CARBON QUANTUM DOTS FROM CARROT AS FLUORESCENCE PROBES FOR HIGH-SENSITIVITY DETECTION OF LIDOCAINE

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Abstract. In this article, a simple and effective carbon quantum dots (CQDs) was designed by one-step hydrothermal method from common vegetable carrots. This carbon quantum dots solution was used as a probe with excellent fluorescence properties for the analysis of local anesthetic lidocaine, and it obtained better recoveries and detection effects in real sample spiked recovery experiments, with a limit of detection of 20.52 nM, a linear detection range of 0.25-50 mM, and the recovery of 82.7-101.3% in actual samples. Highly fluorescence of carrot-CQDs were quenched by lidocaine with inner filter effect. The morphology of the carrot-CQDs and the surface functional groups were characterized using transmission electron microscopy, Fourier transform infrared spectroscopy, X-ray photoelectron spectroscopy, ultraviolet-visible spectroscopy and fluorescence spectrophotometry. The CQDs exhibited good acid and alkali resistance, salt resistance, and photobleaching resistance under different conditions. Therefore, it provided a new insight on the detection of lidocaine by the carrot-CQDs as nanosensors.
Keywords: *carbon nanomaterial, biomass, inner filter effect, nanosensors, pharmaceutical analysis*

Introduction

Lidocaine is a local anesthetic and antiarrhythmic drug. It is a derivative of cocaine, but it contains no hallucinogenic and addictive component of cocaine (Chagas et al., 2020). The hydrochloride salt of lidocaine is a white crystalline powder, which is extremely soluble in water, and its toxicity is equivalent to that of procaine. However, the local anesthetic effect is strong and lasting, and has good surface penetration. It can be injected or used as surface anesthesia (Krishnakumar et al., 2022). It generally takes effect 1–3 min after application, and the effect lasts for 1–3 h. It is used to treat oral ulcer. As an arrhythmia drug, it is not often used because some people worry that it will have long-term side effects. A few people are allergic to lidocaine. It was used to treat arrhythmia in 1963. It is a drug for preventing and treating acute myocardial infarction and various heart diseases complicated with rapid ventricular arrhythmia. It is the first choice for the treatment of ventricular premature beats, ventricular tachycardia and ventricular fibrillation in acute myocardial infarction (Kaszyński et al., 2022; Jin et al., 2022). Lidocaine is mainly used as drug for local anesthesia. Generally, 2%~4% of the solution for surface anesthesia generally does not exceed 100 mg, and the amount of the drug injected once does not exceed 4.5 mg/kg body weight or 7 mg/kg body weight.

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The use of local anesthesia has an important role in medical processes, such as avoiding pain, alleviating toothache, and performing painless gastroscopy during small clinical operations. At present, the adverse reactions of local anesthetics mainly involve local anesthetic allergy, tissue and neurotoxicity, and cardiac and central nervous system toxicity. The factors involved include traumatic injection methods, excessive drug concentrations, malabsorption, and other mechanical factors that can cause macroscopic or microscopic tissue damage. Therefore, in medical and daily life, it is necessary to test the content of residual local anesthesia in the body, which can provide qualitative basis for solving medical accidents and criminal cases. Excessive lidocaine can cause optic neuritis, dizziness, nausea, vomiting, fatigue, language confusion, sensory abnormalities, muscle tremors, convulsions, confusion, and respiratory depression. It was also discovered that lidocaine was illegally added to cosmetics, making people unable to feel the skin pain caused by sunlight, if cosmetics or pharmaceutical preparations added with lidocaine were thrown into the environment or water, it would bring great harm to humans or animals, it is necessary to reduce or discontinue the medication (Agarwal et al., 2022; Matos et al., 2022). So, it is very important to find a fast, efficient and sensitive method for the analysis of lidocaine in clinical tests.

At present, the main quantitative methods to detect lidocaine are HPLC (Bhusal et al., 2017; Qin et al., 2010), LC/MS/MS (Leung et al., 2007; Kwok et al., 2010), GC (Koster et al., 2000), GC/MS (Watanabe e al., 1998), CE (Junger and Daniel, 2019; Chik et al., 2007) and fluorescence spectrometry (Zhang et al., 2018), etc. Among them, chromatographic analysis technology is widely used and is also the default standard detection method at home and abroad. However, spectral analysis technology is a fast and convenient detection method rising in recent years, and also has great research value.

CQDs are novel nano carbon materials that are composed of dispersed spherical carbon particles with extremely small dimensions (below 10 nm) and have fluorescence properties (Thangadurai et al., 2022). CQDs have many merits, such as excellent optical properties, wide source of raw materials and good biocompatibility (Algarra et al., 2019). Since the first discovery of CQDs in 2004, many synthesis methods have been developed, including arc discharge, laser ablation, chemical oxidation, microwave synthesis, template method, and so on (Thakur et al., 2014). CQDs have wide range of applications in environmental monitoring, chemical analysis, and so on (Huang et al., 2012; Liu et al., 2014; Hsu et al., 2017), environmental monitoring (Hou et al., 2015, 2017; Xiao et al., 2013), chemical analysis (Huang et al., 2013; Lim et al., 2015; Liu et al., 2016), catalyst preparation (Li et al., 2011; Fernando et al., 2015), energy development and so on (Wang and Hu, 2014; Jia et al., 2012; Wang et al., 2011). According to literature reports, common foods such as vegetables (Niu et al., 2015; Jin et al., 2017) and fruits (Miao et al., 2016; Ding et al., 2017) are used as precursor materials for the preparation of CQDs. In this study, carrots are rich in antioxidant vitamins, quercetin, potassium succinate, and other components, so it is a potential precursor for the preparation of CQDs.

Herein, carrot-CQDs are prepared by one-step hydrothermal method, and it have good water solubility and fluorescence properties. The fluorescence of carrot-CQDs can be effectively quenched by lidocaine through inner filter effect. Moreover, the fluorescent probe has been successfully used in the detection of actual samples and achieved good detection results. Therefore, the probe is a promising medical detection method for lidocaine.

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Experimental

Reagents and instruments

All chemical reagents were purchased from Shanghai Mai Ruier Chemical Technology Co., Ltd. (China), including lidocaine, azithromycin, vitamin B_6 hydrochloride, norfloxacin, roxithromycin, enrofloxacin, lincomycin, phosphate and ethylenediamine, which were all analytical grade. Carrots were purchased from the farmers' market near the school.

All optical measurements were made at room temperature. The fluorescence spectrum was measured on F2700 fluorescence spectrophotometer, and the absorption spectrum was recorded on Cary50 UV-visible spectrophotometer. The experimental water was prepared by the laboratory pure water ultra-pure water system (UPT-II-40L, China). The experimental operation was completed at room temperature.

Preparation of carrot-CQDs

The CQDs were obtained by one-step hydrothermal method with carrots as carbon material. The 5.0 g carrots powder and ethylenediamine were dissolved with 50 mL deionized water and then transferred to a 100 mL high-pressure autoclave for reaction at 200°C for 8 h. The product was cooled naturally, centrifuged (4000 g, 30 min), filtered by 0.22 μm filter membrane, and stored (4°C).

Fluorescence detection of lidocaine

Typically, 40 μL of purified carrot-CQDs solution was added with different concentrations of lidocaine solution 1 mL, and then diluted to 5.0 mL with distilled water. The fluorescent value of carrot-CQDs was measured on the fluorescence spectrophotometer with the slit width of 10 nm at 4 min. In order to estimate the coexisting interference, the selectivity of carrot-CQDs towards various substances, such as lidocaine, azithromycin, vitamin B_6 hydrochloride, norfloxacin, roxithromycin, enrofloxacin and lincomycin, was determined.

Cell toxicity

The cytotoxicity of carrot-CQDs was evaluated by 3-(4, 5-dimethylthiazole-2)-2, 5-diphenyltetrazolium bromide (MMT) method. Weigh 0.5 g of MTT and dissolve it in 100 mL of PBS to prepare MTT solution (5 mg/mL), 0.22 μM filter and store in dark at 4°C. U2OS and HT29 were cultured in 96-well plates respectively, and the carrot-CQDs was cultured by 100 μL/well, at least 3 times empty, incubate in an incubator containing 5% CO_2 at 37°C for 48 h, and add 20 μL MTT (5 mg/mL), culture for 4 h, and absorb the medium in the hole. 150 μL for each hole dimethyl sulfoxide (DMSO), shaking table at low speed for 10 min, fully dissolve the crystal. Detecting the absorbance value of each hole at 490 nm with the enzyme marker, MTT value = absorbance value of the experimental hole/absorbance value of the control hole ×100%.

Lidocaine of detection in real samples

In order to explore the performance and practicability of this method in actual samples, we used the standard addition method to evaluate the accuracy of carrot-CQDs fluorescence probe in detecting lidocaine in actual samples, and mixed three different concentrations of lidocaine standard into blood samples for spiking recovery

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experiment. Carry out the test according to the experimental method, and take the average value for three parallel determinations of each sample to reduce the errors.

Results and discussion

Characterization of carrot-CQDs

The carrot-CQDs were prepared from carrot by one-step hydrothermal method, and the synthesis process was shown in *Figure 1*. The morphology and elemental analysis of carrot-CQDs were performed by the TEM instrument. As shown in the *Figure 2* (A and B), the TEM image showed that the average size distribution of carrot-CQDs was smaller than 20 nm. The functional group information of carrot-CQDs was obtained through FTIR spectroscopy (*Figure 3*). The characteristic vibration bands around 3400 cm^{-1} (-OH stretching vibration), the peaks at 1520-1720 cm^{-1} were attributed to the C = O groups' stretching vibration. An obvious band at 1403 cm^{-1} was derived from the COO^- stretching vibration. The bands at 1260 cm^{-1} and 1080 cm^{-1} were attributed to C-N and C-O groups, respectively.

The XPS was further employed to identify the chemical status of the CQDs, from the survey spectrum shown in *Fig. 4*, the CQDs were mainly composed of C, N and O elements free of other impurities, showing the carbonaceous framework of CQDs with doping or decoration of N and O groups. The peaks at 285 eV, 400 eV and 532 eV were attributed to C1s, N1s and O1s by XPS, respectively (*Figure 4*).

The structure and composition of the carrot-CQDs leaded to the diversity of their properties. One of the highlights was that it had two strong absorption peaks in the ultraviolet region and a long tail in the visible region. The absorption peaks band were mainly concentrated at 260-340 nm, the characteristic peaks were about 274 nm and 337 nm (*Fig. 5*), which might be caused by the π→π* transition of C = C bond and the n→π* transition of C = O bond, respectively.

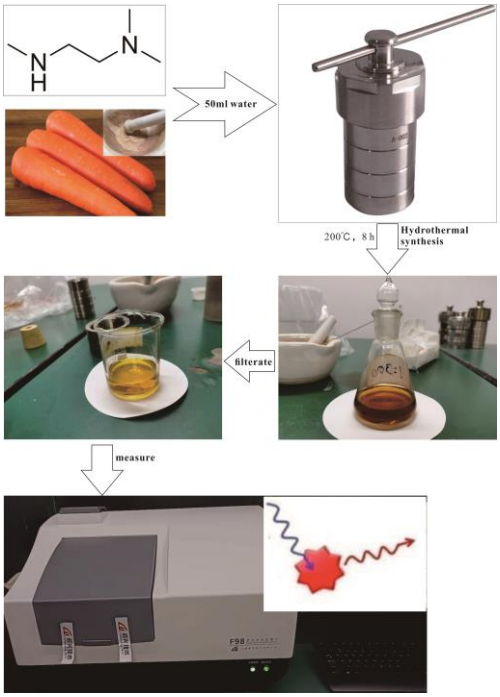

Figure 1. *Illustration of the preparation of the CQDs from carrot*

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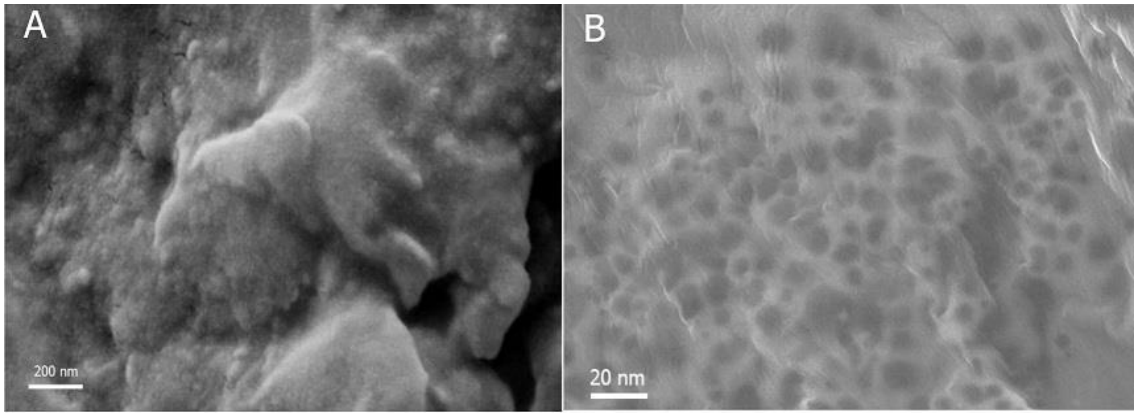

Figure 2. *TEM of the carrot-CQDs*

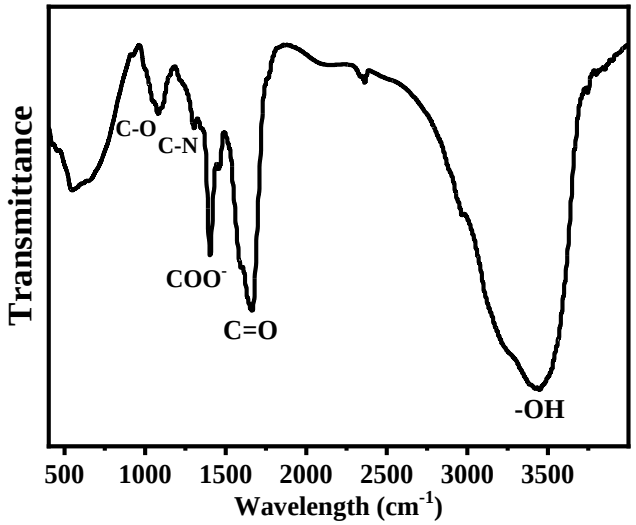

Figure 3. *FTIR spectrum of the carrot-CQDs*

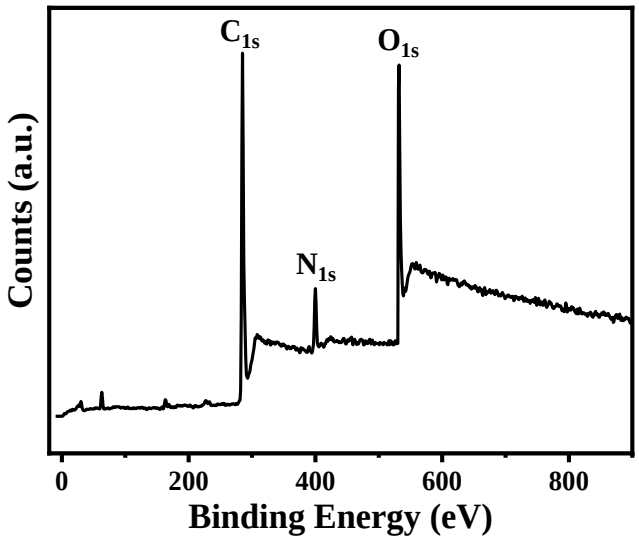

Figure 4. *XPS full scan spectrum of the carrot-CQDs*

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As shown in *Figure 5*, the fluorescence spectrum of carrot-CQDs was relatively symmetrical, because the CQDs had ultra-small particle size distribution. The Figure also showed that the maximum emission wavelength was 415 nm under the excitation wavelength of 310 nm. *Figure 6* showed the fluorescence emission spectra at different excitation wavelengths, which shown the wavelength tunability and dependence of the CQDs. The position of the peak had small blue shift.

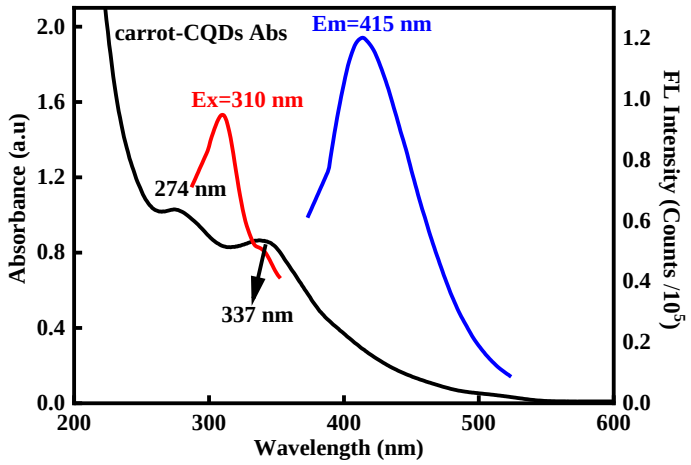

Figure 5. *The UV-vis, excitation and emission spectra of carrot-CQDs*

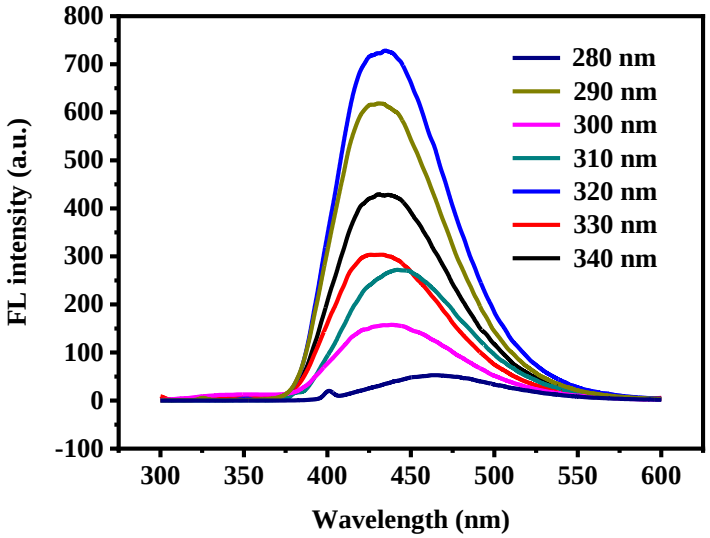

Figure 6. *Emission of carrot-CQDs at various excitation wavelengths*

Selective investigation experiment of the carrot-CQDs

By monitoring the ratiometric fluorescent value of different possible interfering substances, the selectivity of carrot-CQDs was investigated. Possible interfering substances included lidocaine, azithromycin, vitamin B_6 hydrochloride, norfloxacin, roxithromycin, enrofloxacin, lincomycin. The analyte and the interference presented at the same time to verify the interference. As shown in *Figure 7*, only lidocaine could effectively quench the fluorescence intensity of the carrot-CQDs in these substances,

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and other substances had no obvious change in the fluorescence intensity of the carrot-CQDs. This shown that lidocaine responded to the high selectivity of carrot-CQDs, and carrot-CQDs could be used as fluorescent nanoprobe to quench and detect lidocaine.

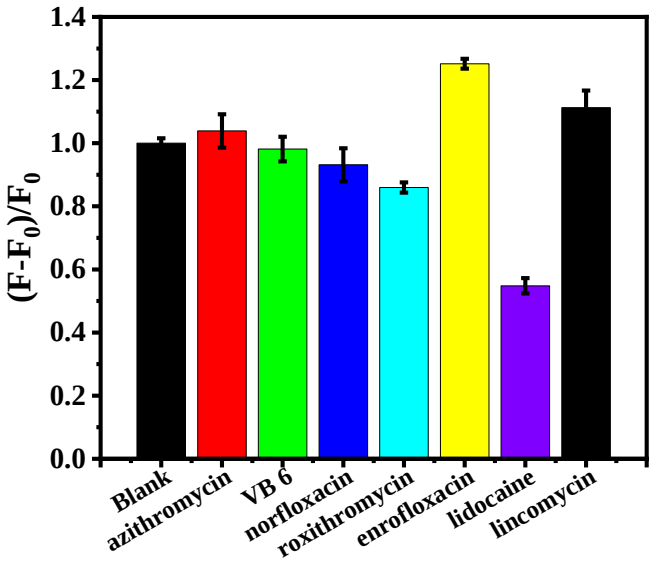

Figure 7. *Fluorescence quenching efficiency of different substances to carrot-CQDs*

Photostability experiment of carrot-CQDs

Under the experimental conditions of Ex = 310 nm and Em = 415 nm, the fluorescence intensity of 40 μL carrot-CQDs stored at room temperature for 3 h and 4°C refrigerator for one month were determined. The determination results are as shown in *Figure 8*. The fluorescence intensity remained stable without obvious change, and there was no floating matter and sediment.

Take 40 μL of carrot-CQDs and add buffer solution with pH of 2.0~8.0. The experimental results were shown in *Figure 9*. When the pH of buffer solution changed from 2.0 to 8.0, the fluorescence intensity changed slightly before pH 6.0, and decreased significantly at pH 8.0. This shown that carrot-CQDs probe could be used as fluorescent nanoprobe in acidic media.

Figure 10 showed the effect of ionic strength on the fluorescence intensity of carrot-CQDs. It could be seen that different concentration of NaCl solution had no obvious effect on the fluorescence intensity of carrot-CQDs, but with the gradual increase of the concentration of NaCl solution, the fluorescence intensity only fluctuated slightly. It could be seen that carrot-CQDs had strong stability under high ionic strength environment.

Optimization experiment of detection of lidocaine

In order to obtain the best fluorescence effect in the experiment, some key factors such as solution pH and reaction time were investigated and optimized. Adding 40 μL of carrot-CQDs into the centrifuge tube respectively, then add 50 μL of lidocaine, and add the buffer solution of pH 2.2-12. The volume was fixed to 4 mL, and the ultrasonic reaction was 10 min. Their fluorescence intensity was measured at Ex = 310 nm and Em = 415 nm. The experimental results were shown in *Figure 11*. When the pH was 8.0, the fluorescence quenching efficiency was the highest.

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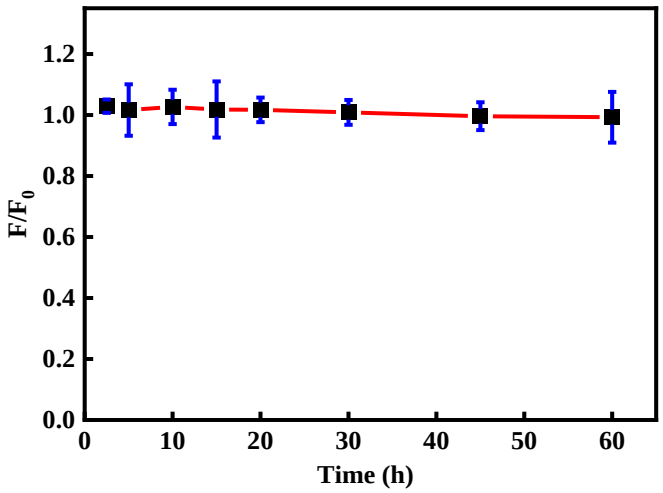

Figure 8. *Effect of different storage time on fluorescence efficiency of carrot-CQDs*

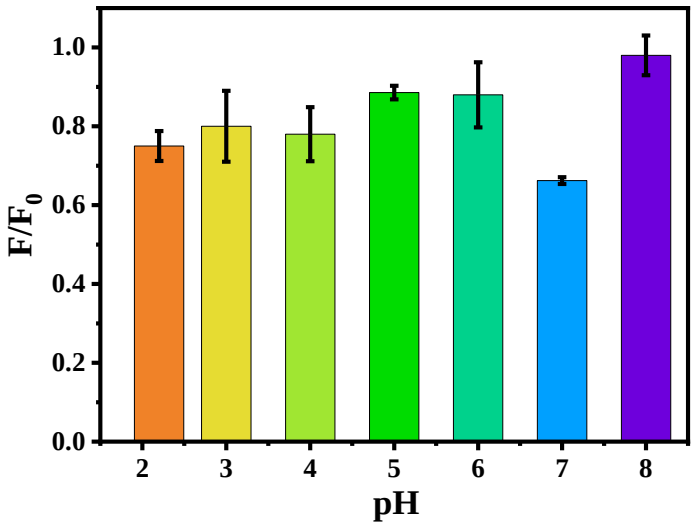

Figure 9. *Effect of different pH on fluorescence efficiency of carrot-CQDs*

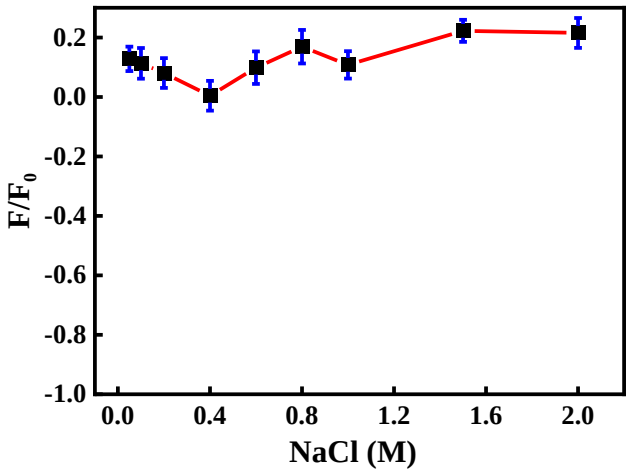

Figure 10. *Effect of different ionic strength on fluorescence efficiency of carrot-CQDs*

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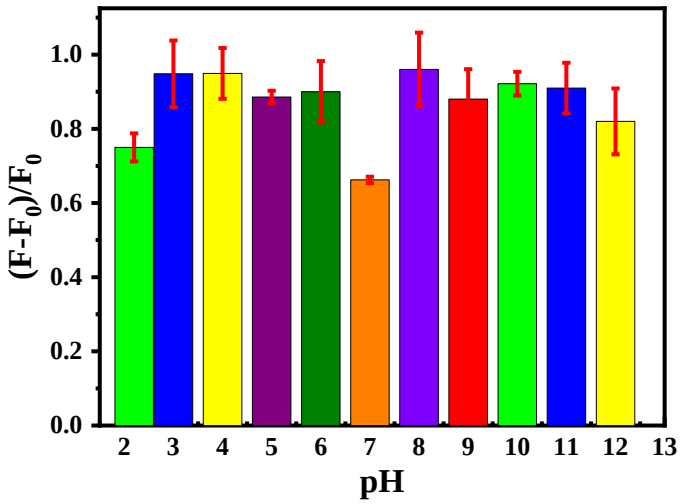

Figure 11. *Effect of different pH on lidocaine detection by carrot-CQDs system*

According to the above experimental method, except for the inconsistent ultrasonic time, the ultrasonic time was 0-30 min respectively, and its fluorescence intensity was measured under the same measuring conditions. The experimental results were shown in *Figure 12*. With the increase of ultrasonic time, its fluorescence quenching efficiency changed. When the ultrasonic time was 10 min, its fluorescence quenching efficiency reached the maximum value. Therefore, in the subsequent experiments, the reaction time was 10 min.

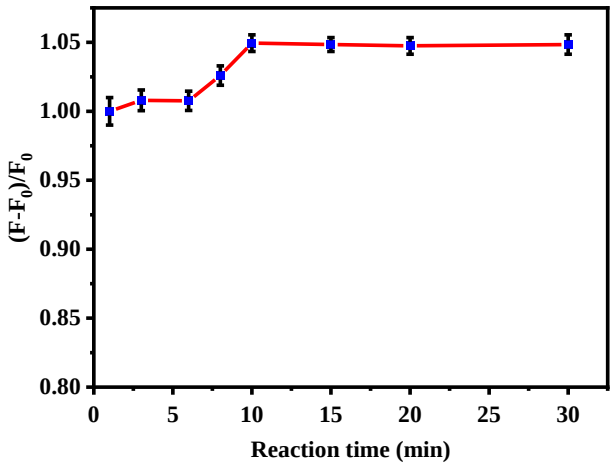

Figure 12. *Effect of different reaction time on lidocaine detection by carrot-CQDs system*

Calibration curve and detection limit

The relationship between the fluorescence intensity of carrot-CQDs and the increase of lidocaine concentration was studied. The fluorescence intensity was measured at Ex 310 nm and different Em. The experimental results were shown in *Figure 13a*. The fluorescence intensity of carrot-CQDs shown regular gradual decrease with the increase of lidocaine concentration, showing the good potential of CQDs as credible fluorescence probe for quantitatively detection of lidocaine. From *Figure 13b*, the

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fluorescence emission of carrot-CQDs system varies linearly with the concentration of lidocaine within 0.25-50 mM. The linear equation was F/F0 = 0.0094C + 0.2712 (C was the concentration of lidocaine), the regression coefficient R^2 was 0.992, and the detection limit was 20.52 nM.

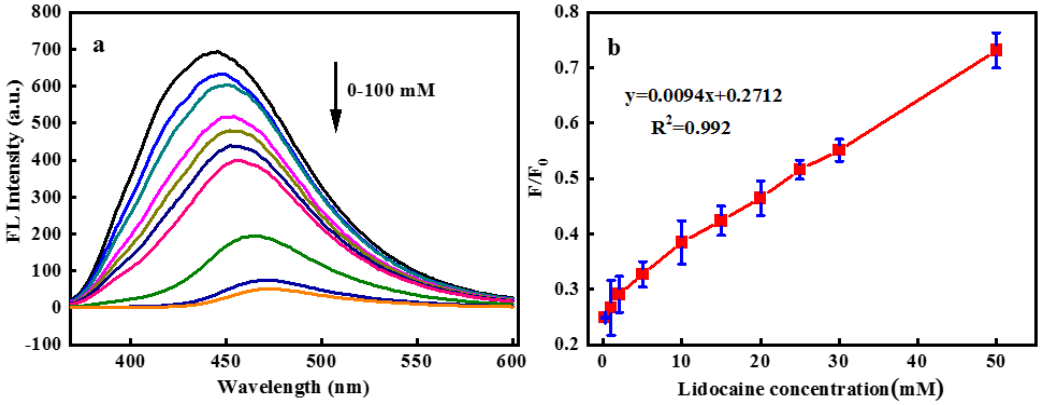

Figure 13. *Fluorescence spectra of carrot-CQDs with various lidocaine concentrations (0-100 mM) (a). The linear relationship between F/F_0 and lidocaine concentrations (0.25-50 mM) (b)*

Cell viability

The cytotoxicity of carrot-CQDs was evaluated by MTT method. The results showed that under the different concentrations of CQDs, HT29 and U2OS cells were incubated with carrot-CQDs, and the cell survival rate was above 80% (*Fig. 14*). Therefore, compared with other nanoparticles, the synthesized carrot-CQDs had low toxicity.

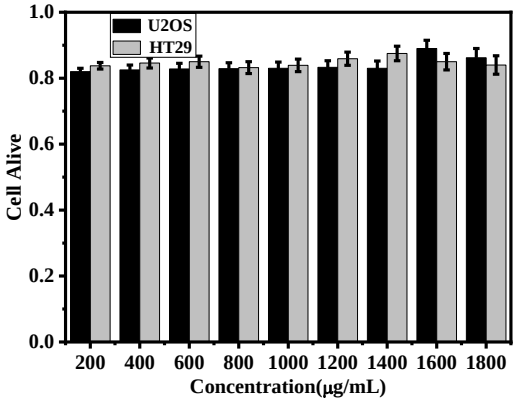

Figure 14. *The evaluation chart of cytotoxicity of different concentrations of carrot-CQDs*

Detection of lidocaine in real samples

In order to explore the performance and practicability of carrot-CQDs system in the actual sample, the standard addition method to evaluate the accuracy of carrot-CQDs in detecting lidocaine in the actual sample was used, and mixed three different concentrations of lidocaine standard into the blood sample for the spiking recovery experiment. The test was carried out according to the experimental method. Three parallel determinations were carried out for each sample, and the results were expressed

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by the average value. The results were shown in *Table 1*. In all samples, the recovery rate of lidocaine was 82.7-101.3%, and the relative standard deviation (RSD) was 1.2-2.5%, which proved that the actual detection accuracy of carrot-CQDs for lidocaine was very good (see also *Table 2*).

Table 1. *Detection results of lidocaine by carrot-CQDs system*

Analyte	Spiked (μg/mL)	Found (μg/mL)	Recovery (%)	RSD (%, n = 3)
Ultrapure water	1.0	0.993	99.3	1.2
	5.0	4.725	94.5	2.4
	10.0	8.270	82.7	2.1
Blood sample	1.0	1.002	100.2	1.3
	5.0	4.790	95.8	1.7
	10.0	8.590	85.9	2.5
Lake water	1.0	1.013	101.3	1.8
	5.0	4.680	93.6	2.0
	10.0	8.460	84.6	2.3

Table 2. *Comparison results between this method and the methods reported in literature*

Methods	LODs	Linear ranges	References
HPLC	0.025 μg/mL	0.4-50 μg/mL	Bhusal et al. (2017)
Capillary electrophoresis	0.31 mg/L	10-50 mg/L	Junger and Daniel (2019)
N,O-CDs (Fish scale)	0.054 mM	0.185-1.295 mM	Zhang et al. (2018)
Carrot-CQDs	20.52 nM	0.25-50 mM	This method

Conclusions

In this study, a fluorescent sensor for detecting lidocaine by carrot-CQDs was established based on the IFE. The CQDs were characterized by UV spectrophotometry and fluorescence spectrophotometry. The optimum pH and reaction time were investigated and optimized. Through the method performance study, the results showed that lidocaine could quench the fluorescence of carrot-CQDs. In the range of 0.25-50 mM, the fluorescence quenching efficiency was proportional to the concentration of lidocaine, and the detection limit was 20.52 nM. The lidocaine standard was added to the real sample for the spiked recovery experiment, and the higher recovery rate and lower RSD were obtained, indicating that the sensitivity, accuracy and selectivity of the sensor were very good. Therefore, this method was hopeful to be applied to the rapid detection of lidocaine in clinical testing.

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Author contributions. Meng Lifen: methodology, writing-original draft. Wu Haizhi: writing-reviewing, investigation, validation and editing.

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Availability of data and materials statement. All data generated or analyzed during this study are included in this published article.

Conflict of interests. Authors declare no competing interest.

Ethics approval/declarations. This study was approved by the plant ethics committee of Guizhou University of Engineering Science. All of the procedures were performed in accordance with the Declaration of Helsinki and relevant policies in China.

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