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## Original Research Article

## Ultrasensitive electrochemical determination of metronidazole based on polydopamine/carboxylic multi-walled carbon nanotubes nanocomposites modified GCE

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## ABSTRACT

An ultrasensitive electrochemical sensor based on polydopamine/carboxylic multi-walled carbon nanotubes (MWCNTs–COOH) nanocomposites modified glassy carbon electrode (GCE) was presented in this work, which has been developed for highly selective and highly sensitive determination of an antimicrobial drug, metronidazole. The preparation of polydopamine/MWCNTs–COOH nanocomposites/GCE sensor is simple and possesses high reproducibility, where polydopamine can be coated on the surface of MWCNTs–COOH via a simple electropolymerization process. Under optimized conditions, the proposed sensor showed ultrasensitive determination for metronidazole with a wide linear detection range from 5 to 5000  $\mu\text{mol}/\text{dm}^3$  and a low detection limit of 0.25  $\mu\text{mol}/\text{dm}^3$  ( $S/N = 3$ ). Moreover, the proposed sensor has been successfully applied for the quantitative determination of metronidazole in real drug samples. This work may provide a novel and effective analytical platform for determination of metronidazole in application of real pharmaceutical and biological samples analysis.

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## 1. Introduction

Metronidazole, one of nitroimidazole derivative drugs (Fig. 1) well-known for its antimicrobial properties, is effective against trichomonas [1–3], Vincent's organisms [4] and anaerobic bacteria [5–7]. However, overuse and long-term use of metronidazole will cause toxicity [8], peripheral neuropathies [9] and optic neuropathy [10,11]. Therefore, it is necessary to monitor metronidazole concentration in patients under antibiotic therapy. Several analytical methods have been reported for the determination of metronidazole, including spectrophotometry [12,13] and chromatography [14–17]. However, these methods could not realize high selectivity of metronidazole determination, and such determination processes were costly and time consuming. Hence, it is important to develop an alternative method for metronidazole determination with high sensitivity and selectivity.

Nowadays, electrochemical methods have been widely used in environmental analysis and biological samples analysis [18–22]. Particularly, electrochemical sensors and biosensors have been developed for pharmaceutical, food, agricultural and

environmental analyses due to the advantages of fast response and good sensitivity [23–26].

Electrochemical determination based on electrochemical sensor possesses the advantages of high sensitivity low cost and easy operation, which was widely used in analytical chemistry, and separation step is usually used to increase the selectivity prior to the determination [27–29]. Electrochemical sensors fabricated by different modified electrode materials have been developed for electrochemical determination [27,29]. Polydopamine is a conductive and biocompatible polymer, which has versatile applications due to its many attractive properties [30–33]. Polydopamine can be coated on different materials and can be a good support for loading metal nanoparticle to form nanocomposites [34,35], which finally was applied in various electrochemical biosensors [36–39]. Moreover, the polymerization method of dopamine was facile, and its surface morphology and layer thickness can be better controlled [40–42]. Furthermore, polydopamine can be easily coated on the materials surface through a very strong chemical bond [43,44]. Carboxylic multi-walled carbon nanotubes (MWCNTs–COOH) have been widely applied for the development of chemical sensors due to their excellent electrical conductivity, high surface area, remarkable mechanical strength and good chemical stability [45,46].

In this work, we developed a novel electrochemical sensor based on polydopamine/MWCNTs–COOH nanocomposites, where polydopamine can be easily electropolymerized to the surface of

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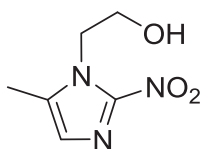


Fig. 1. Chemical structure of metronidazole.

MWCNTs–COOH to form nanocomposites, and finally successfully realized the ultrasensitive determination for metronidazole with a wide linear detection range from 5 to 5000  $\mu\text{mol}/\text{dm}^3$  and a low detection limit of 0.25  $\mu\text{mol}/\text{dm}^3$  ( $S/N = 3$ ). Most importantly, the proposed sensor has been successfully applied for the quantitative determination of metronidazole in real drug samples. This work would provide an effective analytical strategy for metronidazole determination in application of real pharmaceutical and biological samples analysis.

## 2. Experimental

### 2.1. Reagents

Metronidazole (99%, analytical grade) was purchased from Macklin Biochemical Co., Ltd. (Shanghai, China). Carboxylic multi-walled carbon nanotubes were purchased from Aladdin Industrial Company (Shanghai, China). Dopamine hydrochloride (98%, analytical grade) was purchased from J&K Chemical (Beijing, China). Drug samples were obtained from Huayueyang Biotechnology Co., Ltd. (Beijing, China). All other reagents were of analytical grade and used without further purification. 0.1 M phosphate buffer solution (PBS) was prepared by mixing  $\text{NaH}_2\text{PO}_4$  and  $\text{Na}_2\text{HPO}_4$ , and then adjusted to the required pH values with  $\text{H}_3\text{PO}_4$  or NaOH solution. All aqueous solutions were prepared with doubly distilled water.

### 2.2. Fabrication of polydopamine/MWCNTs–COOH nanocomposites/GCE sensor

First, the bare GCE was polished with 0.3 and 0.05  $\mu\text{m}$  of alumina powders, then rinsed ultrasonically with absolute alcohol and distilled water, and finally dried in the nitrogen stream. 5  $\mu\text{L}$  of 0.5 mg/mL MWCNTs–COOH homogeneous suspension was dropped onto the electrode surface and then was dried under the infrared lamp, thus obtaining MWCNTs–COOH/GCE. Finally the polydopamine was electropolymerized onto the surface of MWCNTs–COOH by cyclic voltammetry in 5 mmol/ $\text{dm}^3$  dopamine in 0.1 M PBS (pH = 5) between  $-0.4$  V and  $+0.7$  V at a scan rate of

50 mV/s for 10 cycles, thus obtained polydopamine/MWCNTs–COOH nanocomposites/GCE sensor.

### 2.3. Apparatus and method

Cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS) and differential pulse voltammetry (DPV) experiments were performed on a CHI 660B electrochemical workstation, purchased from Chenhua Co, Ltd. (Shanghai, China). A conventional three-electrode system was used with a glassy carbon electrode (3 mm diameter) as the working electrode, a saturated calomel reference electrode (SCE) and a Pt wire as the counter electrode. The differential pulse voltammetry scans ranged from  $-0.4$  V to  $-1.0$  V with amplitude of 0.05 V, pulse width of 0.05 s, pulse period of 0.5 s, sampling width of 0.0167, and increment of 0.004 V. For CV, scan rate was 50 mV/s, sample interval was 0.001 V. Electrochemical impedance spectroscopy was obtained in 5 mmol/ $\text{dm}^3$   $\text{K}_3[\text{Fe}(\text{CN})_6]/\text{K}_4[\text{Fe}(\text{CN})_6]$  solution containing 0.1 M KCl under open circuit potential with frequency range from 0.1 Hz to 100 kHz and 5 mV amplitude. The surface morphology was characterized using a field emission scanning electron microscope (FE-SEM; Zeiss Ultra55, Germany).

For the determination of metronidazole, the detection limit ( $C_m$ ) was obtained using the following equation:

$$C_m = 3S_b/m$$

Where  $m$  is the slope of the calibration plot in the linear range, and  $S_b$  is the standard deviation of the blank response which was obtained from 20 replicate measurements of the blank PBS buffer solution.

## 3. Results and discussion

### 3.1. Characterization of polydopamine/MWCNTs–COOH nanocomposites modified GCE

The SEM images of MWCNTs–COOH/GCE and polydopamine/MWCNTs–COOH nanocomposites/GCE are shown in Fig. 2. The MWCNTs–COOH can be obviously observed in Fig. 2A, when the polydopamine was electropolymerized onto the electrode surface, a rough polymer film could be obviously observed on the surface of MWCNTs–COOH, indicating the successful preparation of polydopamine/MWCNTs–COOH nanocomposites/GCE sensor (Fig. 2B).

Fig. 3A shows cyclic voltammograms of bare GCE, MWCNTs–COOH/GCE and polydopamine/MWCNTs–COOH nanocomposites/GCE in the presence of 5 mmol/ $\text{dm}^3$   $\text{K}_3\text{Fe}(\text{CN})_6/\text{K}_4[\text{Fe}(\text{CN})_6]$  solution containing 0.1 M KCl. A pair of reversible oxidation and reduction peaks were observed at 0.26 and 0.17 V, respectively, for the bare GCE (curve a). After being modified with the MWCNTs–COOH (curve b), it showed obvious increased redox peak currents because MWCNTs–COOH can dramatically increase the electrode

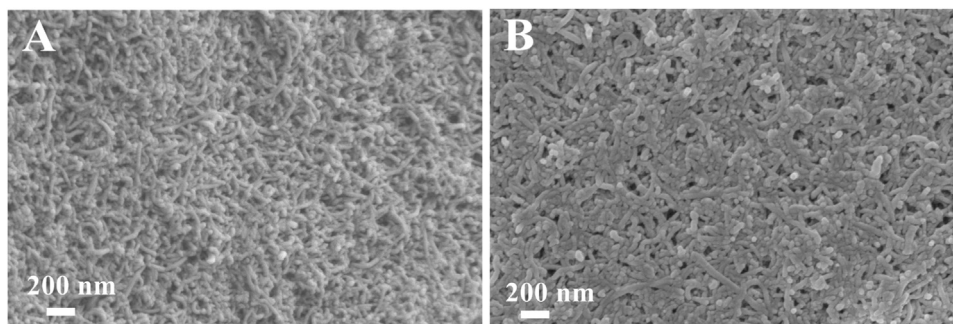
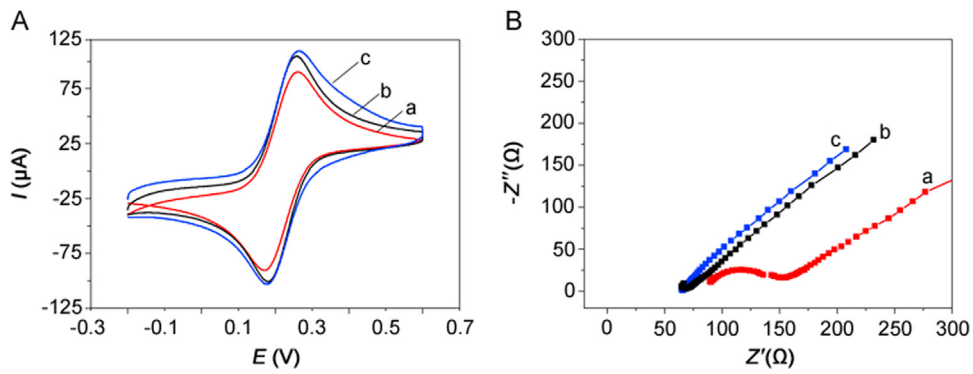
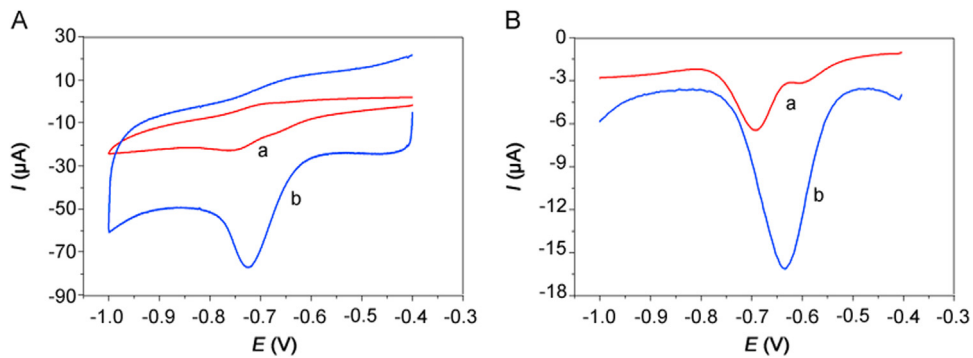


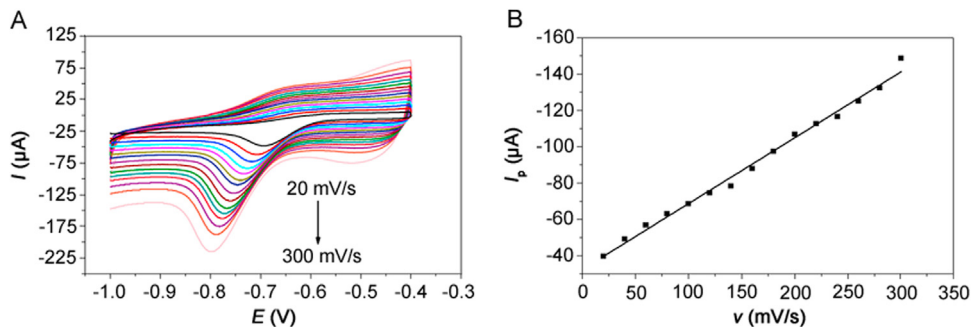
Fig. 2. SEM images of (A) MWCNTs–COOH/GCE and (B) polydopamine/MWCNTs–COOH nanocomposites/GCE.



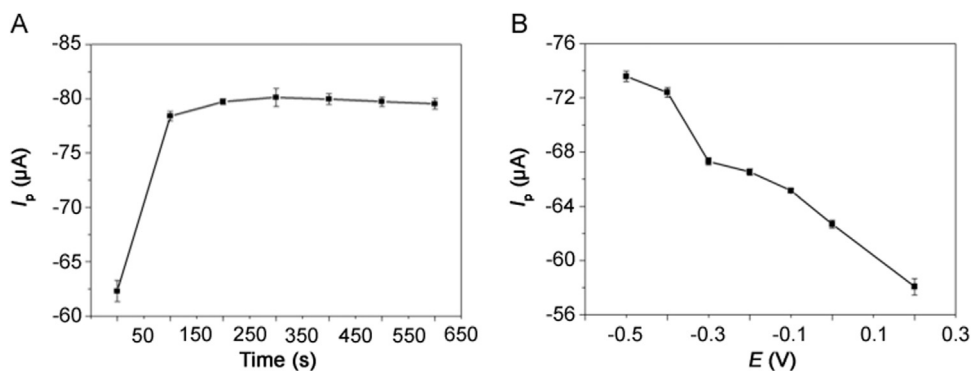
**Fig. 3.** (A) Cyclic voltammograms and (B) Electrochemical impedance spectroscopy obtained at (a) bare GCE, (b) MWCNTs-COOH/GCE and (c) polydopamine/MWCNTs-COOH nanocomposites/GCE in  $5 \text{ mmol/dm}^3$   $\text{K}_3[\text{Fe}(\text{CN})_6]/\text{K}_4[\text{Fe}(\text{CN})_6]$  solution containing  $0.1 \text{ M}$  KCl.



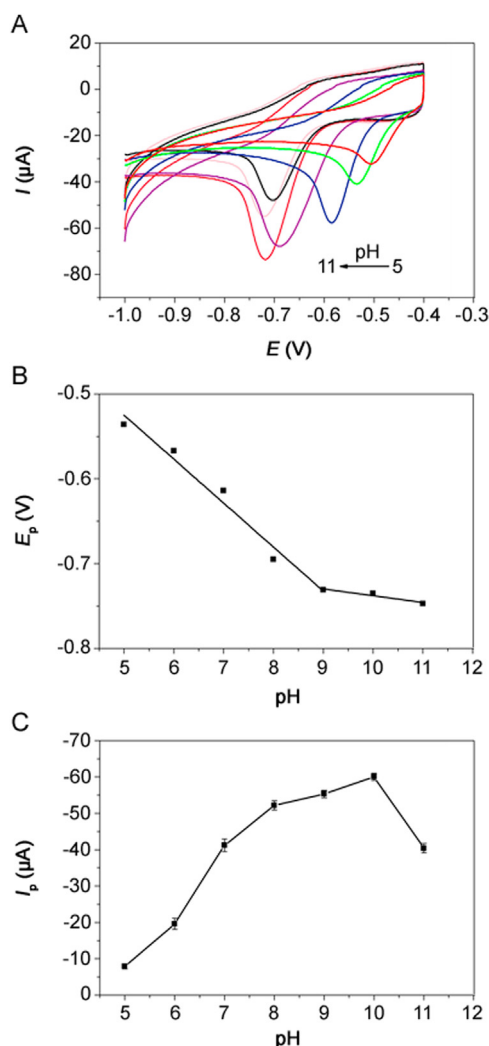
**Fig. 4.** (A) CVs and (B) DPVs of  $500 \text{ μmol/dm}^3$  metronidazole in  $0.1 \text{ M}$  PBS ( $\text{pH} = 10$ ) buffer solution at (a) bare GCE and (b) polydopamine/MWCNTs-COOH nanocomposites/GCE.



**Fig. 5.** (A) CVs of  $500 \text{ μmol/dm}^3$  metronidazole at the polydopamine/MWCNTs-COOH nanocomposites/GCE in  $0.1 \text{ M}$  PBS ( $\text{pH} = 10$ ) buffer solution at different scan rates. (B) The relationship between the reduction peak currents and scan rates.



**Fig. 6.** The effect of (A) accumulation time and (B) accumulation potential on the reduction peak current of  $500 \text{ μmol/dm}^3$  metronidazole in  $0.1 \text{ M}$  PBS ( $\text{pH} = 10$ ) buffer solution at the polydopamine/MWCNTs-COOH nanocomposites/GCE.



**Fig. 7.** (A) CVs of 500  $\mu\text{mol}/\text{dm}^3$  metronidazole in 0.1 M PBS (pH = 10) buffer solution at different pH values at the polydopamine/MWCNTs-COOH nanocomposites/GCE. The relationship of (B) reduction peak potentials vs. pH values and (C) reduction peak currents vs. pH values.

surface area and possesses good electrical conductivity [47]. Moreover, the polydopamine/MWCNTs-COOH nanocomposites/GCE (curve c) showed further enhanced redox peak currents compared with MWCNTs-COOH/GCE because polydopamine can accelerate the electron transfer efficiency between the electrode surface and solution.

Electrochemical impedance spectroscopy (EIS) is a powerful tool for studying the surface-modified electrode. Fig. 3B shows the EIS plots of bare GCE, MWCNTs-COOH/GCE, polydopamine/MWCNTs-COOH nanocomposites/GCE at 5  $\text{mmol}/\text{dm}^3$   $\text{K}_3[\text{Fe}(\text{CN})_6]/\text{K}_4[\text{Fe}(\text{CN})_6]$  in 0.1 M KCl. The bare GCE (curve a) possesses a small resistance. When MWCNTs-COOH was modified onto the bare GCE surface (curve b), it displayed a straight line in the Nyquist plot because the resistance was significantly decreased. Moreover, the polydopamine/MWCNTs-COOH nanocomposites/GCE (curve c) also displayed a straight line in the Nyquist plot, which almost showed the resistance same as MWCNTs-COOH/GCE, because polydopamine/MWCNTs-COOH nanocomposites also possess excellent electron transfer efficiency. Therefore, both the CV and EIS plots proved the successful preparation of polydopamine/MWCNTs-COOH nanocomposites/GCE sensor.

### 3.2. Electrochemical behavior of metronidazole at the polydopamine/MWCNTs-COOH nanocomposites/GCE sensor

The electrochemical behavior of bare GCE and polydopamine/MWCNTs-COOH nanocomposites/GCE for determination of 500  $\mu\text{mol}/\text{dm}^3$  metronidazole in 0.1 M PBS (pH 10.0) buffer solution is shown in Fig. 4A. The reduction peak current and peak potential of metronidazole at the bare GCE (curve a) were  $I_p = -8.44 \mu\text{A}$  and  $E_p = -0.749 \text{ V}$ . However, compared to the bare GCE, the polydopamine/MWCNTs-COOH nanocomposites/GCE (curve b) exhibited significantly increased reduction peak current ( $I_p = -41.12 \mu\text{A}$ ) and significantly increased reduction peak potential ( $E_p = -0.721 \text{ V}$ ) of metronidazole. The significantly increased reduction peak potential and significantly increased reduction peak current both confirmed the polydopamine/MWCNTs-COOH nanocomposites possess strong catalytic activity towards the reduction of metronidazole. Moreover, the DPVs results in Fig. 4B correspond with the CVs in Fig. 4A. Therefore, the polydopamine/MWCNTs-COOH nanocomposites/GCE sensor can be successfully utilized for the determination of metronidazole.

### 3.3. The effect of scan rate

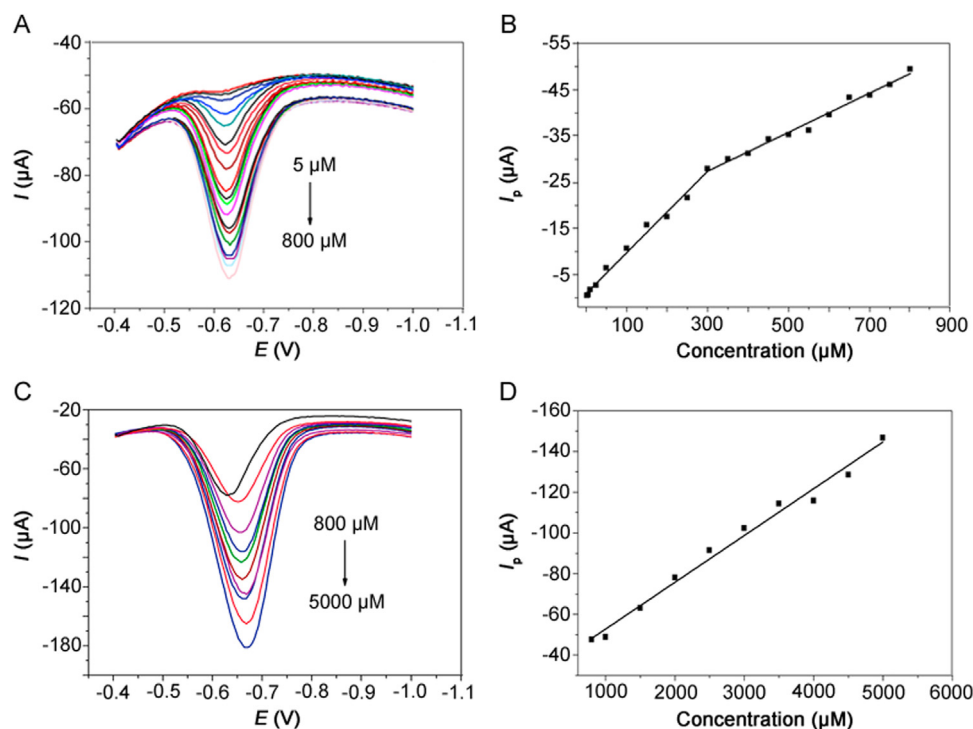
The CVs of polydopamine/MWCNTs-COOH nanocomposites/GCE in 500  $\mu\text{mol}/\text{dm}^3$  metronidazole at different scan rates are shown in Fig. 5A, where the reduction peak currents showed linearity with the scan rates. And the linear regression equation can be expressed as  $I_p(\mu\text{A}) = -0.363v(\text{mV}/\text{s}) - 32.399$  ( $R = -0.9914$ ) in Fig. 5B, indicating that the reduction of the metronidazole is a typical adsorption controlled process. Therefore, it is necessary to study the effect of accumulation time and accumulation potential in order to obtain more sensitive determination for metronidazole.

### 3.4. The effect of accumulation time and accumulation potential

The effect of accumulation time and accumulation potential for the determination of metronidazole was studied by DPVs in Fig. 6. As shown in Fig. 6A, at the accumulation potential of  $-0.5 \text{ V}$ , the reduction peak current increased gradually with the accumulation time and reached the maximum value when the accumulation time was 200 s. However, the reduction peak current almost remained the same after 200 s due to the saturation of surface active catalytic sites of polydopamine/MWCNTs-COOH nanocomposites/GCE. Thus, the optimal accumulation time of 200 s was employed in our experiments. With the optimal accumulation time determined above, we further studied the effect of accumulation potential on reduction peak current of metronidazole. As shown in Fig. 6B, the reduction peak current decreased gradually with the increase of accumulation potential; therefore, the accumulation potential was chosen at  $-0.5 \text{ V}$  for determination of metronidazole in our later experiments.

### 3.5. The pH effect

The effect of pH value on the electrochemical response of 500  $\mu\text{mol}/\text{dm}^3$  metronidazole in 0.1 M PBS with pH value ranging from 5.0 to 11.0 at the polydopamine/MWCNTs-COOH nanocomposites/GCE was investigated by CV (Fig. 7A). The reduction peak potentials showed linearity with pH values ranging from 5.0–9.0 and 9.0–11.0, with the linear regression equations of  $E_p = -0.0518\text{pH} - 0.266$  ( $R = -0.9687$ ) and  $E_p = -0.008\text{pH} - 0.658$  ( $R = -0.9462$ ), respectively (Fig. 7B), indicating two different reaction mechanisms of metronidazole. According to previous reports [39,48], the reaction mechanisms of metronidazole are listed below:

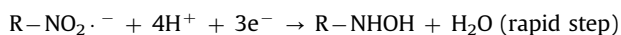
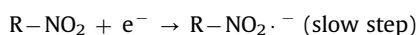


**Fig. 8.** DPVs of metronidazole at (A) 5–800  $\mu\text{mol}/\text{dm}^3$  and (C) 800–5000  $\mu\text{mol}/\text{dm}^3$  in 0.1 M PBS (pH = 10) buffer solution at the polydopamine/MWCNTs–COOH nanocomposites/GCE. Linear relationships between reduction peak currents and concentrations at (B) 5–800  $\mu\text{mol}/\text{dm}^3$  and (D) 800–5000  $\mu\text{mol}/\text{dm}^3$ .

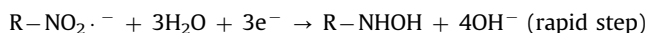
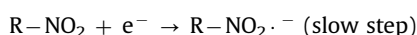
**Table 1**  
Linear regression equations of metronidazole under different concentration ranges.

Equation	Concentration range ( $\mu\text{M}$ )	Linear regression equation	R
1	5–300	$I_p(\mu\text{A}) = -0.08837c (\mu\text{M}) - 0.91$	$R = -0.9881$
2	300–800	$I_p(\mu\text{A}) = -0.0423c (\mu\text{M}) - 14.71$	$R = -0.9842$
3	800–5000	$I_p(\mu\text{A}) = -0.02298c (\mu\text{M}) - 29.78$	$R = -0.9813$

In pH values of 5.0–9.0:



In pH values of 9.0–11.0:



**Table 2**  
Comparison of performances of the polydopamine/MWCNTs–COOH nanocomposites/GCE with other modified electrodes.

Electrode	Detection limit/ $(\mu\text{mol}/\text{dm}^3)$	Linear range/ $(\mu\text{mol}/\text{dm}^3)$	Ref.
P-AgSA-CE	0.6	2–100	[49]
Carbon fiber microdisk electrode	0.5	1–22	[50]
Carbon nanotubes/GCE	0.063	0.1–200	[51]
DNA/GCE	1	1.0–54.3	[52]
Activated GCE	1.1	2–600	[53]
Graphene-ionic liquid/GCE	0.047	0.1–25	[54]
Cu-poly(Cys)/GCE	0.37	0.5–400	[55]
Polydopamine/MWCNTs–COOH nanocomposites/GCE	0.25	5–5000	This work

Moreover, as shown in Fig. 7C, because the reduction peak current achieved the maximum value in pH = 10.0, the pH value of 10.0 was chosen as the best pH value for the determination of metronidazole.

### 3.6. The quantitative determination of metronidazole

The quantitative determination of metronidazole at the polydopamine/MWCNTs–COOH nanocomposites/GCE was achieved by DPV under optimal conditions addressed above. As shown in Fig. 8, the reduction peak currents of metronidazole at the polydopamine/MWCNTs–COOH nanocomposites/GCE increased linearly with concentration ranges of 5–300  $\mu\text{mol}/\text{dm}^3$ , 300–800  $\mu\text{mol}/\text{dm}^3$  and 800–5000  $\mu\text{mol}/\text{dm}^3$ , and their corresponding linear regression equations are listed in Table 1.

The detection limit of metronidazole was determined to be 0.25  $\mu\text{mol}/\text{dm}^3$  ( $S/N = 3$ ). Moreover, compared with recently most reported electrochemical sensors [49–55] for determination of metronidazole, our proposed nanocomposites sensor could finish the ultrasensitive determination of metronidazole with a much wider linear ranges and a much lower detection limits (Table 2).

**Table 3**

Practical determination of metronidazole in real drug samples ( $n = 3$ ). (Sample responses are expressed as a confidence interval of 95% probability).

Sample	Added ( $\mu\text{mol}/\text{dm}^3$ )	Founded ( $\mu\text{mol}/\text{dm}^3$ )	Recovery (%)	RSD (%)
1	20	23.66 $\pm$ 1.86	118.3	3.2
2	50	55.70 $\pm$ 3.97	110.1	2.9
3	200	206.64 $\pm$ 3.21	103.3	0.6
4	300	291.39 $\pm$ 3.84	93.4	0.6
5	500	506.70 $\pm$ 2.35	104.9	0.2

### 3.7. Selectivity, stability and reproducibility of the polydopamine/MWCNTs–COOH nanocomposites/GCE sensor

Selectivity, stability and reproducibility of the proposed sensors are key factors for their practical application. The proposed sensor was not affected by additions of 100-fold concentrations of various inorganic ions ( $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Na}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$ ,  $\text{SO}_4^{2-}$ ,  $\text{F}^-$ ,  $\text{CO}_3^{2-}$ ,  $\text{NO}_3^-$  and  $\text{Cl}^-$ , signal change below 3%) and 10-fold concentrations of some organic compounds (oxalic acid, ascorbic acid, glucose, citric acid, cystine, alanine and tartaric acid, signal change below 6%). This results suggested that the proposed sensor possesses excellent selectivity for the determination of metronidazole. After the prepared electrode was stored at 4 °C in a refrigerator for 1 month, the reduction peak current of metronidazole remained 95.2% of its initial value, indicating that the proposed sensor possesses good stability. Moreover, four modified electrodes were fabricated to estimate the sensor's reproducibility, and the relative standard deviation (RSD) of detection measurements was calculated to be 2.5% for metronidazole, suggesting that the proposed sensor possesses high reproducibility. Therefore, the polydopamine/MWCNTs–COOH nanocomposites/GCE sensor is promising for determination of metronidazole with excellent selectivity, stability and reproducibility.

### 3.8. Real samples determination

The practical analytical application of the polydopamine/MWCNTs–COOH nanocomposites/GCE sensor was evaluated by determination of metronidazole in real drug samples by standard-addition technique. Three parallel experiments were performed on all measurements. As shown in Table 3, the recovery of the real samples ranged between 93.4% and 118.3%, and the RSD values were less than 4%, indicating that the our proposed sensor can be successfully applied for the practical determination of metronidazole in real samples.

## 4. Conclusions

In summary, we successfully develop an ultrasensitive electrochemical sensor for metronidazole determination, which was based on polydopamine/MWCNTs–COOH nanocomposites. Moreover, the fabrication of polydopamine/MWCNTs–COOH nanocomposites/GCE sensor was simple, where polydopamine can coat on the surface of MWCNTs–COOH via a simple electropolymerization process. Under optimized conditions, the proposed sensor showed wider linear detection range from 5 to 5000  $\mu\text{mol}/\text{dm}^3$  and a low detection limit of 0.25  $\mu\text{mol}/\text{dm}^3$  ( $S/N = 3$ ) for metronidazole, and was successfully applied for the practical determination of metronidazole in real drug samples. The proposed sensor shows broad potential in application of real pharmaceutical and biological samples analysis.

### Conflicts of interest

The authors declare that there are no conflicts of interest.

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