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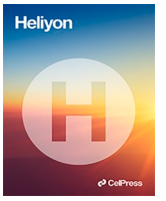

Research article

Utilizing nitrogen, sulfur, phosphorus, and chlorine co-doped carbon dots as a fluorescent probe for determination of vancomycin in exhaled breath condensate

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ABSTRACT

Vancomycin is employed to treat infections caused by gram-positive bacteria. Ensuring precise vancomycin dosages is essential to avoid the emergence of bacterial resistance. In the current study, a fluorescent nanoprobe was designed for vancomycin determination in exhaled breath condensate samples. The nanoprobe was based on carbon dots (CDs) doped with nitrogen, sulfur, phosphorus, and chlorine (NSPCl-doped CDs). Vancomycin significantly reduced the fluorescence of NSPCl-doped CDs and presented a quenching process in the analytical response of the probe within a concentration range of 0.01–2.0 μg mL^{-1} due to forming a non-fluorescent complex. The nanoprobe's intra-day and inter-day relative standard deviations were 1.4 % and 3.2 %, respectively. This nanoprobe was successfully used to determine vancomycin in the patients receiving this drug collected from the expiratory circuit of the mechanical ventilator.

1. Introduction

Vancomycin, the first-ever discovered glycopeptide antibiotic, has been used in clinical settings for approximately 60 years [1,2]. It is used to treat severe bacterial infections caused by gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* and in patients allergic to beta-lactam antibiotics [3]. Vancomycin prevents bacterial synthesis through three main mechanisms. Firstly, it inhibits peptidoglycan synthesis by avoiding adding N-acetylmuramic acid and N-acetylglucosamine to the peptidoglycan in the cell wall. Secondly, it changes cell membrane permeability. Finally, it interferes with RNA synthesis in the cytoplasm [4]. Vancomycin rapidly distributes throughout the body after injection, achieving therapeutic concentrations in the heart, lungs, synovial fluid, bone, peritoneal fluid, and kidneys [5]. The therapeutic concentration range for this drug in plasma and serum samples is 5.0–40 μg mL^{-1}.

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This antibiotic has a narrow therapeutic range, where the effective concentrations are close to toxic concentrations. Insufficient drug concentration can lead to bacterial resistance, while high concentration can cause harmful effects like fever, red man syndrome, nephrotoxicity, ototoxicity, phlebitis, and toxic epidermal necrolysis [6]. Therefore, its therapeutic drug monitoring in body fluids is essential to personalize dosage and maintain effective therapeutic ranges [7]. Several methods have been developed to quantify vancomycin in pharmaceutical and biological samples, including chemiluminescence [8], spectrofluorimetry, UV spectrophotometry [9], chromatographic techniques such as liquid chromatography (LC)–mass spectrometry (MS) [10,11], HPLC-UV [12,13] and capillary electrophoresis [14]. Although these developed methods have their advantages and disadvantages, developing a new and easy-to-use method for measuring drug concentrations in biological samples is a challenging issue for researchers. Fluorescence-based optical techniques are popular for being easy to use, responsive, and inexpensive in point-of-care devices [15–17]. However, this method suffers from sensitivity and selectivity, which can be compensated by employing nanomaterials.

Recent advancements in nanotechnology have led to the development of nanostructures that possess superior physicochemical properties such as controlled fluorescence, high yield, stability, good solubility, low toxicity, and biocompatibility. These properties have made them widely popular in the sensor design [18,19]. Carbon dots (CDs) are zero-dimensional carbon nanomaterials with sizes less than 10 nm and spherical shape. They contain various surface functional groups and were first discovered in 2004 during the isolation and purification of single-walled carbon nanotubes [20]. CDs are considered one of the most promising nanomaterials for fluorescence probes and sensors due to their outstanding fluorescence property, biocompatibility, low toxicity, stability, efficiency, and solubility [21]. The excellent electronic properties of CDs, as electron donors and acceptors, offer a wide range of possibilities in catalysis and sensing applications [22]. It should be noted that doping with heteroatoms such as boron, sulfur, nitrogen, or phosphorus enhances the fluorescence properties of CDs, increasing their quantum yield and expanding their potential applications [23]. Some of these applications are the determination of tobramycin in milk using N-doped CDs [24], determination of R-/S-mandelic acid using N-doped CDs [25], determination of copper and etidronate disodium using N, S-doped CDs [26], determination of tigecycline using F, N codoping CDs [27], determination of three N-substituted phenothiazine derivatives in dosage forms using S and N co-doped CDs [28] and so on.

This study aims to synthesize CDs doped with four heteroatoms nitrogen (N), sulfur (S), phosphorus (P), and chlorine (Cl) as a sensing platform for the determination of vancomycin in exhaled breath condensate (EBC) samples collected from the expiratory circuit of the mechanical ventilator (MVEBC) as a non-invasive biological sample [29]. EBC is a type of biological sample that is a condensed form of tiny droplets of lung lining fluid that are exhaled during normal breathing [30]. It contains fewer interfering substances compared to other matrices, such as blood, plasma, urine, and sputum, allowing for direct injection into analytical instruments [31].

2. Experimental

2.1. Reagents and solutions

Ethylene diamine (EDA, $C_2H_8N_2$, Sigma Aldrich), glucose ($C_6H_{12}O_6$, Merck, Germany), phosphoric acid (H_3PO_4, Merck, Germany), sulfuric acid (H_2SO_4, Sigma – Aldrich, USA), hydrochloric acid (HCl, Merck, Germany), and ultrapure deionized water (Shahid Ghazi Pharmaceutical Company, Iran) were used in the synthesis of nitrogen, sulfur, phosphorus, and chlorine-doped carbon dots (NSPCl-doped CDs). To prepare the buffer, we used sodium dihydrogen phosphate (NaH_2PO_4, Merck, Germany) and adjusted different pHs with hydrochloric acid (HCl) and sodium hydroxide (NaOH, Merck, Germany). Vancomycin used in the experiment was purchased from Daana Pharmaceutical Company, located in Tabriz, Iran. A solution of vancomycin with a concentration of 1 g L^{-1} was prepared by dissolving the required amount of drug powder in deionized water. The solution was then stored in a refrigerator at a temperature of 4 $^{\circ}$C, away from light. Daily working solutions of vancomycin were prepared by diluting the standard solution with deionized water.

2.2. Instruments and apparatuses

The fluorescence spectra were analyzed using a Jasco FP 750 spectrofluorometer, which was equipped with a xenon lamp source for excitation. A standard 1 mL quartz cell was employed to record the spectral data, with bandwidths set to 10 nm in both the excitation and emission paths. The pH level was adjusted using a digital pH meter, specifically a model 744 from Metrohm Ltd. Attenuated Total Reflectance-Fourier Transform Infrared (ATR-FT-IR) spectroscopy was conducted using the Bruker Tensor 27 instrument, involving the KBr wafer technique, to verify the chemical bonding of the nanoparticles. The spectral range of the FT-IR analysis spanned from 4000 to 400 cm^{-1}. Furthermore, transmission electron microscopy (TEM) was employed using a Philips instrument to examine the shape and size of the prepared nanoprobe. The EDX analysis was carried out by MIRA3 FEG-SEM (Tescan, Czech). MVEBC samples were collected from the expiratory circuit of an Inspiration 5iVentilator (eVent Medical Ltd, Lake Forest, CA 92630, USA). Additionally, EBC samples were obtained from a healthy volunteer using a custom-made setup [32].

2.3. Synthesis of NSPCl-doped CDs

Initially, 0.1 g of glucose and 6 mL of EDA were added to a 100 mL beaker and stirred for 10 min. After that, 1.5 mL of 70 % H_2SO_4, 1.5 mL of concentrated H_3PO_4 and 1.5 mL of concentrated HCl were added to the beaker content, respectively. As a result, a dark brown viscous substance was produced due to the neutralization of acid-base and an exothermic carbonization process of glucose. After cooling to room temperature, the dark brown viscous substance was dissolved in double-distilled water and a brown solution was

obtained. After centrifugation at 8000 rpm for 15 min, the supernatant containing the synthesized NSPCl-doped CDs was collected and stored in a dark place away from sunlight at 4 °C.

2.4. Samples preparation

The solutions utilized in this project were prepared using high-purity chemicals and deionized water. Working standard solutions were freshly prepared each day by diluting the requisite amounts of existing standards with deionized water. A lab-made device was employed to collect EBC samples, specifically designed for collecting exhalations [32]. This device features a cooling trap that enables temperature control from 0 °C to −25 °C. The device rapidly cools the air, condenses water vapor, and removes particles from the trap's surface, allowing for direct analysis without additional processing. Samples were collected from healthy volunteers for method optimization and calibration purposes. For the real sample study, newborns or premature babies under mechanical ventilation were selected as subjects and tracheal aspirates (MVEBC) were collected from the ventilator waste. Written informed consent was obtained from one parent of each sample donor, approved by the Ethics Committee of Tabriz University of Medical Sciences with the code IR.TBZMED.PHARMACY.REC.1402.068.

2.5. General procedure

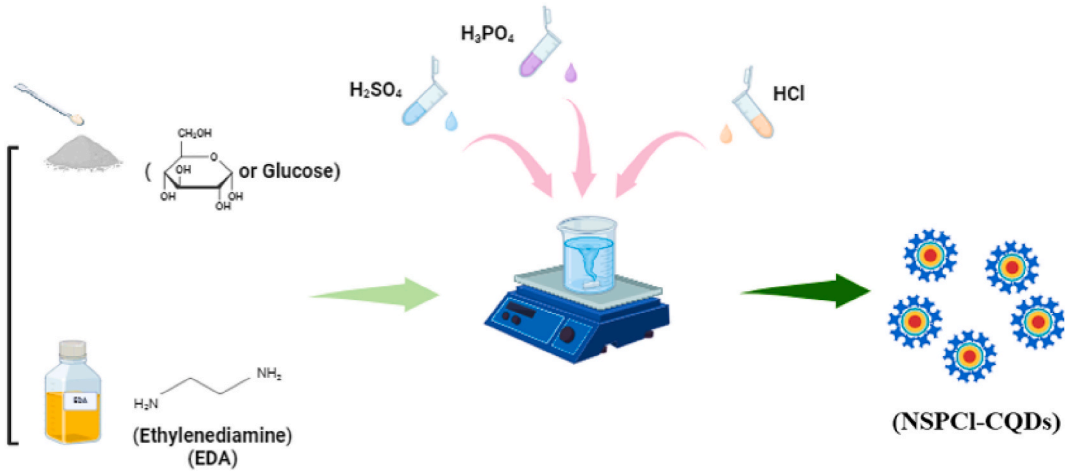
A diagnostic analysis was performed in a 2 mL microtube. The microtube was filled with 10 μL of phosphate buffer (pH 6.0, 0.1 mol L^{-1}) and 100 μL of EBC spiked with various concentrations of vancomycin. A 15 μL volume of NSPCl-doped CDs was added to the mixture, and the solution was then diluted to a final volume of 0.5 mL with deionized water. The mixture was incubated for 5 min. The fluorescence intensity was measured at around $\lambda_{max} = 496$ nm after being excited at 380 nm. In this system, the analytical response was determined by calculating the difference between the probe signal in the presence and absence of vancomycin, denoted as ΔF (F–F_0), where F and F_0 represent the probe fluorescence signal in the presence and absence of vancomycin, respectively. All the experiments were conducted three times at room temperature.

3. Results and discussions

3.1. Characterization of the NSPCl-doped CDs

A spectrofluorimetric sensing nanoprobe based on NSPCl-doped CDs was developed to quantify vancomycin in EBC samples. Scheme 1 outlines the synthesis pathway of NSPCl-doped CDs, produced through an acid-base neutralization and exothermic carbonization process. In this system, glucose was used as the carbon source, and EDA, H_2SO_4, H_3PO_4, and HCl were utilized as N, S, P, and Cl dopants to prepare NSPCl-doped CDs. These reagents not only provide sufficient heat for the carbonization reaction, but also function as dopants, introducing additional elements into the system [33].

The size and shape of the as-prepared nanomaterials were investigated using TEM analysis. As illustrated in Fig. 1A, it was evident that the NSPCl-CDs exhibit nearly uniform and spherical shapes with individual particle sizes lower than 10 nm. Additionally, ATR-FT-IR spectroscopy was performed to obtain further evidence of the successful synthesis of NSPCl-doped CDs (Fig. 1B). The O-H/N-H stretching was represented by distinct peaks at 3200–3500 cm^{-1} and 2824 cm^{-1}, while the CON-H stretching was represented by a peak at 1539.7 cm^{-1}. The S-H (2591.7 cm^{-1}), P=O (1205.2 cm^{-1}), C-S (1112.9 cm^{-1}), P-O-C (1004.5 cm^{-1}), P-OH (813.8 cm^{-1}), and C-Cl (614.7 cm^{-1}) was confirmed the surface-functionalized groups of carboxyl (COOH), amino (NH_2), amide (CONH), thiol (CS),



Scheme 1. Graphical illustration of the synthesis process of NSPCl-doped CDs by acid-based neutralization and exothermic carbonization method.

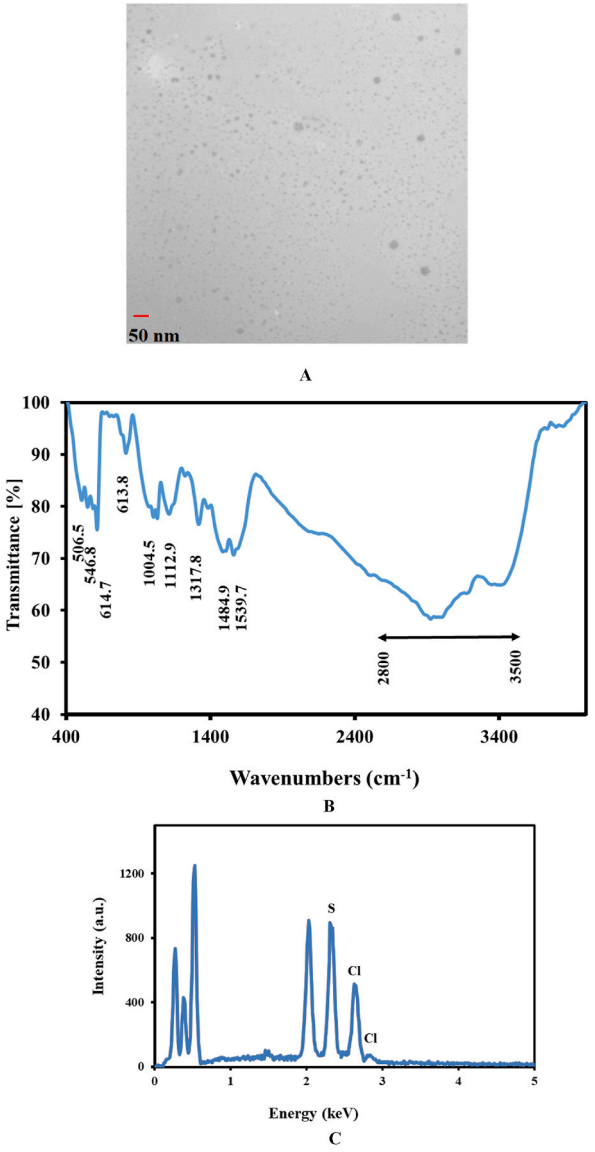


Fig. 1. Characterization study: (A) TEM image; (B) ATR-FT-IR and (C) EDX analysis of NSPCl-doped CDs.

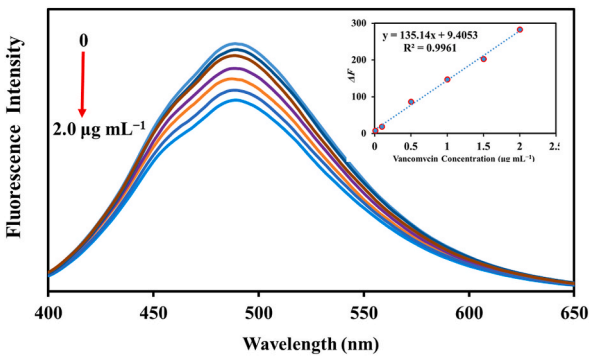


Fig. 2. Fluorescence spectra of the NSPCl-doped CDs probe in the absence and presence of different concentrations of vancomycin: (0.01–2.0 µg mL^{-1}) in EBC sample. Inset: calibration curve. Conditions: pH 6.0, CDs volume of 15 µL, and incubation time of 5 min λ_{ex} = 380 nm.

phosphine oxide (P=O), and chloromethyl (C-Cl). The information in Fig. 1 suggested that NSPCl-doped CDs have been successfully synthesized according to the previous report [33]. Furthermore, the successful synthesis of the NSPCl-CDs was verified by EDX analysis, which revealed the chemical composition. Fig. 1C illustrates the distribution of C, O, P, Cl, N, and S elements, providing conclusive evidence of the probe's successful formation.

3.2. Detection mechanism

After the successful synthesis of NSPCl-doped CD, its response and performance by gradually adding different concentrations of vancomycin to investigate the interactions between the analyte and the nanoprobe. The results showed that the nanoprobe exhibited a distinct peak at 496 nm; when vancomycin was added, the fluorescence intensity of the nanoprobe decreased, indicating an interaction between vancomycin and the NSPCl-doped CD (Fig. 2). The vancomycin molecule interacts with the NSPCl-doped CD through a combination of π-π stacking, electrostatic, and hydrogen bonding interactions. Vancomycin's planar structure and the aromatic rings on the carbon dots could engage in π-π stacking interactions, which are weak attractive forces between delocalized electrons [34]. The amino acid residues with positively charged amine (-NH_2) groups on vancomycin are attracted to the negatively charged functional groups on the NSPCl-doped CD surface, such as carboxyl (-COOH), sulfonate (-SO_3H), and phosphate (-PO_3H_2) groups [35]. Furthermore, the -N and -O containing functional groups on vancomycin are capable of forming hydrogen bonds with the corresponding -N, -S, and -O groups on the CD surface [36]. This interaction led to the formation of a non-fluorescent complex which showed a decrease in the fluorescence intensity of NSPCl-doped CDs. The decrease in fluorescence intensity was directly related to the amount of vancomycin added, suggesting a novel method for monitoring vancomycin levels in the EBC samples.

The fluorescence quenching mechanism was investigated using Stern-Volmer plots, which involved graphing the fluorescence intensity ratio (F_0/F) against the quencher concentration, as described by the equation.

$$\frac{F_0}{F} = 1 + K_{sv}[Q] \tag{1}$$

Where F_0 and F represent the fluorescence intensity in the absence and presence of the quencher, respectively, K_{SV} is the Stern-Volmer constant, and $[Q]$ is the quencher concentration. Stern-Volmer plots can exhibit both static and dynamic quenching modes [37]. A linear Stern-Volmer plot suggests dynamic quenching, where the quencher's primary effect is to increase collisional interactions with the fluorophore, leading to efficient energy transfer. An upward/positive deviation in the Stern-Volmer plot can indicate the presence of both static and dynamic quenching mechanisms, which contribute to the decrease in fluorescence intensity. The upward trend in Fig. 3 supports the occurrence of static quenching or complex formation between the fluorophore and quencher, indicating a non-fluorescent ground-state complex.

"Furthermore, the absorption spectra of the NSPCl-doped CD probe in the absence and presence of vancomycin (Fig. 4) provide additional evidence for the interaction between the probe and vancomycin. The shift in the peak position of the probe's absorption spectrum suggests that a non-fluorescent complex is formed, supporting the conclusion of a static quenching mechanism.

3.3. Optimization of the parameters affecting the probe performance

In this step, the effects of key variables such as pH, NSPCl-doped CD nanoparticle concentration, and reaction time were evaluated to maximize the analytical response of the system and achieve optimal detection of vancomycin. Vancomycin with a concentration of 1.0 μg mL^{-1} was used for the optimization procedure. At first, the effect of pH changes in the range of 3.0–11.0 was tested on the response of the probe (Fig. 5A). It was observed that the system had the highest response at pH 6.0 due to the high affinity of positively charged amine (-NH_2) groups on vancomycin in relatively acidic media to the negatively charged functional groups on the NSPCl-doped CD surface [36]. Therefore, pH 6.0 was chosen as the optimal value for the following experiments. In the following, the impact of NSPCl-doped CDs amount on the analytical response was studied in the range of 1–20 μL (Fig. 5B). After analyzing the obtained data, it was observed that the intensity of the fluorescence peak decreased above 15 μL of CDs volume which can be related to

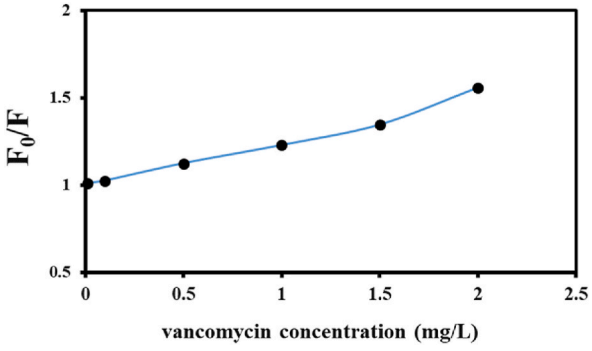


Fig. 3. Stern–Volmer plot for the quenching of NSPCl-doped CD probe by vancomycin.

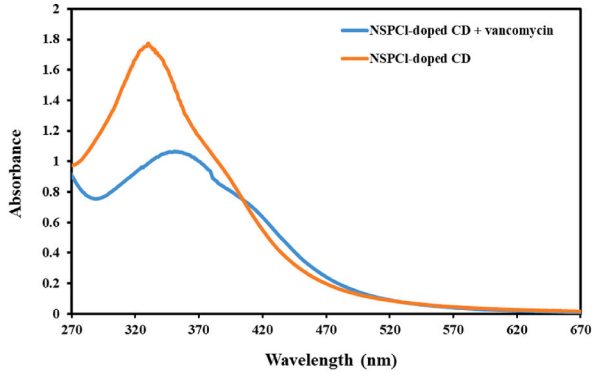


Fig. 4. Absorption spectra of the NSPCl-doped CD probe in the absence and presence of vancomycin.

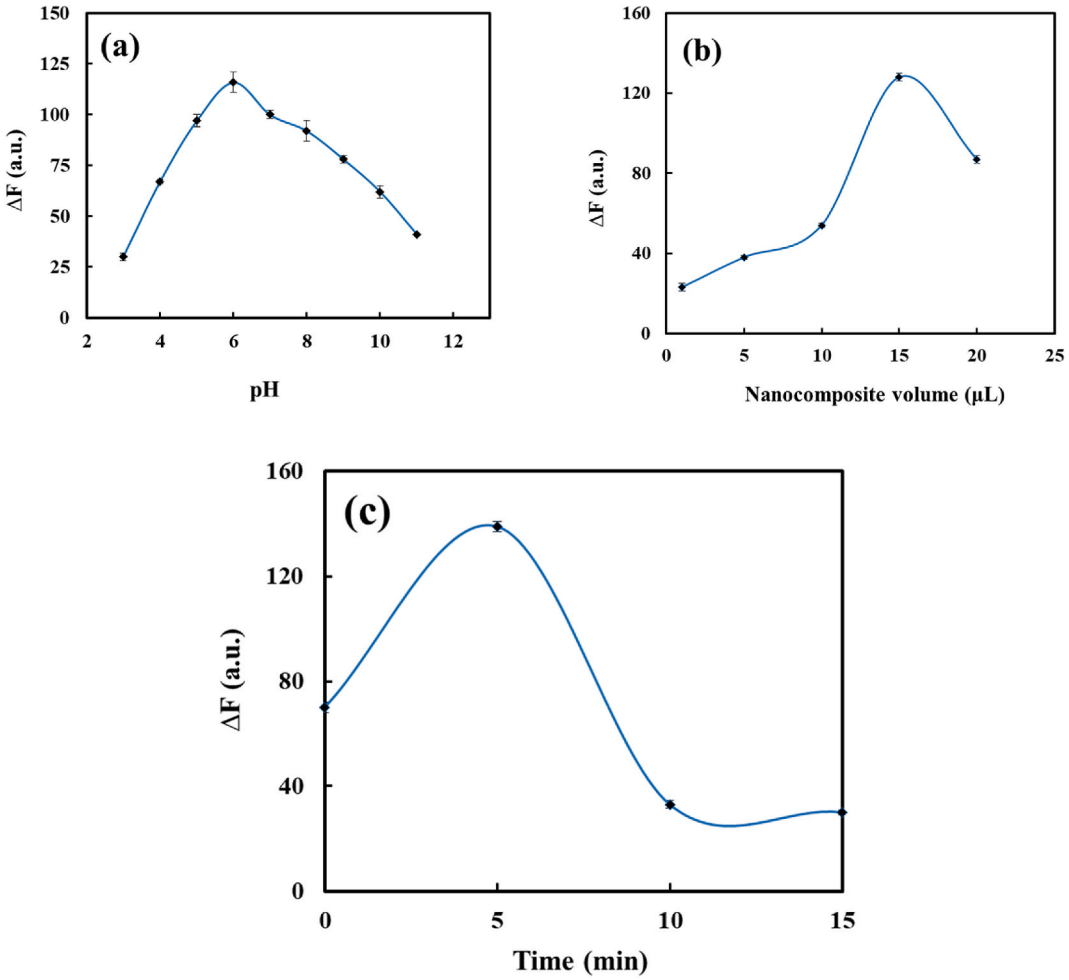


Fig. 5. Optimization procedure for investigation of the effect of (a) pH, (b) NSPCl-doped CDs concentration, and (c) reaction time on the response of nanoprobe.

the probe self-quenching process at high concentrations. Consequently, 15 µL was the optimal value for the upcoming experiments. Finally, the incubation time was investigated at a time range of 0–20 min, and the response of the system in 5 min showed the most significant value (Fig. 5C). In summary, the optimized reaction conditions were: pH 6.0, CDs volume of 15 µL, and incubation time of 5 min.

3.4. Analytical figures of merit

To assess the analytical performance of vancomycin determination in EBC samples, the calibration curve, limit of detection (LOD), accuracy, and precision were evaluated and optimized under optimal conditions, ensuring reliable and precise measurement of vancomycin concentrations. The calibration curve displayed a robust linear relationship for vancomycin within the concentration range of 0.01–2 μg mL^{-1} (Fig. 2). The equation for the regression line was expressed as $\Delta F = 135.14\ C_{Van} + 9.4053$. In this equation, the variable ΔF represents the difference in fluorescence intensity in the absence and presence of vancomycin, while C_{Van} represents the vancomycin concentration in μg.mL^{-1} unit. The value for LOD is established as $3S_b/m$ which S_b denotes the standard deviation of the blank, while m represents the slope of the calibration curve. LOD for the developed method was reported to be 0.005 μg mL^{-1}. The results of five replicate analyses of 1.0 μg mL^{-1} vancomycin on the same day and on different days showed relative standard deviations (*RSDs*) of 1.4 % and 3.2 %, respectively. To compare the capabilities of our method with other reported methods for analyzing vancomycin, the relevant data about some previously developed methods from the literature were collected and presented in Table 1. Our method stood out for its excellent and comparable analytical features compared to other reported methods.

3.5. Investigation of interferences

Analyzing drugs in complex biological samples such as EBC, plasma, and serum can be problematic due to the presence of numerous interfering substances, which can compromise the accuracy and reliability of the results [8]. The selectivity of the developed probe was evaluated in the presence of common interfering substances, including prescribed or over-the-counter drugs. This study examined the effects of various available drugs, including nicotinamide, clonazepam, celecoxib, amoxicillin, diltiazem, ibuprofen, amikacin, pantoprazole, diazepam, losartan, caffeine, chlordiazepoxide, tobramycin, paracetamol, oxazepam, gentamicin, aspirin, and naproxen. For this purpose, we investigated the effect of each intervening compound with a concentration twice as high as the desired analyte (where the vancomycin concentration was 1.0 μg mL^{-1} and the interfering compounds were 2.0 μg mL^{-1}) on the response of the system under optimal conditions. Based on the provided Fig. 6, it can be observed that the most studied species had no significant impact on the response except for amikacin, gentamicin and caffeine. This suggested that the newly developed nanoprobe had acceptable selectivity for detecting vancomycin in real samples. About the interfered drugs, it can be said that the method may not be accurate in quantifying the amount of vancomycin present. To overcome the challenges posed by interfering substances, innovative separation and extraction methods can be developed to improve the detection and quantification of drugs in complex biological samples, thereby enhancing the overall analytical performance. However, the results showed a relatively good selectivity in detecting vancomycin in the presence of other co-administered available medicines.

3.6. Real samples analysis

The efficiency and ability of the developed probe toward vancomycin detection were evaluated by analyzing four MVEBC samples collected from newborns or premature babies under mechanical ventilation and receiving vancomycin. Table 2 displayed the outcomes of the analysis of real samples. To account for potential matrix effects, a standard addition approach was used to correct for any interference from the sample matrix, ensuring accurate and reliable measurements. Analysis of the data revealed that the concentrations of vancomycin in the patient's samples ranged from 0.14 to 0.31 μg mL^{-1}.

4. Conclusion

In this study, a fluorescent nanoprobe based on NSPCl-doped CDs has been designed for the quick, precise, and sensitive detection of vancomycin in EBC samples. It revealed that the fluorescence intensity of the nanoprobe decreased in a concentration-dependent manner as the level of vancomycin in the sample was increased. A significant linear relationship was found between the fluorescence intensity and vancomycin concentration, with a strong correlation observed over a range of 0.01–2 μg mL^{-1}. The method exhibited excellent precision, with low intra-day and inter-day variations of 1.4 % and 3.2 %, respectively. Overall, the NSPCl-doped CDs demonstrated outstanding potential for detecting vancomycin in clinical settings.

Ethical approval and consent to participate

All sample donors or participants filled out and signed the informed consent of project with ethical code IR.TBZMED.PHARMACY.REC.1402.068 confirmed by the ethics committee at Tabriz University of Medical Sciences verified.

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Data availability statement

Data will be made available on request.

Table 1
Comparison of analytical features of the developed system with other literature methods for the determination of vancomycin.

Method	Sample	LOD (μg.mL^{-1})	Linear range (μg.mL^{-1})	Reference
Spectrophotometry	Lyophilized powder	0.72	50–150	[38]
Spectrophotometry	Human serum	0.99	12.5–200	[39]
UV- Spectrophotometric	Pharmaceutical preparations	–	20–100	[40]
Synchronous spectrofluorimetry based on copper nanocluster	EBC	0.06	0.1–8	[41]
Immunoassay method	Cerebospinal fluid	0.4	0–15	[42]
HPLC-UV	Human plasma	–	1–100	[12]
UHPLC-UV	Human serum	–	2.5–120	[13]
LC-MS	Human serum	0.001	0.05–10	[43]
UHPLC–MS/MS	Human plasma	–	1–100	[44]
Spectrofluorimetry based on NSPCl-doped CDs	EBC	0.005	0.01–2	This work

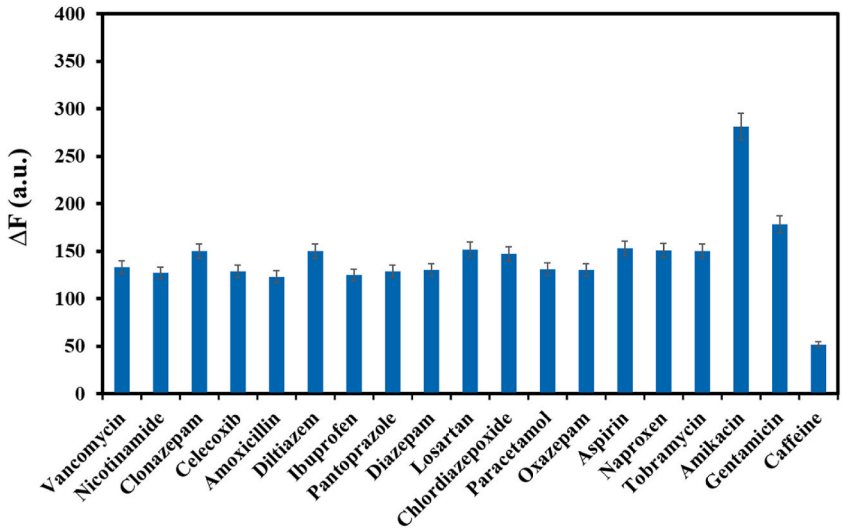

Fig. 6. The study of method selectivity in the presence of interferences (some possible over-the-counter or co-administrated drugs). Vancomycin concentration was 1.0 μg mL^{-1} and the interfering compounds were 2.0 μg.mL-1.

Table 2
Vancomycin analysis using the validated probe in MVEBC samples.

No.	Gender	Receiving dosage (mg)	Co-administrated drugs	Concentration (μg.mL^{-1})
1	Male	58	–	0.31 ± 0.05
2	Male	32	Calcium	0.16 ± 0.08
3	Male	25	Total parenteral nutrition solution	0.14 ± 0.03
4	Male	32	Calcium, Paracetamol, furosemide, Milrinone infusion, Dopamine	0.29 ± 0.04

CRediT authorship contribution statement

Kosar Shirazi: Writing – original draft, Investigation. **Zahra Karimzadeh:** Writing – original draft, Investigation. **Mohammad Bagher Hosseini:** Resources. **Vahid Jouyban-Gharamaleki:** Methodology. **Maryam Khoubnasabjafari:** Methodology. **Jafar Soleymani:** Methodology. **Elaheh Rahimpour:** Writing – review & editing, Supervision, Data curation. **Abolghasem Jouyban:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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