug. The optimum condition, was recorded for different concentration of (AP) drug onto the chitosan-capped AuNPs. The absorbance kinetic Spectrophotometric peaks with linear range of (0.05–12.0 µg L^{-1}) for (AP) drug, respectively [30,31]. The linear regression equations of (AP) drug and coefficients of determination was y = 0.049C + 0.06 (R^2 = 0.994), respectively. LOD of the modified chitosan-capped AuNPs sensor and (AP) drug was calculated based on three times of standard deviation of the blank signals to calibration slope (3S/m). LODs were calculated (0.05 µg L^{-1}) of (AP) drug, respectively. For individual determination of each analyte, the concentration of (AP) drug was kept constant in (10.0 µg L^{-1}), while concentration of (AP) drug was changed from (0.05 to 12.0 µg L^{-1}) in (Fig. 6).

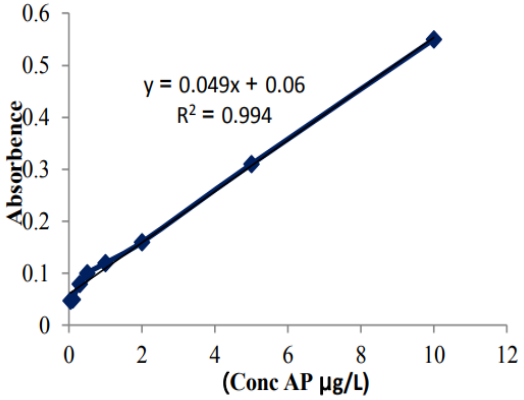

Fig 6. Calibration graph for (AP) drug. (Sample volume, 10 mL: Chitosan-capped AuNPs, 2.5×10^{-2} M, sodium borohydride, 2.0×10^{-3} M, 325 nm).

3.4. Optimum values of parameters

The optimum values of parameters are demonstrated in (Table. 1). The method can be used as an alternative method for (AP) drug 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 (AP) drug
(AP) drug (M)	(10.0 µg L^{-1})
Chitosan-capped AuNPs (M)	(2.5×10^{-2} M)
concentration $NaBH_4$(M)	(2.0×10^{-3} M)
pH	5.0
Equilibration time (min)	(6.0 min)
Linear range (RSD)	(1.9 %)
Detection limit (LOD)	(0.05 µg L^{-1})
Advantages	High repeatability, sensitivity, selectivity, wide linear range

Table 2. Impacts of the matrix medicaments on the retrieving of the examined (AP) drug (n=3).

Drugs	Effects of the matrix drugs (µg L^{-1})
Amoxicillin, Ampicillin, Cyclosporine	500
Sulfacetamide, Epinephrine	200
Tramadol, Methadone	100
Pb^{2+}, Cd^{2+}, Hg^{2+}	200

Table 3. Retrieval of trace (AP) drug from human fluid samples after applying presented procedure (n=3).

Samples	Added (µg L^{-1})	Founded by UV.vis spectrophotometer (µg L^{-1})	HPLC method (µg L^{-1})	Recovery %
Blood	0.0	2.8 ±1.4	2.7 ± 2.3	----
	5.0	7.7 ± 1.6		97.6
	10.0	12.7±1.5		99.0
Urine	0.0	2.9 ± 1.5	3.0 ± 2.3	----
	5.0	8.0 ± 1.8		98.0
	10.0	12.9 ± 1.6		97.7

3.5. Interference Studies

After establishing the measurement method, to evaluate the selectivity of the prepared chitosan-capped AuNPs sensor for determining the (AP) drug, effect of the interaction of different other medications, molecules, and ions in determining the (AP) drug was investigated. The considered limit was considered as the concentration of the annoying species that caused the change intensity of analyte adsorption, more than (5%) of the initial value. To determine the degree of Interference of each species in the measurement of (10.0 µg L^{-1}) solution of (AP) drug, so much was added to this solution of the disturbing species that its absorption intensity changed by 5% compared to the initial absorption intensity [32]. Results is shown in (Table. 2). The results showed that most of the other medications studied did not have much effect on the measurement of (AP) drug and among them, compounds with a more similar structure or with more functional groups are more disturbing, which It may be related to their hydrogen interactions or the molecule of the (AP) drug and thus reduce the measurement of the (AP) drug in the analyte sample. As exhibited in (Table. 2), the tolerance limit was determined as the max concentration of the interfering substance which resulted in an error less than (±5%) for determination of (AP) drug. So, selectivity of the recommended method was proven [33].

3.6. Application of the real sample

In order to evaluate the efficiency of the proposed sensor for determining (AP) drug in real samples,

this chitosan-capped AuNPs sensor was used to measure (AP) drug in urine, and blood human samples according to the instructions mentioned for (AP) drug experiment 3 replicates measuring section [32]. Obtained percentage percentiles in (Table. 3), indicate that the prepared sensor has a very good performance for determining the drug (AP) drug in urine, and blood human samples. Therefore, the determining of (AP) drug in samples was confirmed utilizing standard addition method. The level of the (AP) drug was estimated to be below the detection limit of related element. Based on the outcomes of replicating analyses for each sample, it was shown that the medication retrievals were mainly quantitative with a low RSD [33]. The potentiality of the recommended method for the determination of trace quantities of these elements in distinct samples was proven.

4. CONCLUTION

In this work, chitosan-capped AuNPs were synthesized using sodium borohydride extract as reducing and stabilizing agents. A successful analytical method for measuring (AP) drug was prosperously developed via utilizing a sensitized spectrophotometric with the help of chitosan-capped AuNPs. The method can be used as an alternative method for (AP) drug measurement owing to advantages like excellent selectivity, and sensitivity, low cost, simplicity, low detection limit, and no need in utilizing organic harmful solvent or extraction. The reaction was evaluated by measuring the absorption rate of (AP) drug, the optimum conditions. Which strongly confirms the greater contribution for the deletion of (AP) drug by chitosan-capped AuNPs sensor. The calibration curve was linear in the range of (0.05 to 10.0 µg L^{-1}). The standard deviation of (1.9%), and detection limit of the method (0.05 µg L^{-1} in time 6 min, 325 nm) were obtained for sensor level response chitosan-capped AuNPs with (98.5%) confidence evaluated. The lowest determining error (AP) drug could be obtained in a short time, which strongly confirms the greater contribution for the deletion of (AP) drug by chitosan-capped AuNPs sensor.

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طراحی یک روش اسپکتروفتومتری برای تعیین باقیمانده داروی استامینوفن پس از مصرف در نمونه‌های مایع انسانی با استفاده از نانوذرات طلا با پوشش کیتوزان

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چکیده

در این مطالعه، ما از سنسور نانو ذرات طلا با پوشش کیتوزان برای تعیین مقدار کمی داروی استامینوفن در ماتریس های مختلف مانند مایعات انسانی با روش اسپکتروفتومتری جنبشی استفاده کردیم. منحنی کالیبراسیون خطی در محدوده (۰/۰۵ تا ۱۰/۰میکروگرم در لیتر) بود. انحراف استاندارد (۱/۹ درصد)، و حد تشخیص روش (۰/۰۵ میکروگرم در لیتر، زمان ۶ دقیقه و طول موج ۳۲۵ نانومتر) برای سنسور نانو ذرات طلا با پوشش کیتوزان پاسخ سطح سنسور با اطمینان (۹۵ درصد) ارزیابی شده به دست آمد. نتایج مشاهده شده مناسب بودن روش و حد تشخیص بسیار پایین برای اندازه گیری داروی استامینوفن را تایید کرد. روش معرفی شده برای اندازه گیری داروی استامینوفن در نمونه های واقعی مانند ادرار و خون استفاده شده می تواند برای سایر داروها و نمونه های بیمارستانی مورد استفاده قرار گیرد.

واژه های کلیدی

استامینوفن، کیتوسان، نمونه مایعات انسانی، اسپکتروفتومتری جنبشی.