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Article

# Electrochemiluminescence Sensor for the Detection of Tiapride Hydrochloride with Chitosan-Ru(bpy)$_3^{2+}$-SiO$_2$NPs/MCNT/Nafion Modified Electrode

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Chitosan-Ru$_2$(bpy)$_3^{2+}$-SiO$_2$ composite nanoparticles (CRuS NPs) were prepared by reverse microemulsion method for the electronic attraction between negative charge of hydroxyl groups in chitosan and positive charge in Ru$_2$(bpy)$_3^{2+}$. Based on the multi-walled carbon nanotubes (MCNT)/Nafion composite membrane technology, CRuS NPs was effectively and steadily immobilized on the surface of a glassy carbon electrode. The CRuS NPs synthesized were characterized by transmission electron microscope (TEM), UV-Vis spectroscopy and fluorescence spectroscopy, while the modification was confirmed by cyclic voltammetry and electrogenerated chemiluminescence (ECL). The ECL studies revealed that the sensor had a good response to different concentrations of tiapride hydrochloride and the increased ECL intensity was directly related to the logarithm of tiapride hydrochloride concentrations in the range from 0.01 to 3.0 μmol L$^{-1}$ with a detection limit of 6.0 nmol L$^{-1}$. The sensor was successfully applied to the determination of tiapride hydrochloride in pharmaceutical.

**Keywords:** electrogenerated chemiluminescence, chitosan, tiapride hydrochloride

## Introduction

Tiapride hydrochloride, *N*-(2-diethylaminoethyl)-2-methoxy-5-methylsulfonyl benzamide hydrochloride (Figure 1), was synthesized in 1974 and introduced by Synthélabo (now Sanofi) in 1977.[1] It was an atypical antipsychotic agent, a selective dopamine D2 and D3 receptor antagonist, which has been used successfully in the treatment of different neurologic and psychiatric disorders, including extrapyramidal motor disorders, tardive dyskinesia, withdrawal symptoms and Huntington's disease.[2] Consequently, different analytical methods including non-aqueous titration,[3] high-performance liquid chromatography (HPLC) using tandem UV photodiode-array and fluorescence,[4] liquid chromatography-tandem mass spectrometry,[5,6] column-switching high-performance liquid chromatographic method with fluorescence,[7] LC methods,[8] spectrofluorimetric,[9] chemiluminometric,[10] electrochemical[11] and electrochemiluminescence analytical techniques,[12,13] have been developed for the detection of tiapride hydrochloride.

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Among those, electrogenerated chemiluminescence (ECL) technology is one of the most important methods because it has some obvious advantages over other existing methods such as being simple, rapid, sensitive, low-cost and portable.[14] To date, ECL has become a very powerful analytical technique and been widely used in the areas of immunoassay, food, water testing and drug reagent detection.[15] Among the reported ECL systems, Ru(bpy)$_3^{2+}$ has been used widely since it can provide several advantages, such as high quantum yield and creating a regenerable sensor, however, the biggest drawback is the high cost. In recent years, to prepare the solid phase electrochemical luminescence sensors through fixing Ru(bpy)$_3^{2+}$ on the electrode surface can save the expensive luminescent reagents and improve the sensitivity, broaden the application of electrochemical luminescence method in analytical chemistry.

Chitosan is a good film-forming substance which is deacetylated from chitins and rich in amino and hydroxyl groups, and it has been considered as a promising candidate for fabricating ECL sensors or biosensors.[16-18] In this work, the chitosan-Ru$_2$(bpy)$_3^{2+}$-SiO$_2$ composite nanoparticles (CRuS NPs) were synthesized by silica, chitosan and

$Ru(bpy)_3^{2+}$, then, the CRuS NPs were self-assembled on the multi-walled carbon nanotubes (MCNT)/Nafion coating film electrode based on the stronger electrostatic interactions between the positive charge of amino in chitosan embedded in CRuS NPs and negative charge in Nafion on the electrode surface. Compared to the previous method, the proposed ECL sensing method is simple and low cost because it is a label-free strategy, which eliminates the labeling, separation, and immobilization steps.

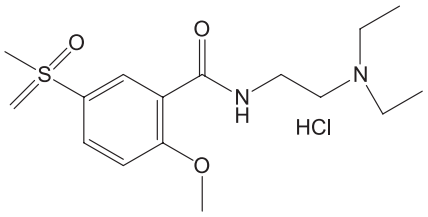


**Figure 1.** The structural formula of tiapride hydrochloride.

## Experimental

### Apparatus

ECL measurements were performed with a MPI-E ECL detector (Xi'an Remax Electronics, Xi'an, China). A commercial cylindroid glass cell was used as an ECL cell, which contained a conventional three-electrode system consisting of a modified glassy carbon electrode (GCE) as the working electrode, a platinum sheet as the counter electrode, and an Ag/AgCl (saturated KCl) as the reference electrode, respectively. ECL emissions were detected with a photomultiplier tube (PMT) that was biased at −800 V unless otherwise stated. Cyclic voltammetric measurements were performed on a Zennium electrochemical workstation (ZAHNER, Germany). The UV-Vis spectra was recorded using a UV-Vis spectrophotometer (UV-1600PC, Meipuda Instruments Co., Shanghai, China), and the fluorescence spectrum was recorded with an F-4600 spectrofluorometer (Hitachi, Japan). A multiposition magnetic stirrer (IKA, Germany) and a high-speed centrifuge (5804 R, Eppendorf) were used to stir the synthesizing CRuS NPs and separate nanoparticles, respectively.

### Reagents

Tris-(2,2'-bipyridyl)-dichlororuthenium(II) hexahydrate($Ru(bpy)_3Cl_2{\cdot}6H_2O$), chitosan, Nafion 117 (5% in a mixture of lower aliphatic alcohols and water), Triton X-100 and tetraethylorthosilicate (TEOS) were purchased from Sigma (USA), while cyclohexane, *n*-hexanol, acetone, and ethanol were purchased from Tianjin Chemical Reagent Factory. Multiwalled carbon nanotubes (MWNTs, diameter of 10 nm, length of 5-15 mm) were obtained from Shenzhen Nanotech Port Co., Ltd. (China).

0.05 g MCNTs were dispersed in 60 mL of 2.2 mol $L^{-1}$ $HNO_3$ for 20 h at room temperature with the aid of ultrasonic agitation for 30 min, then washed with distilled water to neutrality, and dried in an oven at 37 °C. A 0.5% m/m chitosan solution was prepared by dissolving 50 mg of chitosan in 10 mL of 1.0% v/v acetic acid solution and stirred for 30 min at room temperature until complete dissolution occurred, and the chitosan solution was stored under refrigeration at 4 °C when not in use. A concentration of 0.1 mol $L^{-1}$ phosphate buffer saline (PBS, pH 7.4, 0.10 mol $L^{-1}$ NaCl + 0.1 mol $L^{-1}$ $KH_2PO_4/K_2HPO_4$) was prepared in highly pure water (sterile Minipore water, 18.3 MΩ) and was used as hybridization buffer and washing solution.

### Preparation of the CRuS NPs

The ECL sensor was synthesized according to the reverse microemulsion system with the following steps. Briefly, 1.77 mL of Triton X-100, 7.5 mL of cyclohexane, 1.8 mL of 1-hexanol, and 300 μL of water were mixed together, after stirring for 30 min, 50 μL 0.01 mol $L^{-1}$ $Ru(bpy)_3^{2+}$ aqueous solution and 100 μL 0.5% chitosan were added to the above mixture, and NaOH solution was added to adjust the pH (pH = 7), then the mixture was stirred for 1 h. After that, in the presence of 90 μL of TEOS, a polymerization reaction was initiated by adding 60 μL of $NH_4OH$ and the hydrolysis reaction was allowed to continue for 24 h. At last, acetone was then added to destroy the emulsion, followed by centrifuging and washing with ethanol and water, then the orange CRuS NPs were obtained and were saved in refrigerator at 2 °C.

### Preparation of the ECL sensor

A bare GCE was polished carefully to a mirror-like surface with 0.3-0.05 μm alumina aqueous slurry, and then successively washed in an ultrasonic cleaner with ethanol and water. Prior to modification, the bare GCE was cyclic voltammetry scanned from −0.2 to 0.6 V in 0.01 mol $L^{-1}$ $Fe(CN)_6^{3-}$ solution containing 0.1 mol $L^{-1}$ KCl supporting electrolyte until a pair of rather well-defined redox peaks were obtained. Then, 1.5 mg MCNT were dispersed in 3.0 mL of 0.05% Nafion solution and the mixture were ultrasonicated to homogeneously distribute the nanotubes. After that, 10 μL of the mixture solution (MCNT with Nafion) were drop-coated onto the surface of the pretreated GCE and dried for about 30 min at room temperature to form a MCNT/Nafion modified GCE. After being washed with washing water,

the modified GCE was immersed in 300 μL CRuS NPs solution for 30 min. During this process, CRuS NPs were self-assembled onto the surface of the GCE based on the stronger electrostatic interactions between the positive charge of chitosan embedded in the CRuS NPs and negative charge of Nafion. Finally, the electrode was washed thoroughly with 0.10 mol $L^{-1}$ PBS (pH 7.4) to remove the nonspecifically adsorbed nanoparticles to minimize the background response. It was noted that for preparing the electrodes with a good reproducibility, the original synthesized CRuS NPs should be centrifuged at 3000 rpm for 10 min to separate the bigger particles from the solution, then, the retained solution was further centrifuged at 7000 rpm to get the final CRuS NPs. The principle diagram of ECL sensor was shown in Figure 2.

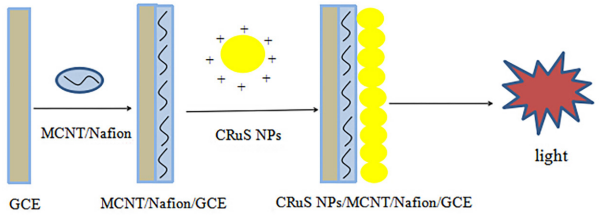


**Figure 2.** The principle diagram of electrochemical luminescence sensor.

### ECL measurements

The CRuS NPs/MCNT/Nafion GCE was immersed in an ECL cell, which contained 3.0 mL of 0.10 mol $L^{-1}$ PBS (pH 7.4) with different concentrations of tiapride hydrochloride, then the ECL signals were recorded, when the interaction time of tiapride hydrochloride with the CRuS NPs/MCNT/Nafion GCE was 20 min and the electrode potential was scanned from 0 to 1.4 V at the scan rate of 100 mV $s^{-1}$. The negative voltage of the PMT was −800 V in the process of detection. The concentration of tiapride hydrochloride was quantified by the ECL intensity.

## Results and Discussion

### Characterization of CRuS NPs

The synthesized CRuS NPs were characterized by spectroscopy and transmission electron microscope (TEM) for size and morphology. The TEM images in Figure 3 showed that the nanoparticles prepared presented the uniform size of about 50 nm. As shown in Figure 4, the spectral behaviors of CRuS NPs were also characterized through UV-Vis spectroscopy and fluorescence spectroscopy. It was shown in Figure 4A, the UV-Vis absorption spectra were the same for the pure $Ru(bpy)_3^{2+}$ and synthesized CRuS NPs. Nevertheless, the emission spectra of the pure $Ru(bpy)_3^{2+}$ and CRuS NPs had a tiny difference, that was the pure $Ru(bpy)_3^{2+}$ showed maximal emission at 594 nm while the excitation was at 458 nm, the shorter-wavelength shift in the fluorescence emission of CRuS NPs (Figure 4B). The phenomenon can be explained that the $SiO^-$ groups in CRuS NPs had a negative charge and possessed stronger electrostatic adsorption ability to the positive charge of $Ru(bpy)_3^{2+}$, and the most $Ru(bpy)_3^{2+}$ molecules resided at the bulk of the silica nano particle. Hence, when these nanoparticles were dispersed in water, they had less interaction with the surrounding water molecules and showed fluorescence emission at a lower relative wavelength.

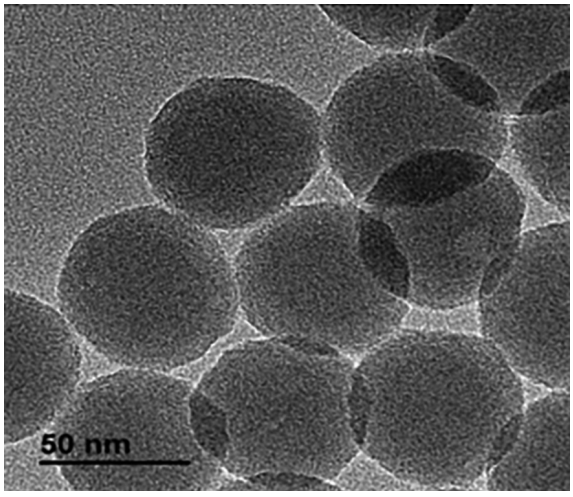


**Figure 3.** TEM images of CRuS NPs.

### Characterization of the ECL sensor

The ECL sensor prepared was investigated by cyclic voltammetry and ECL, respectively (Figure 5A). Our results showed that, the current at the MCNT/Nafion GCE (Figure 5A, curve b) was obviously enhanced, compared to the bare GCE (Figure 5A, curve a), which indicated that the MCNT/Nafion was successfully coated on the GCE. Simultaneously, the self-assembling of CRuS NPs on MCNT/Nafion GCE was also studied by the CV technique (Figure 5A, curve c), showing results that a new redox wave was observed in 0.1 mol $L^{-1}$ PBS (pH = 7.4) at 1.15 and 1.03 V, respectively, which was the typical redox wave of $Ru(bpy)_3^{2+}$. The results indicated that the CRuS NPs were successfully self-assembled on the MCNT/Nafion film electrode, meanwhile, it also could indicate that the reason for the CRuS NPs assembled on the electrode was due to the electrostatic interaction between the positively charged CRuS NPs and the negatively charged Nafion film.

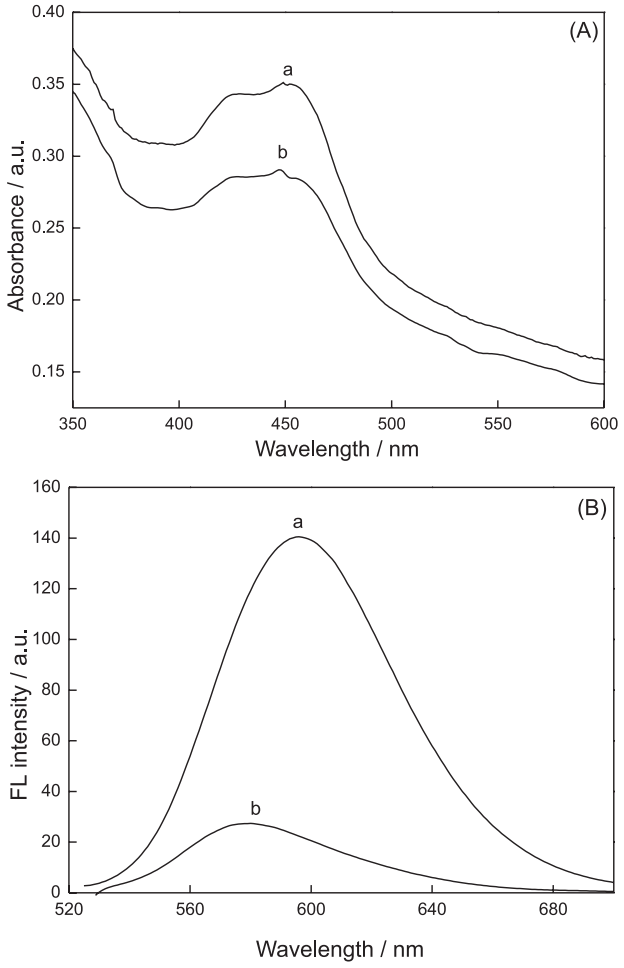


**Figure 4.** (A) UV-Vis spectra and (B) fluorescence (FL) spectra of (a) $Ru(bpy)_3^{2+}$ and (b) CRuS NPs.

The ECL behavior of the sensor was investigated and the intensity-potential curves were shown in Figure 5B. As shown in Figure 5B, no ECL signal appearance at the bare GCE (Figure 5B, curve a) and the MCNT/Nafion GCE (Figure 5B, curve b). However, a peak ECL intensity occurred at about 1.25 V at the CRuS NPs/MCNT/Nafion GCE (Figure 5B, curve c), and this was the typical ECL profile of $Ru(bpy)_3^{2+}$, which indicated that the $Ru(bpy)_3^{2+}$ inside CRuS NPs on GCE could effectively do its ECL reaction.

Furthermore, the stability of the CRuS NPs/MCNT/Nafion composite films on the electrode was investigated. Figure 5C shows the ECL intensity-time curves of the CRu NPs/MCNT/Nafion GCE in 0.1 mol $L^{-1}$ pH 7.4 PBS containing 50 mmol $L^{-1}$ TPA between +0.2 and +1.4 V after placed in 0.1 mol $L^{-1}$ pH 7.4 PBS for 2 weeks. As shown in Figure 5C, under continuous potential scanning for 10 cycles, the relative standard deviation (RSD) of ECL signals was less than 5%, which indicated that the prepared ECL sensor displayed a good ECL stability and reproducibility and can be used for the subsequent experiment.

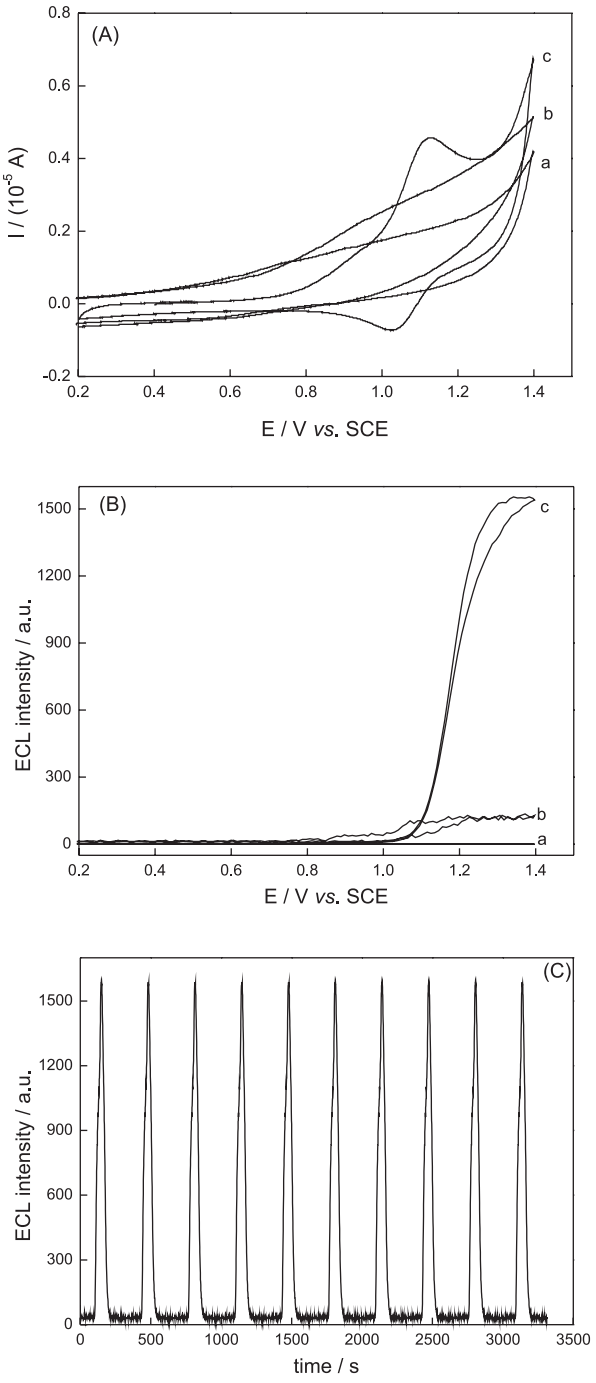


**Figure 5.** (A) Cyclic voltammograms obtained at different electrodes in 0.1 mol $L^{-1}$, pH 7.4 PBS; (B) ECL intensity-potential profiles obtained at different electrodes in 0.1 mol $L^{-1}$, pH 7.4 PBS containing 50 mmol $L^{-1}$ TPA; (C) ECL intensity-time curves of CRu NPs/MCNT/ Nafion/GCE obtained in 0.1 mol $L^{-1}$ pH 7.4 PBS containing 50 mmol $L^{-1}$ TPA from continuous potential scanning over ten cycles. (a) GCE; (b) MCNT/Nafion/GCE; (c) CRu NPs/MCNT/Nafion/GCE.

## ECL behaviors of tiapride hydrochloride at the CRuS NPs/MCNT/Nafion modified electrode

The ECL behaviors at CRuS NPs/MCNT/Nafion GCE in the absence and presence of tiapride hydrochloride

were investigated. Figure 6 shows the corresponding ECL-potential curves at CRuS NPs/MCNT/Nafion GCE in 0.1 mol $L^{-1}$ pH 7.4 PBS with inexistence (curve a) and containing 0.03 μmol $L^{-1}$ tiapride hydrochloride (curve b) under consecutive potential scans from 0 to 1.4 V with a scan rate of 100 mV $s^{-1}$. As shown in Figure 6, in comparison with the blank ECL intensity, the ECL intensity obviously increased in the presence of 0.03 μmol $L^{-1}$ tiapride hydrochloride.

It was reported that tertiary amines were easier to oxidize because of their lower ionization potentials originating from electrons in the nitrogen orbitals, and within the group of tertiary amines, the ionization potential decreased when the length of the alkyl chain increased,[19] the electron donating effected the emission intensity as they react with $[Ru(bpy)_3]^{3+}$.[20] It was well known that tri-*n*-propylamine (TPrA) may serve as the co-reactants for $[Ru(bpy)_3]^{2+}$ ECL reaction, as well as a wide range of amine compounds.[21-23] Tiapride hydrochloride contains tertiary amines group in the structure, so $[Ru(bpy)_3]^{2+}$ ECL increases when tiapride hydrochloride exists.

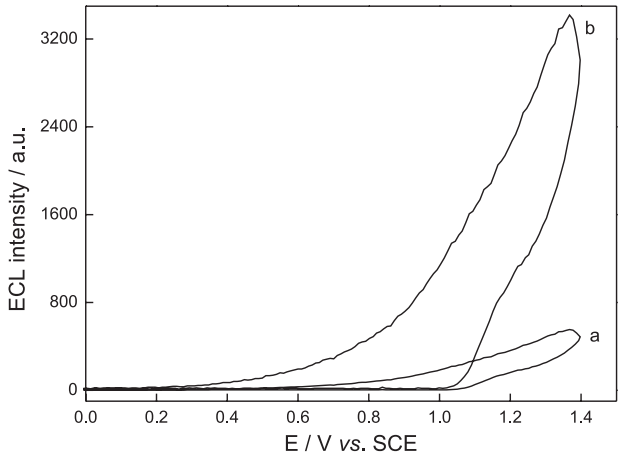


**Figure 6.** ECL intensity-potential profiles obtained at CRuS NPs/MCNT/Nafion/GCE in the (a) absence and (b) presence of 0.03 μmol $L^{-1}$ tiapride hydrochloride with 0.1 mol $L^{-1}$, pH 7.4 PBS.

## Optimization of the preparation and test conditions

Generally, the self-assembly time of CRuS NPs on the MCNT/Nafion GCE affected the ECL intensity. The modified electrode was prepared according to the protocol described in Preparation of the ECL sensor section except the self-assembly time of the CRuS NPs with the MCNT/Nafion GCE. Our results found that the ECL peak intensity increased with the increasing of the self-assembly time from 5 to 40 min and reached a plateau at 20 min. In order to ensure that CRuS NPs was completely adsorbed on the MCNT/Nafion GCE, 30 min was chosen as the optimal self-assembly time.

Additionally, the test conditions for the determination of tiapride hydrochloride by the CRuS NPs/MCNT/Nafion GCE was discussed. Firstly, the applied potential for the ECL detection was studied by changing from +0.9 to +1.4 V. Our result found that when the applied potential was less than +1.1 V, light emission was not observed since $Ru(bpy)_3^{2+}$ was not oxidized on the electrode. When the applied potential was above +1.1 V, the ECL intensity increased and reached the maximum values at +1.25 V. So +1.25 V was selected as the optimum potential for the ECL detection. Then, the interaction time of the tiapride hydrochloride with the CRuS NPs/MCNT/Nafion GCE was investigated, the ECL intensity after interaction with 0.03 μmol $L^{-1}$ tiapride hydrochloride in different time was examined and the result is shown in Figure 7A. As can be seen from Figure 7A, the ECL peak intensity increased with the increasing of the interaction time from 0 to 15 min and then slightly increased from 15 to 30 min. Considering the fact that a lower concentration of tiapride hydrochloride needs a longer time, 20 min was chosen as the optimal interaction time of tiapride hydrochloride with the CRuS NPs/MCNT/Nafion GCE in the following experiments. Beyond this, pH of the system also affected the ECL intensity because of the synthetic composite CRuS NPs containing chitosan, and the amino proton on chitosan had a corresponding specific buffer value, thus had a certain influence on the ECL intensity. The ECL intensity before and after interaction with 0.03 μmol $L^{-1}$ tiapride hydrochloride on the CRuS NPs/MCNT/Nafion GCE with different pH was examined (Figure 7B). As seen from Figure 7B, the ECL intensity increased with the pH increasing from 5.8 to 8.0 and then reached a peak value in the pH of 7.4. Therefore, pH of 7.4 was chosen as the optimal condition in the experiment.

## Analytical performance of the ECL sensor

Figure 8 displayed the ECL intensity of the ECL sensor before and after the interaction with different concentrations of tiapride hydrochloride in 0.1 mol $L^{-1}$ PBS (pH = 7.4). It could be seen that the ECL intensity in the presence of tiapride hydrochloride was higher than that in the absence of tiapride hydrochloride, and the ECL intensity increased gradually with the increasing concentrations of tiapride hydrochloride. This is attributed to the fact that tiapride hydrochloride contains tertiary amine groups similarly to TPrA, which may serve as the co-reactants for $Ru(bpy)_3^{2+}$ ECL reaction. So, the tiapride hydrochloride concentration could be determined by the ECL sensor. From the inset of Figure 8, it can be seen that the increased integrated ECL intensity was directly related to the logarithm of tiapride

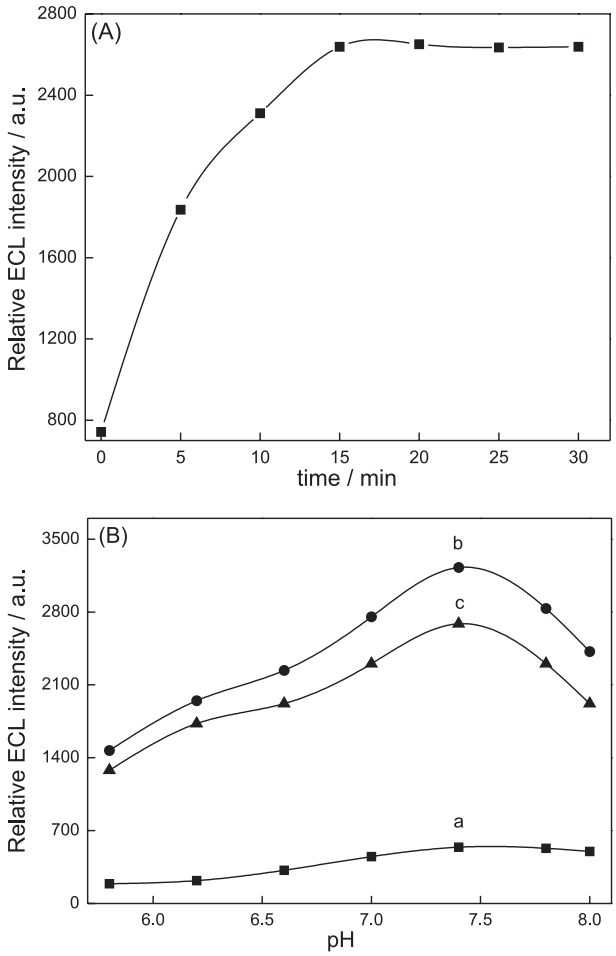


**Figure 7.** The effect of the (A) interaction time and (B) pH on the ECL intensity with 0.03 μmol $L^{-1}$ tiapride hydrochloride on CRuS NPs/MCNT/Nafion modified electrode at 100 mV $s^{-1}$ in 0.10 mol $L^{-1}$ PBS (pH 7.4). Curves (a) and (b) are the ECL intensity in the absence and presence of tiapride hydrochloride, respectively, and curve (c) is the relative ECL intensity.

hydrochloride in the range from 0.01 to 3.0 μmol $L^{-1}$. The regression equation was $\Delta I = 10402.85 + 1028.57 \lg C$ with a correlation coefficient of 0.9862. The detection limit was 6.0 nmol $L^{-1}$ using 3s / S, where s is the RSD of the blank solution with 11 parallel measurements, and S is the slope of the calibration curve. As shown in Table 1, the detection limit in this work was lower than those of the previous methods with the exception of Yan *et al.*[12] work.

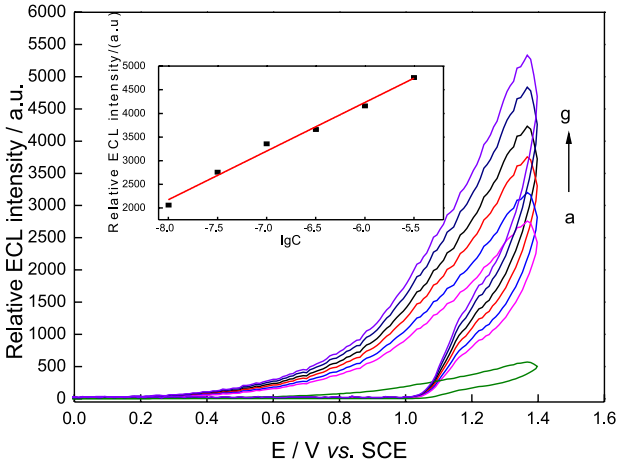


**Figure 8.** ECL intensity-potential curves with different concentrations of tiapride hydrochloride: (a) blank; (b) 0.01 μmol $L^{-1}$; (c) 0.03 μmol $L^{-1}$; (d) 0.1 μmol $L^{-1}$; (e) 0.3 μmol $L^{-1}$; (f) 1.0 μmol $L^{-1}$; (g) 3.0 μmol $L^{-1}$. Inset: calibration curve for tiapride hydrochloride.

## Selectivity and reproducibility of ECL sensor

The selectivity of the ECL sensor prepared for tiapride hydrochloride was evaluated in the presence of other additives including methanol, ethanol, sulpiride, sultopride, glucose, starch, maltose, sucrose, respectively, especially for sulpiride and sultopride. The results showed that the ECL intensity of 0.03 μmol $L^{-1}$ tiapride hydrochloride was almost equivalent to the ECL intensity of the mixture of 0.03 μmol $L^{-1}$ tiapride hydrochloride-0.03 μmol $L^{-1}$ additives (RSD < 5.0%). This suggested that the present sensor had an excellent selectivity for tiapride hydrochloride detection.

The reproducibility of the method proposed in this work was checked. The RSD for 11 times determination of 0.03 μmol $L^{-1}$ tiapride hydrochloride was 2.9% with the same sensor. Furthermore, the reproducibility was also checked by using five ECL sensors which were prepared at the same time, each measurement using one fabricated sensor was performed for 0.03 μmol $L^{-1}$ tiapride hydrochloride. The results showed that the RSD of five measurements was 3.1%. This indicated that the method proposed in this work had a good reproducibility.

**Table 1.** Detection line range and limits for tiapride hydrochloride using different sensors

| Method | Line range / (μmol $L^{-1}$) | Detection limit / (μmol $L^{-1}$) | Reference |
|---|---|---|---|
| ECL | 0.1-100 | 0.00067 | 12 |
| ECL | 0.1-100 | 0.015 | 13 |
| CZE | 2.74-274 | 0.0274 | 2 |
| Electrochemical | 10-10000 | 0.25 | 11 |
| This paper ECL method | 0.01-3.0 | 0.006 | – |

ECL: electrochemiluminescence; CZE: capillary zone electrophoresis.

**Table 2.** Determination of tiapride hydrochloride in pharmaceutical

| Sample | Marked concentration / (μmol $L^{-1}$) | Measured / (μmol $L^{-1}$) | Added / (μmol $L^{-1}$) | Found / (μmol $L^{-1}$) | RSD / % | Recovered / % |
|---|---|---|---|---|---|---|
| 1 | 27.6 | 26.6 | 25.0 | 51.8 | 2.7 | 100.8 |
| 2 | 27.6 | 28.5 | 25.0 | 53.0 | 2.9 | 98.2 |
| 3 | 27.6 | 28.9 | 25.0 | 55.1 | 3.3 | 104.1 |

### Application

To evaluate the applicability of the proposed method, it was applied to the determination of tiapride hydrochloride in tiapride hydrochloride tablets (Tasly Di Yi Pharmaceutical Company, JiangSu, China). Firstly, the tiapride hydrochloride tablets should be grinded, and then the stock sample solutions were prepared by dissolving 10 mg powder to 1000 mL with water after filtration, then, the stock sample solution was diluted for 100-fold as the analytical sample. The tiapride hydrochloride was determined according to the experimental procedures and the recoveries were also performed by the standard addition method (Table 2). The RSD of each sample for five times parallel detections was less than 3.3% and the recovery ratio on the basis of this method was between 99.2 and 102.8%. This indicated the determination of tiapride hydrochloride using the proposed method was effective and feasible. Compared with the previous reported methods, the advantages of using the present method had a good reproducibility and sensitivity.

## Conclusion

In summary, chitosan, a cationic polysaccharide containing amino and hydroxyl groups, was used to synthesize CRuS NPs as the ECL sensing indicator by the electronic attraction between chitosan and $Ru(bpy)_3^{2+}$, then, a novel ECL sensor has been designed using CRuS NPs immobilized on the MCNT/Nafion GCE. This method was practical and valuable for the determination of tiapride hydrochloride in the medicament. According to the proposed ECL mechanism for the determination of tiapride hydrochloride, this sensing platform may be extended to sensitively detect other amine compounds. In addition, the design and self-assembling of CRuS NPs on MCNT/Nafion electrode in this work could open up a new way for molecular sensing.

## Acknowledgments

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