

# Analytical Methods

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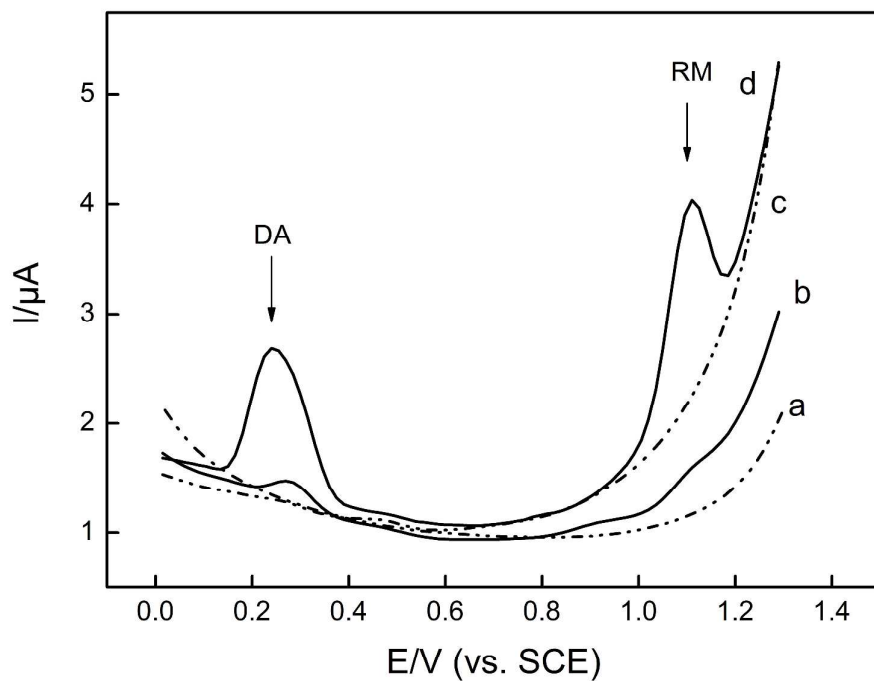
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4 An electrochemical sensor based on poly (sulfosalicylic acid) was  
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6 fabricated for individual and simultaneous determination of  
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8 roxithromycin and dopamine with sensitive detection limit and satisfied  
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10 detecting result of real samples.  
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4 **Simultaneous detection of roxithromycin and dopamine using a sensor platform**  
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7 **based on poly (sulfosalicylic acid) and its application in human serum**  
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16

17 **Abstract**

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20 A novel poly-sulfosalicylic acid modified glassy carbon electrode (PSA/GCE)  
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22 was developed to detect roxithromycin (RM) and its simultaneous determination with  
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24 dopamine (DA). The morphologies and interface properties of PSA film were  
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26 examined by scanning electron microscopy (SEM) and electrochemical impedance  
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28 spectroscopy (EIS). Fourier transform infrared spectra (FTIR) indicated that PSA was  
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30 successfully modified on electrode. The electro-catalytic oxidation of RM on the  
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32 PSA/GCE was investigated, individually and simultaneously, using cyclic  
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34 voltammetry (CV) and differential pulse voltammetry (DPV) under optimum  
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36 conditions. The proposed method exhibited wide linear dynamic range from  $2 \times 10^{-8}$   
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38 to  $1 \times 10^{-5}$  M with a low detection limit (S/N = 3) of  $6.67 \times 10^{-9}$  M for roxithromycin.  
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40 The modified electrode showed good stability, reproducibility and high selectivity,  
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42 and also demonstrated its feasibility for analytical purpose and human serum samples.  
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52 **Key words:** roxithromycin; sensors; simultaneous detection; dopamine;  
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55 electrochemistry.  
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## 1. Introduction

Roxithromycin is a semi-synthetic 14-membered-ring macrolide antibiotic. Its antibacterial effect is similar to that of erythromycin *in vitro*, but stronger than erythromycin 1-4 times *in vivo*<sup>1</sup>. Erythromycins exhibit high activity against nearly all the Gram-positive and Gram-negative bacteria<sup>2,3</sup>. They are administered to the people who are allergic to penicillins<sup>4</sup>. Dopamine (DA) is an important neurotransmitter in the central nervous system of mammals and human beings<sup>5-7</sup>. The anaphylactic shock<sup>8</sup> often requires dopamine infusion. Thus, our research interest falls in the development of electrodes for simultaneous electrochemical detection of RM and DA in a biological system.

There have been formed a great variety of methods for the determination of RM, such as liquid chromatographic<sup>9</sup>, liquid chromatography-mass spectrometry (LC-MS)<sup>10-12</sup>, spectrophotometry<sup>13,14</sup>, flow injection chemiluminescence procedure<sup>15</sup>, Fourier-transform infrared (FTIR) transmission spectroscopy<sup>16</sup> and solid-phase extraction (SPE) combined with high-performance liquid chromatography-ion trap tandem mass spectrometry<sup>17</sup>. However, the above are mostly time-consuming and/or overly complicated. Although roxithromycin was detected through electrochemical methods since it can be oxidized under proper conditions, there is little literature available that concerns this area. For example, Zhang et al. studied the behaviors of roxithromycin at poly(3,4-ethylenedioxythiophene) modified gold electrode<sup>18</sup>; Wan et al. reported the direct electron transfer and voltammetric determination of roxithromycin at a single-wall carbon nanotube coated glassy carbon electrode<sup>19</sup> and

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4 Avramov et al. completed the research of electrochemical behaviors of macrolide  
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6 antibiotics based on gold electrode<sup>20-24</sup>. Till now, there have been rare papers  
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8 reporting the simultaneous determination of roxithromycin and dopamine.  
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11 In this work, sulfosalicylic acid was used as the modifier to obtain a polymer of  
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13 poly-sulfosalicylic acid film (PSA) on glassy carbon electrode (PSA/GCE) by  
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15 electrochemical polymerization. Due to the high electron density of carbonyl (COO<sup>-</sup>)  
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17 and sulfonic (SO<sup>3-</sup>) groups in sulfosalicylic acid molecule, the PSA film has high  
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19 concentrations of negatively charged surface-functional groups. As a result, the  
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21 modified electrode manifested excellent electrocatalytic properties of analytes and  
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23 achieved simultaneous determination of roxithromycin and dopamine. Furthermore, it  
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25 presented a number of attractive features such as high stability, good reproducibility,  
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27 wide linear range, and low detection limit, which made it quite suitable for analytical  
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29 purpose and clinic use.  
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## 40 41 **2. Experiment**

### 42 43 2.1 Apparatus and reagents

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45 All the electrochemical experiments were performed on a CHI 660D  
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47 electrochemical workstation (Shanghai Chenhua Co. Ltd., China), with a conventional  
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49 three-electrode system including a modified electrode as working electrode, a Pt wire  
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51 counter electrode and a saturated calomel electrode (SCE) reference electrode. All the  
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53 potential values shown as below were referred to the SCE. Fourier transform infrared  
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55 spectra (FTIR) were carried out on AVATAR 370 Fourier transform infrared  
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4 spectrometer (USA).  
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7 All chemicals and reagents used in this work were of analytical grade and put  
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9 into use without further purification. Dopamine, alanine, phenylalanine and leucine  
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11 were purchased from Aladdin Chemical Reagent Co., Ltd. (Shanghai, China).  
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13 Sulfosalicylic acid was supplied by Shanghai No.1 Chemical Reagent Factory.  
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15 Glutamic acid and other reagents were obtained from Sinopharm Chemical Reagent  
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17 Co., Ltd. (Shanghai, China). Fresh serum samples extracted from healthy people were  
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19 offered by Shanghai University Hospital.  
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## 25 26 27 28 2.2. Fabrication of PSA /GCE 29

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31 The bare GCE was successively polished on chamois leather with 0.3 and 0.05  
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33  $\mu\text{M}$   $\text{Al}_2\text{O}_3$  slurry, and then washed with  $\text{HNO}_3$  (1: 1, v/v), ethanol and doubly distilled  
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35 water in an ultrasonic bath, respectively. Then the GCE was immersed in 10 mM  
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37 sulfosalicylic acid (pH 5.5) by CV from  $-1.0$  to  $2.0$  V at  $100$   $\text{mV s}^{-1}$  for 5 cycles until  
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39 the characteristic of reproducible CV was obtained. The poly-sulfosalicylic acid  
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41 (PSA/GCE) was preserved in a refrigerator under  $4$   $^\circ\text{C}$  after being washed within  
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43 double distilled water.  
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## 49 50 51 52 2.3. Experimental measurements 53

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55 For FTIR spectroscopy analysis, the poly (sulfosalicylic acid) was obtained by  
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57 using the method discussed in Section 2.2, except that the working electrode was  
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59 replaced by a polished aluminum sheet. EIS was performed at bare GCE and  
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4 PSA/CPE in 5.0 mM  $[\text{Fe}(\text{CN})_6]^{3-/4-}$  (1:1) containing 0.1 M KCl. CV was carried out  
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6 in quiescent solution at a scan rate of 100 mV s<sup>-1</sup>. DPV was performed in an  
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8 electrochemical cell filled with 10 mL 0.1 M PBS (pH 5.5).  
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#### 13 14 15 2.4 Human serum samples 16

17 Blood sample obtained from healthy people was supplied by Shanghai  
18 University Hospital. In general, 0.15 mL perchloric acid was added into each of the 1  
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20 mL blood sample, vortex-mixed for 1 min and centrifuged at 2500 rpm for 15 min.  
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23 And then, the supernatant was directly injected into pH 5.5 PBS to give a total volume  
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25 of 10 mL.  
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### 33 3. Result and Discussion 34

#### 35 36 3.1 Characterization of PSA/GCE 37

38 To investigate the morphology of the modified electrode, PSA film was prepared  
39 by electro-polymerization of sulfosalicylic acid at GCE as described above. Fig. 1A  
40 reveals the typical morphology of PSA film by scanning electron microscope (SEM),  
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42 indicating that the film had a fine cluster-like structure. The surface of PSA film was  
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44 smooth and homogeneous, which verified that the PSA film had been successfully  
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46 polymerized on the electrode surface and might enhance the interaction between the  
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48 modified electrode and the roxithromycin.  
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57 The FTIR spectra (Fig. 1B) illustrated the differences between the fine curves of  
58 sulfosalicylic (a) and disappearing curve of PSA (b), which was attributed to the  
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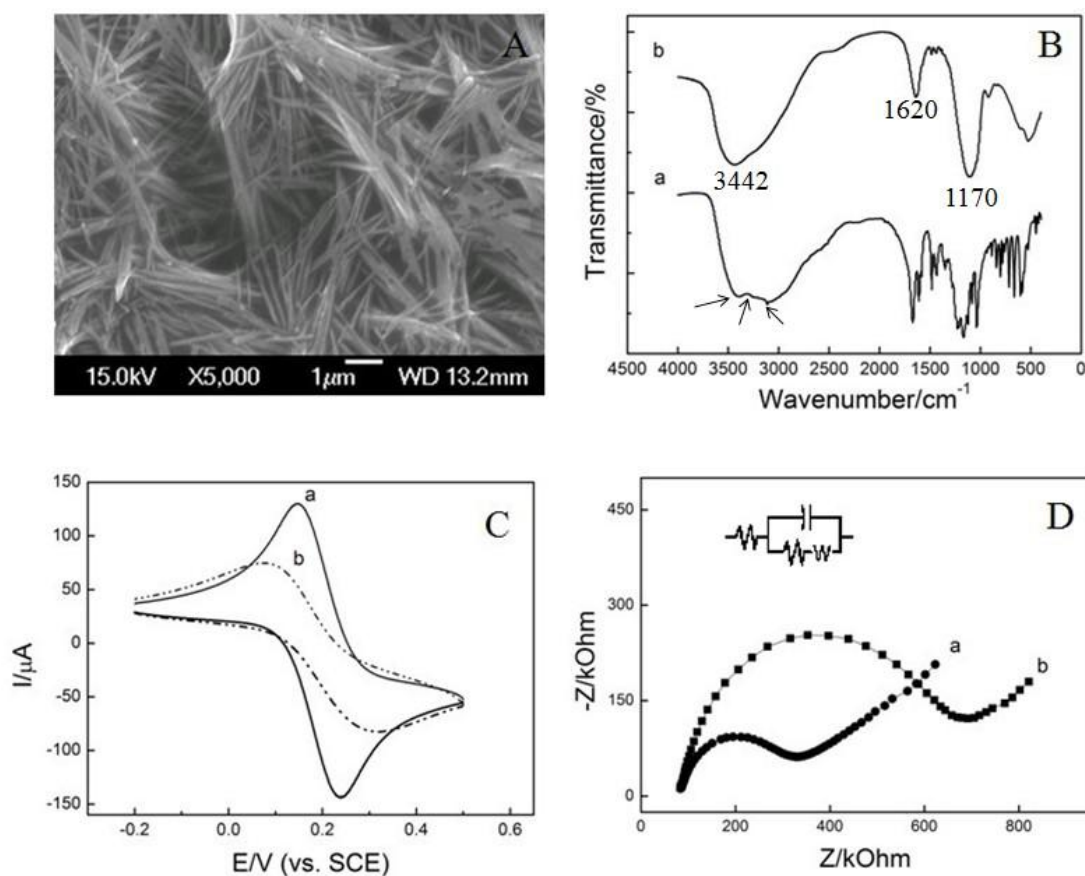
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4 polyreaction of sulfosalicylic acid. In the FTIR absorption spectra of sulfosalicylic  
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6 acid (a), the wide peaks between  $3200\text{ cm}^{-1}$  and  $3500\text{ cm}^{-1}$  are O-H stretching  
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8 vibra-tion and  $3112\text{ cm}^{-1}$  is C-H stretching vibration peak. Seen from the curve (b), it  
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10 is obvious that the peaks at  $3442\text{ cm}^{-1}$ , the peaks of S-O stretching vibration ( $1350$   
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12  $\text{cm}^{-1}$  and  $1170\text{ cm}^{-1}$ ) and  $\text{-COO}^-$  stretching vibration ( $1620\text{ cm}^{-1}$  and  $1469\text{ cm}^{-1}$ ) got  
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14 broader due to poly-reaction of sulfosalicylic acid, implying that the monomers have  
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16 formed into PSA polymer.  
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23 CV experiments were also investigated in  $5.0\text{ mM } [\text{Fe}(\text{CN})_6]^{3-/4-}$  (1:1)  
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25 containing  $0.1\text{ M KCl}$  solution. As shown in Fig. 1C, the redox peaks at the bare GCE  
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27 are well-shaped while the peak shape was deteriorated at PSA/GCE. All the above  
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29 speak volume for the successful polymerization process of sulfosalicylic acid onto the  
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31 surface of electrode.  
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36 Electrochemical impedance spectroscopy (EIS) is a powerful, nondestructive and  
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38 very informative technique for probing into charge transfer properties at the  
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40 electrode/solution interface. The curve of the EIS includes a semicircular part and a  
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42 linear part, in consistence with the electron transfer resistance and the diffusion  
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44 process, respectively. The diameter of the semicircle is usually equal to the electron  
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46 transfer resistance, which normally reflects the conductivity and the electron transfer  
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48 process<sup>25</sup>. Fig. 1D displayed the typical results of electrochemical impedance spectra  
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50 (presented in the form of the Nyquist plot) of bare GCE and PSA/GCE, respectively.  
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52 Compared with the bare GCE (curve a), the electron-transfer resistance for PSA/GCE  
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54 was larger (curve b), which could be ascribed to the electrostatic repulsion force  
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between the negatively charged  $[\text{Fe}(\text{CN})_6]^{3-/4-}$  and the poly(sulfosalicylic acid) film<sup>26</sup>.

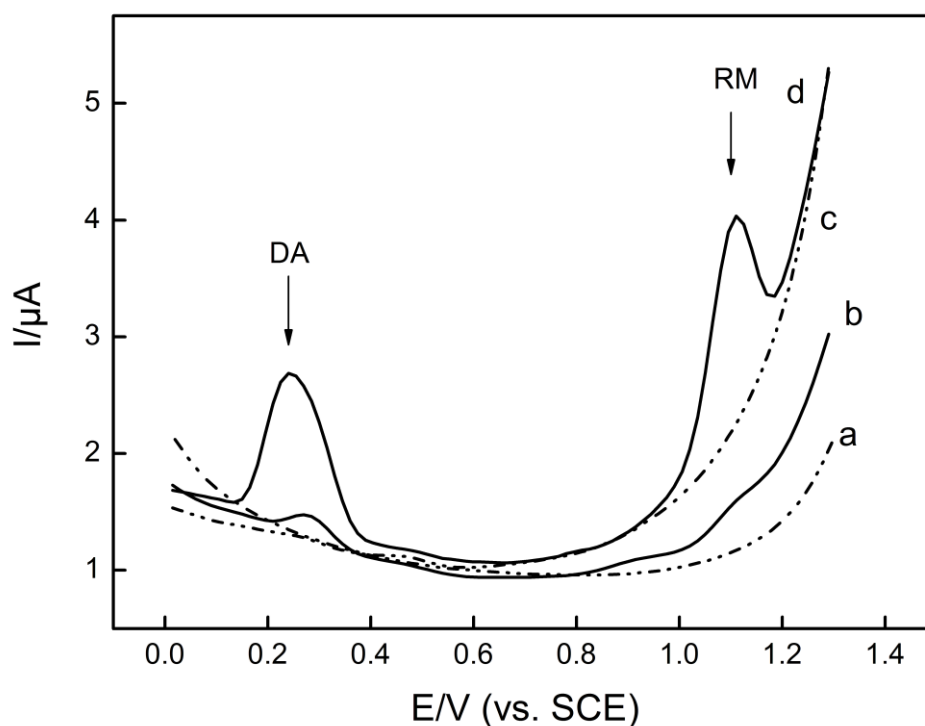


**Fig. 1** Characterization of PSA/GCE: Scanning electron micrographs of the PSA/GCE (A). Fourier transforms infrared spectra of sulfosalicylic (a) and PSA films (b) (B). Cyclic voltammograms (C) and EIS (D) of bare GCE (a) and PSA/GCE (b) in 5.0 mM  $[\text{Fe}(\text{CN})_6]^{3-/4-}$  (1:1) containing 0.1 M KCl. Inset is the equivalent circuit diagram.

### 3.2 Electrochemical behavior of RM and DA at bare GCE and PSA/GCE

The electrochemical behaviors of PSA/GCE were demonstrated by comparing the differential pulse voltammograms (DPVs) at different electrodes in 0.1 M PBS (pH 5.5). The differential pulse voltammograms of bare GCE (a and b) as well as PSA/GCE (c and d) in the absence (a and c) and presence (b and d) of 8  $\mu\text{M}$  roxithromycin and 4  $\mu\text{M}$  dopamine were displayed in Fig. 2. It can be seen that the

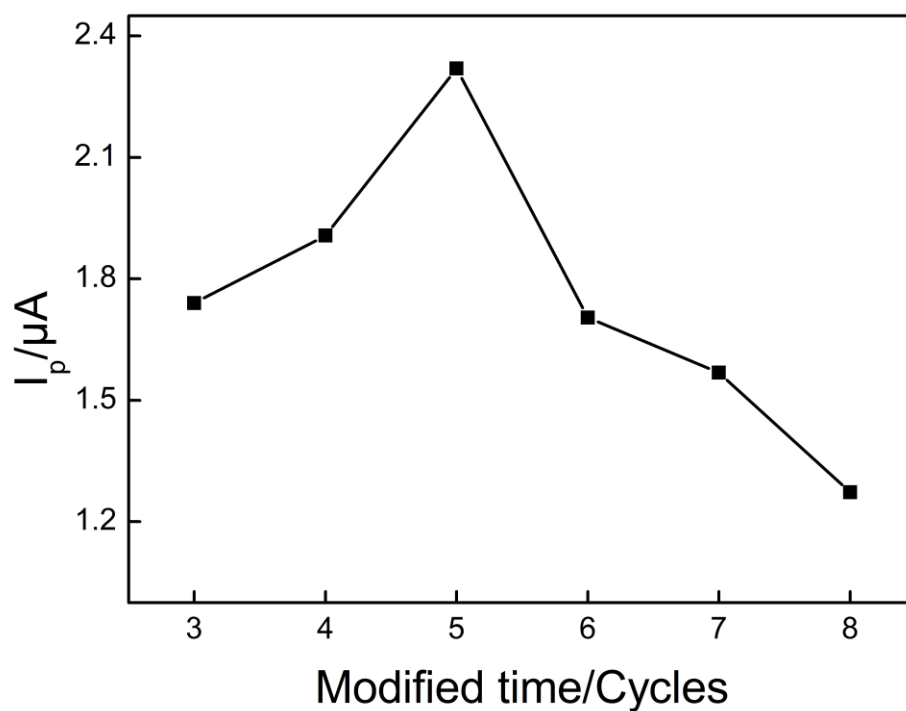
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4 oxidation peak current of RM and DA at PSA/GCE (curve d) was enhanced and its  
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6 peak appeared sharper than that of bare GCE (curve b). Meanwhile, hardly any peak  
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8 of RM was obtained at bare GCE (curve b) and the peak potential shifts negatively  
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10 of RM was obtained at bare GCE (curve b) and the peak potential shifts negatively  
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12 from 0.28 V to 0.23 V of DA (curve b and d), hinting that the PSA film performed  
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14 good electro-catalytic activity towards RM and DA. The oxidation peak potentials of  
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16 RM and DA separated distinctly (over 800 mV), which actually indicated that  
17  
18 RM and DA separated distinctly (over 800 mV), which actually indicated that  
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20 PSA/GCE would be utilized to simultaneously determine RM and DA.  
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**Fig. 2** Differential pulse voltammograms of the bare GCE (a and b), PSA/GCE (c and d) in the absence (a and c) and presence (b and d) of 8  $\mu\text{M}$  RM and 4  $\mu\text{M}$  DA in 0.1 M PBS (pH 5.5).

### 3.3 The influence of electro-polymerization cycles

The thickness and permeation of polymeric films can be controlled by the potential and current applied; also, they can significantly activate the electrocatalytic properties of substrates, increase the reaction rate and improve the reproducibility of the electrode response in the area of electroanalysis<sup>27,28</sup>. Studies<sup>29–32</sup> have reported that polymer film modified electrodes show an enhanced response to the determination of various important biological and clinical species.

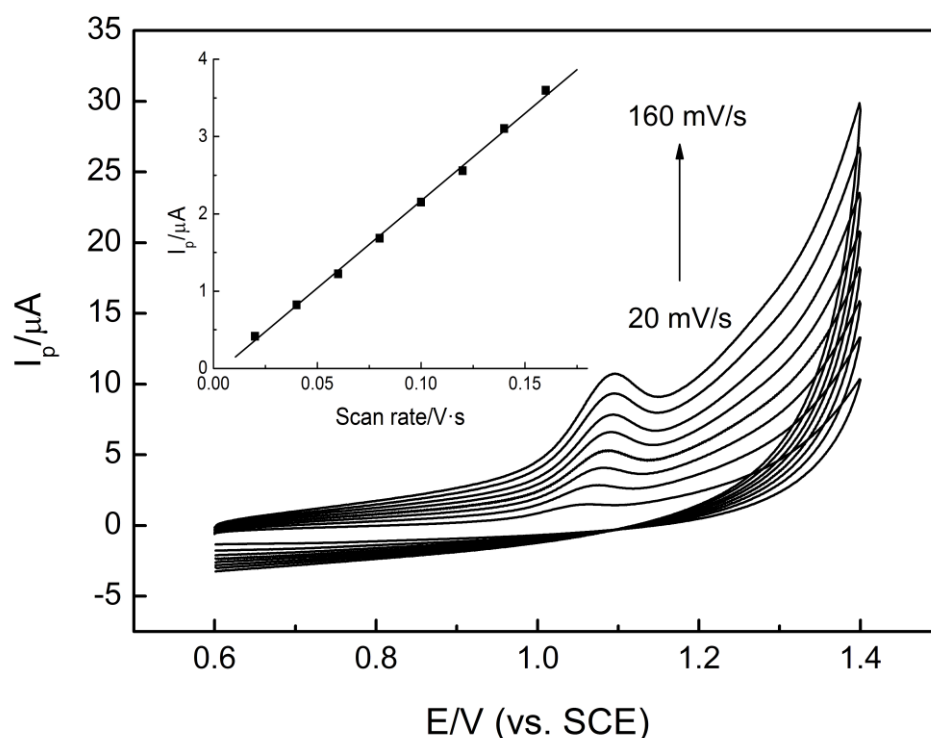


**Fig. 3** The effect of electro-polymerization cycles of sulfosalicylic acid on the oxidation current response of 10  $\mu\text{M}$  roxithromycin at PSA/GCE.

Regarding current optimization, different electro-polymerization cycles were investigated. The Fig. 3 clearly demonstrated a gradual increase of the current of 10  $\mu\text{M}$  RM on PSA/GCE from 3 to 5 cycles, but the current decreased when the cycles continued to increase. This may be associated with the thickness of PSA film related

to the obstruction of electron transfer on the electrode surface. Based on the above discussion, the electro-polymerization cycles of 5 were selected.

### 3.4 The influence of scan rate on the electrochemical properties of roxithromycin



**Fig. 4** Cyclic voltammograms of PSA/GCE in 0.1 M PBS (pH 5.5) with 10 μM roxithromycin at different scan rates (a–h: 20, 40, 60, 80, 100, 120, 140, 160 mV s<sup>-1</sup>, respectively). Inset is the linear relationship of scan rate vs. current.

To investigate the determination mechanism of roxithromycin on the PSA/GCE, this project also individually studied the effects of scan rate on the oxidative reaction of 10 μM RM. CV (Fig. 4) was adopted to test the varied responses of PSA/GCE to RM at scan rates ranging from 20 to 160 mV s<sup>-1</sup> and the anodic peak currents increase

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4 linearly in line with the scan rate. Therefore, the equation of calibration curve was  
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6 described as:  $I_p/\mu A = -0.0994 + 22.7113 \nu / mV s^{-1}$  with a correlation coefficient of  $R =$   
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8 0.999, which evidenced that the electrochemical reactions of RM on the modified  
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10 electrode surface were an adsorption-controlled process. Furthermore, the oxidation  
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12 peak potential ( $E_p$ ) of roxithromycin shifted to positive potentials with an increasing  
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14 scan rate ( $\nu$ ), and the equation was  $E_p (V) = 0.0457 \log \nu (V s^{-1}) + 1.1277$  ( $R = 0.996$ ).  
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19 According to Laviron's theory:

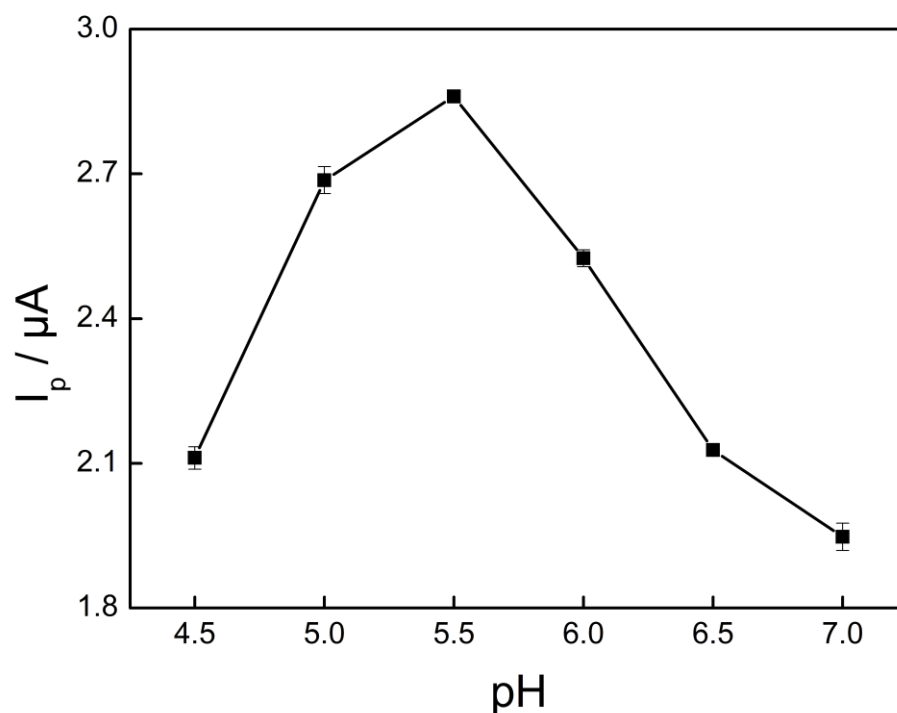
$$E_p = \frac{2.303RT}{2(1-\alpha)nF} \log \nu + K \quad (1)$$

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Where  $n$  refers to the number of electrons involved in the rate-determining step,  
R, T and F represent gas, temperature and Faraday constant, respectively, and  $\alpha$  stands  
for the cathodic electron transfer coefficient. On the basis of the equation (1),  $n = 0.7$   
was attained, which demonstrated that one electron was involved in the oxidation  
process of roxithromycin at PSA/GCE.

### 3.5 The influence of pH on the electrochemical properties of roxithromycin

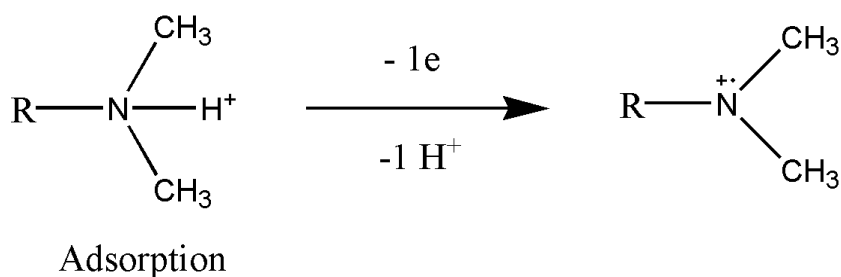
Furthermore, the effects of pH on the electrochemical response of the PSA/GCE  
were investigated (Fig. 5). The highest peak current was found to appear at pH 5.5.  
Therefore, pH 5.5 was chosen for further experiments. In addition, as pH increased,  
the peak potentials shifted towards negative potentials owing to the hindrance of the  
oxidation at low concentrations of protons. The relationship between oxidation  
potentials ( $E_p$ ) and pH can be expressed by the equation:  $E_p/V = 1.2729 - 0.0278 pH$   
( $R=0.997$ ), indicating the participation of the same electron and proton in the

electrochemical process.



**Fig. 5** The effect of pH value on the oxidation current response of 10  $\mu\text{M}$  roxithromycin at PSA/GCE.

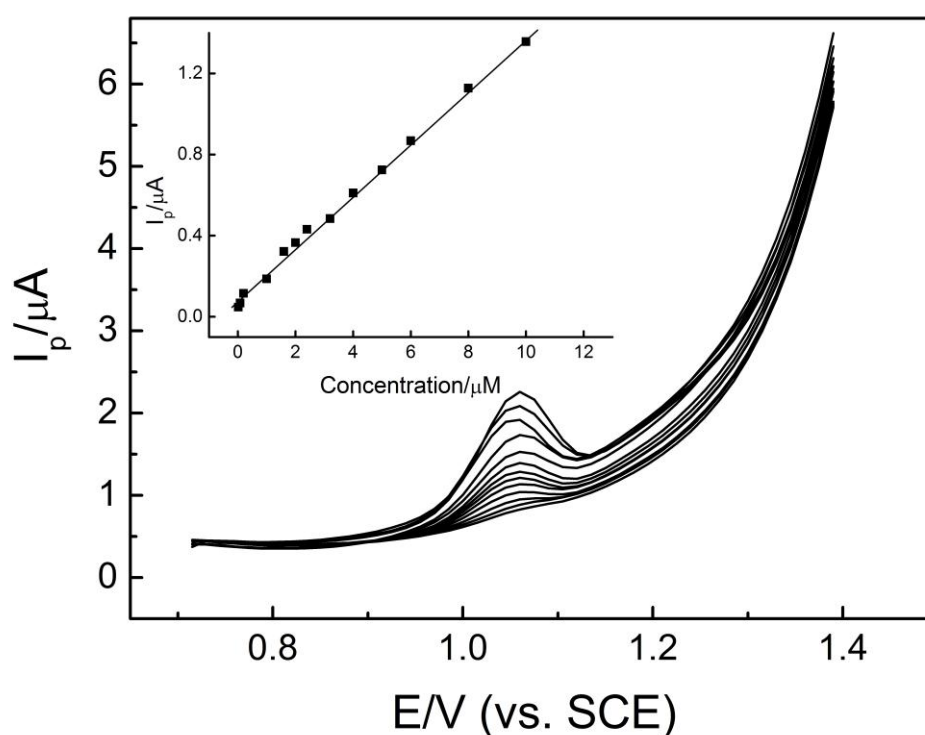
These conclusions (section 3.4 and 3.5) indicated that one electron and one proton were involved in the process of RM at PSA/GCE. The mechanism (Scheme 1) of roxithromycin electrochemical reactions may be inferred as following:



**Scheme 1** The mechanism of roxithromycin electrochemical reactions

### 3.6 Individual voltammetric determination of roxithromycin

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4 The individual electrochemical responses of PSA/GCE towards roxithromycin in  
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6 0.1 M PBS (pH 5.5) were performed by differential pulse voltammetry. As shown in  
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8 Fig. 6, the oxidation peak currents increased linearly with concentrations in the range  
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10 of  $2 \times 10^{-8}$  to  $1 \times 10^{-5}$  M. The equation of calibration curves can be described as  
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12 follows:  $I_p/\mu\text{A} = 0.0813 + 0.1299 c/\mu\text{M}$  ( $R=0.998$ ). The detection limit ( $S/N = 3$ ) was  
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50 **Fig. 6** Differential pulse voltammograms of roxithromycin on PSA/GCE in 0.1 M PBS (pH 5.5).

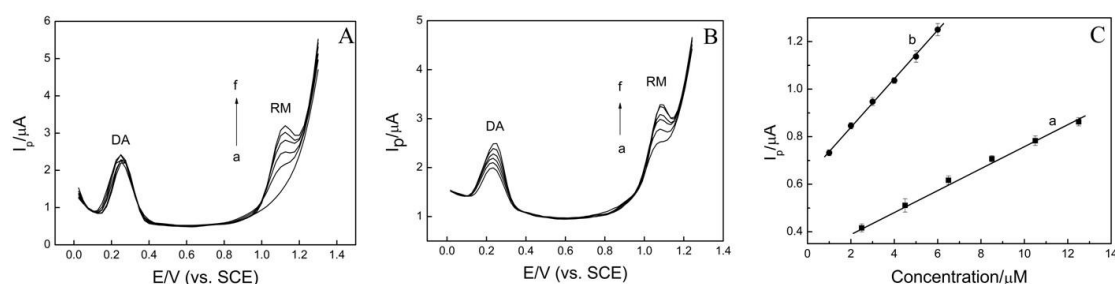
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Insert is calibration curve of roxithromycin with different concentrations.

### 3.7 Simultaneous determination of roxithromycin and dopamine at PSA/GCE

To further investigate the applicability of PSA/GCE to the simultaneous

determination of both analytes in a mixture, DPV was used to record the current responses of these species. First, the concentration of roxithromycin (a→f, 0–10  $\mu\text{M}$ ) was changed while the concentration of dopamine (2 $\mu\text{M}$ ) was remained in 0.1 M PBS (pH 5.5). As shown in Fig. 7A, it was shown that the existence of dopamine had no effect on the determination of roxithromycin.

Then, by changing the concentrations of both roxithromycin and dopamine, the possibility of simultaneous determination was further investigated. Seen from Fig. 7B and C, the peak currents of the two analytes increase linearly with correlation coefficients of 0.998 and 0.999 respectively, while the oxidation peak currents of RM and DA were proportional to their concentrations in the range of 2.5–12.5  $\mu\text{M}$  for RM ( $I_p/\mu\text{A} = 0.3131 + 0.0448 c/\mu\text{M}$ ,  $R=0.998$ ) and 1–6  $\mu\text{M}$  for DA ( $I_p/\mu\text{A} = 0.6364 + 0.1015 c/\mu\text{M}$ ,  $R=0.999$ ) with the detection limits of 0.83  $\mu\text{M}$  and 0.33  $\mu\text{M}$ , respectively. The above results proved that PSA/GCE can be successfully used for the simultaneous detection of RM and DA.



**Fig. 7** A: Differential pulse voltammograms of PSA/GCE at different concentrations of roxithromycin (a→f, 0–10  $\mu\text{M}$ ) and 2 $\mu\text{M}$  dopamine in 0.1 M PBS (pH 5.5); B: Differential pulse voltammograms of PSA/GCE at different concentrations of roxithromycin (a→f, 2.5–12.5  $\mu\text{M}$ ) and dopamine (a→f, 1–6  $\mu\text{M}$ ) in 0.1 M PBS (pH 5.5); C: The calibration curves for the simultaneous determination of roxithromycin (a) and dopamine (b).



### 3.8 Interference, reproducibility and stability studies

Under the optimized condition, the effects of some foreign species on investigating the anti-interference ability of the PSA/GCE on the determination of roxithromycin (10  $\mu\text{M}$ ) were evaluated in detail. Facts prove that such species as 50-fold NaCl, KCl,  $\text{CaCl}_2$ , glucose, sucrose, citric acid, L-phenylalanine, leucine, and L-glutamic acid, 20-fold ascorbic acid, uric acid, L-tryptophan, epinephrine and L-tyrosine, have almost no influence on the current responses of roxithromycin (the signal change below 5%). Thus, it can be said that the proposed method has good selectivity to the determination of roxithromycin.

The reproducibility was examined by measuring the current responses to three successive mixed samples containing 10  $\mu\text{M}$  roxithromycin. Relative standard deviations (RSDs) of 4.02% were obtained.

The stability was also tested. After measurements, the modified electrode was stored at 4  $^{\circ}\text{C}$ . One week later, the modified electrode was used to detect roxithromycin again. It was found that there was only a slight decline of 9.7% in terms of the peak current intensities. In conclusion, the modified electrode showed high selectivity, favorable reproducibility and good stability.

### 3.9 Analytical applications

In order to verify the applicability of the proposed sensor in clinical applications, PSA/GCE was utilized to detect roxithromycin concentration in human serum samples. As shown in Table 1, the recovery of 104% was obtained in serum sample.

Moreover, the relative standard deviation (R.S.D.) was lower than 5%, indicating the high precision of this method which can satisfy the requirements of microanalysis. In short, the developed electrochemical method is applicable to the determination of roxithromycin.

**Table 1** Determination of roxithromycin in human serum samples

Analytes	Added( $\mu\text{M}$ )	Found ( $\mu\text{M}$ )	Recovery (%)	RSD (%)
	2	1.95	97.5%	1.1
roxithromycin	5	4.61	92.2%	2.3
	9	9.19	102.1%	0.9

#### 4. Conclusions

In summary, we have proposed a novel poly-sulfosalicylic acid modified glassy carbon and demonstrated its feasibility in the simultaneous determination of roxithromycin and dopamine. This method is simple and fast. By modifying the electrode, the oxidation peak potentials of roxithromycin and dopamine get enhanced and separated distinctly. The further investigations of individual and simultaneous determination of roxithromycin and dopamine were also satisfactory. Besides, this method had successfully detected of the concentration of roxithromycin in human serum samples.

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