

Preparation of Au@Ir/C as sensor for Methimazole Detection

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Au@Ir/C nanocomposite as an electroactive material for methimazole detection has been synthesized via polyol reduction method. Physical tests demonstrate that ultrafine nanoparticles of Au@Ir composite (2-4 nm) are evenly dispersed on carbon. This structure helps enhance its activity and stability. Electrochemical tests prove that Au@Ir/C has high response sensitivity to methimazole and well supports precise methimazole determination. Within a concentration range from 0.001 to 5.0 mM, methimazole concentration (c) and peak current (i_p) possesses a linear correlation, and the linear regression equation is expressed as: $i_p=5.4775c+9.2488$ ($R=0.9987$, $P < 0.0001$). Also, chronoamperometry result proves the high stability of Au@Ir/C on methimazole measurement, suggesting a superior reliability for this method.

Keywords: Methimazole; Au@Ir/C composite; Electrochemical sensor; Concentration determination

1. INTRODUCTION

Methimazole is the first choice for the treatment of hyperthyroidism for its effective inhibition on the synthesis of hormones and its significant efficacy [1-3]. In the preparation, pharmacokinetic study, and the development of methimazole dosage, methimazole concentration determination is the key technology which is concerned with the quality and the level of the drugs [4-6]. Currently, the detection methods towards methimazole are mainly spectrophotometry [7-11] and high performance liquid chromatography [12-16]. These methods have shown many disadvantages, such as tedious process, long-time test cycle, low experimental efficiency, and poor data reliability. Thus, it is necessary to establish a high-efficiency and reliable methimazole detection method to meet the needs of the drug development.

Electrochemical sensor is a newly developed drug detection method with advantages of fast

response and high sensitivity. It can act as a substitute for traditional detection method. Li's groups [17,18] studied the preparation method of cobalt phthalocyanine-modified film electrodes and the electrochemical behavior of a methimazole on these electrodes. And an approach to methimazole determination using cyclic voltammetry technique was established. Wang's group [19] prepared a heme-modified carbon paste electrode, which was successfully used to measure the concentration of methimazole and showed good selectivity and anti-jamming effect. They obtained the linear correlation between peak current and methimazole concentration. In these researches, electrochemical sensors displayed many successes on drug detection, but its disadvantages in practical operation are not neglected, for example, the preparation processes of the modified electrodes are tedious, and the modification material is often unstable, resulting in short working lifetime.

In this work, an Au@Ir/C composite is prepared and used as the electroactive material for methimazole detection. In order to enhance the response activity of electroactive material, a special structure of Au @ Ir/C core-shell is designed, in which Ir nanoparticles is firstly loaded on Vulcan XC-72, and then Au atoms are gradually grown on the surface of Ir nanoparticles so as to make Au fully exposed. Electrochemical technique is applied and allowed to establish a linear correlation between methimazole concentration and peak current. The expected results as initially designed have been achieved. The advantages of this method lies in: 1) high reactive response and sensitivity; 2) high stability and long lifetime; 3) simplification of processing of samples and high efficiency.

2. EXPERIMENTAL

2.1. Instruments and reagents

The main instruments used in this experiment: Microcomputer microwave chemical reactor (MCR-3, Shanghai, China); Electrochemical workstation (CHI760E, Shanghai, China). And the main reagents: Vulcan XC 72, 5 wt% Nafion solution (Dupond, USA); Chloroauric acid, Chloroiridic acid and Methimazole (Shanghai Chemical Reagent Corp., China).

2.2. Experimental method

2.2.1. Material preparation and characterization

The core-shell structured Au@Ir/C composite was prepared via microwave-assisted polyol processes (MAPP) [20]. It underwent two steps: 1) to load Ir nanoparticle on Vulcan XC-72; 2) to grow Au on Ir so as to make Au sufficiently exposed.

Eighty milligram of Vulcan XC-72 was added into 50 ml of the solution (glycol : isopropanol=4:1, v : v), followed by ultrasonical dispersion for 1 h. After that, 0.72 ml of 0.03612 M $\text{H}_2\text{IrCl}_6/\text{EG}$ solution was added into the mixture, and kept stirring for 2 h. Adjusted the pH value to 12 with 0.5 M NaOH/EG. After stirring for 2 h, the mixture was subjected to a reaction at 135°C in a Microwave Reactor for 60 s. The mixture was cooled and stirred for 10 h. Finally, the product, Ir/C, was obtained by filtration and dryness.

Au@Ir/C composite was synthesized with the same method as above except that Ir/C composite substitutes for Vulcan XC-72 support and H_2AuCl_4 substitutes for H_2IrCl_6 precursor. The components of Au@Ir/C were 5 wt% Ir, 15 wt% Au, and 80 wt% C.

For material characterization, transmission electron microscopy (TEM) images were taken on Tecnai 20U-TWIN (Netherlands) with a spatial resolution of 0.19 nm and an operating voltage of 136 KeV. X-ray diffraction (XRD) patterns were recorded using a D/max-rB X-ray diffractometer (Japan) with a Cu $\text{K}\alpha$ radiation source and an operating voltage of 45 kV.

2.2.2. Electrode modification

Glassy carbon electrode (GCE) with a surface area of 0.07065 cm^2 was treated with $0.05 \mu\text{m}$ alumina. The ink of Au@Ir/C (2 mg mL^{-1}) was prepared by mixing Au@Ir/C with ethanol in an ultrasonic bath for 30 min. Eight microliters ($4 \mu\text{L}$ each time, 2 times) of the ink was loaded on the GCE and dried in N_2 flow. And then $3 \mu\text{L}$ of dilute Nafion solution was covered on the surface to form a Nafion film [21].

2.2.3. Electrochemical measurements on methimazole

The electrochemical measurements were carried out in a standard three-electrode electrochemical cell controlled by CHI760E electrochemical analysis instrument. RDE loaded with Au@Ir/C serves as the working electrode, Pt foil (1 cm^2) as the counter electrode, and the saturated calomel electrode (SCE) as the reference electrode [21].

Meanwhile, prepare a series of methimazole solution with concentrations of 5.0, 2.0, 1.0, 0.1, 0.01, 0.001 mM with Phosphate buffer solution (PBS). The dissolved O_2 in the solution was removed by bubbling N_2 for 20 min before each test. For cyclic voltammetry determination, the CV curves were recorded in the potential range of -0.38 - 1.0 V at a scan rate of 20 mV s^{-1} , For determination of electrochemical response to methimazole, *i-t* curves were recorded under the potential of 0.56 V at intervals of 600 s. For stability test, *i-t* curves were recorded with a period of 7200 s. Besides, the potential used in this work was converted to the standard hydrogen potential.

3. RESULTS AND DISCUSSION

3.1. Characterization of Au@Ir/C composite

In order to investigate the morphology and the microstructure of the home-made Au@Ir/C composite, the TEM measurements are performed and the results are presented in Figure 1. From Figure 1a we can observe that ultra fine Au@Ir composite nanoparticles are supported on carbon material and shown an excellent distribution. From Figure 1b, an enlarged high-resolution TEM image, we can recognize the particle state and the particle size (ca. 2-4 nm) more clearly. This is the desired state for Au@Ir/C composite because fine nanoparticles of active material possesses large sum of active sites, and high distribution can help obtain outstanding stability. Figure 1c displays the XRD

pattern of Au@Ir/C composite. The main diffraction peaks at 38.2° , 44.4° , 64.6° , and 77.5° (2θ) in this pattern are generated by Au metal [22], and the weak diffraction peaks by trace Ir metal [23] also appear. Besides, the peak located at about 24.5° (2θ) is attributed to the carbon material [24]. According to the relevant papers, these results are consistent with their analyses and further confirm the existence of each component in the Au@Ir/C composite.

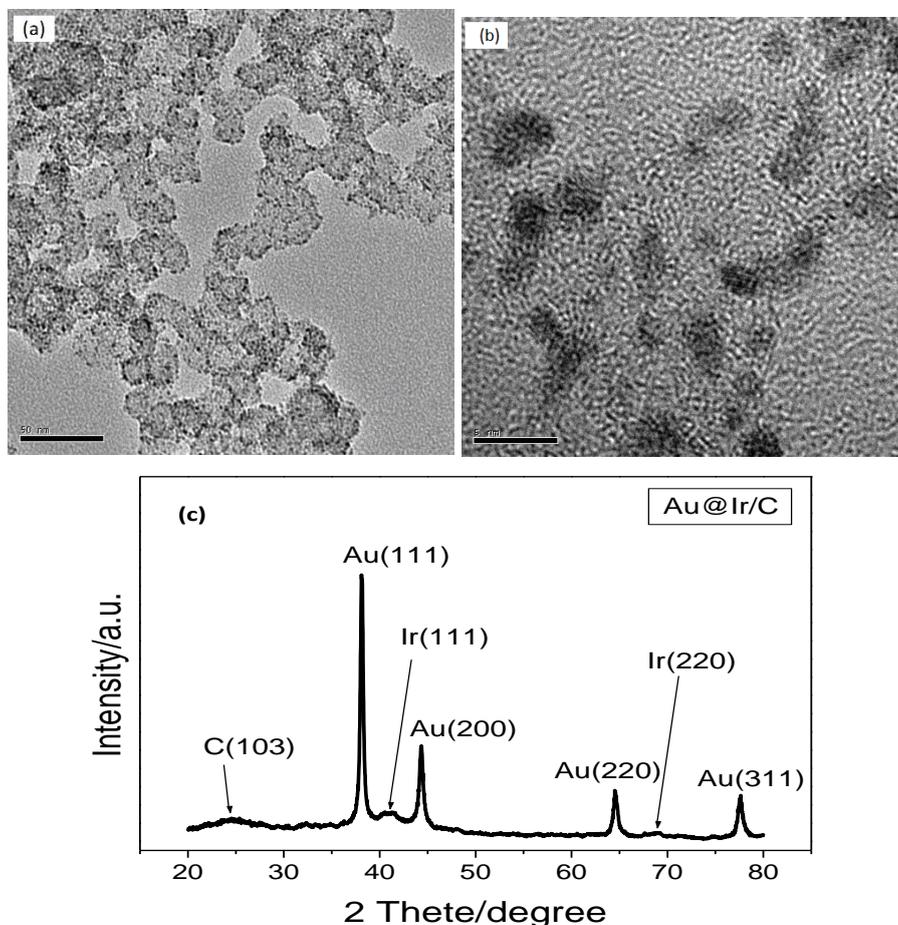


Figure 1. The TEM images and the XRD pattern of Au@Ir/C composite.

3.2. Electrochemical response to methimazole

Figure 2 shows the results of the cyclic voltammetry measurements recorded in PBS and 0.001 M methimazole/PBS solution at a scan rate of 20 mV s^{-1} using Au@Ir/C as active material. As seen in Figure 2a, the electrochemical response to PBS solution is flat and there is almost no current peaks observed. It suggests that PBS solution, which can simulate the body physiological environment, provides an appropriate test condition with nearly no interference to methimazole measurements. Figure 2b displays the CV curve of methimazole/PBS sample obtained under the same testing condition as PBS solution. It is clearly observed that in the potential range of $+0.10 \sim +0.80 \text{ V}$, there are two pairs of redox peaks appeared, which are related to the anodic and cathodic polarization processes on the working electrode. Considering that there is a completely weak response in PBS background

solution, these polarization peaks must be generated by methimazole sample [25,26]. By comparison the second pair of redox peaks (O_2/R_2) have sharper and more distinguishable images with no interference. So the oxidation peak (O_2) is selected as response peak to determine the methimazole concentration.

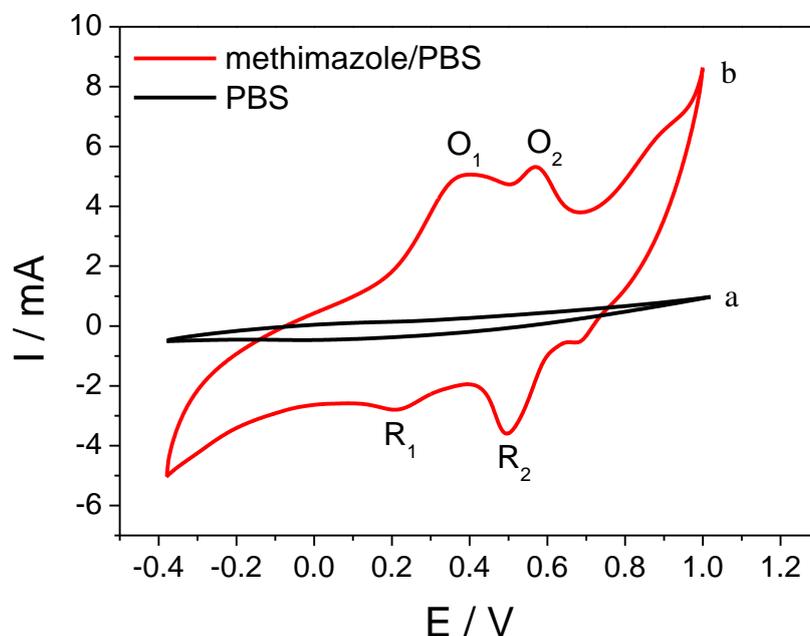


Figure 2. The CV polarization curves of Au@Ir/C composite in PBS (a) and methimazole/PBS solution (b) (25°C , scan rate= 20 mV s^{-1}).

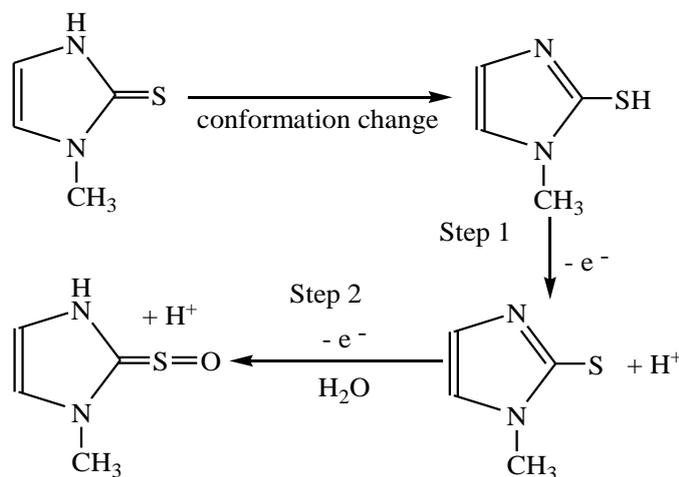


Figure 3. The oxidation mechanism of methimazole

As we studied with the related literature, there is almost no researches appeared regarding the electrochemical behavior of methimazole on Au metal or its composite. The mechanisms of reactions corresponding to the redox peaks are undefined. However, similar investigation for methimazole detection on Ag/Graphene has been reported by Saeed's group [25], in which 2 e^- mechanism for

electro-oxidation of methimazole was proposed. Here we assume that the reaction process undergoes two-step mechanism (as shown in Figure 3). At the initial state, there are two kinds of conformations with interconversion. The first-step reaction, corresponding to the O₁/R₁ peaks, involves the dehydrogen process on the sulfhydryl group. The second-step reaction, corresponding to the O₂/R₂ peaks, undergoes the further oxidation of the sulfur atom.

3.3. Methimazole concentration determination and i_p - c correlation

In order to establish the correlation between the peak current (i_p) and the concentration of methimazole (c), a series of methimazole solution with different concentration is prepared and subjected to CV tests on Au@Ir/C active material. The test results are shown in Figure 4. It can be seen from Figure 4 that with the increase of methimazole concentration (c), the peak current (i_p) values at peak O₂ are gradually increased, indicating a sensitive polarization current response correlation to concentration variation. The peak currents at peak O₂ for every curve are obtained and the data are listed in table 1. With these data the plot of peak current (i_p) versus methimazole concentration (c) is drawn and shown in Figure 5. All the data points in Figure 5 are fitted to a straight line, which suggests that within the concentration range from 0.001 to 5.0 mM, methimazole concentration and peak current possesses a linear correlation and the detection limit is 4.6×10^{-4} mM. The linear regression equation is expressed as: $i_p = 5.4775c + 9.2488$ ($R = 0.9987$, $P < 0.0001$).

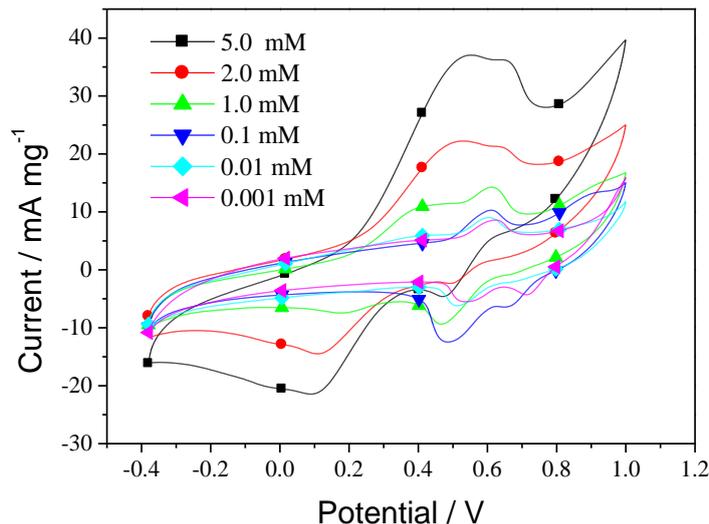


Figure 4. Cyclic voltammetry of a series of methimazole solution (25°C, scan rate=20 mV s⁻¹).

For comparison with the other related papers, the relevant literatures [7,25,27,28] are examined and the results are listed in table 2. It can be observed that the different methods are carried out in different test conditions. The traditional method, e.g., UV-visible spectrophotometry, usually possesses narrow detection range with poor accuracy. In contrast, the electrochemical methods, both potentiometric titration or electrochemical sensors, exhibit much broad test ranges with excellent

accuracy (lower test limit). The electrochemical sensor-Au@Ir/C used in the present study also shows a superior test range among the listed methods, which is beneficial to the practical applications in drug detection.

Table 1. The correlation between concentration of methimazole and peak current

c/ mM	5.0	2.0	1.0	0.1	0.01	0.001
i_p/ mA	36.25	21.31	14.39	10.26	9.032	8.679

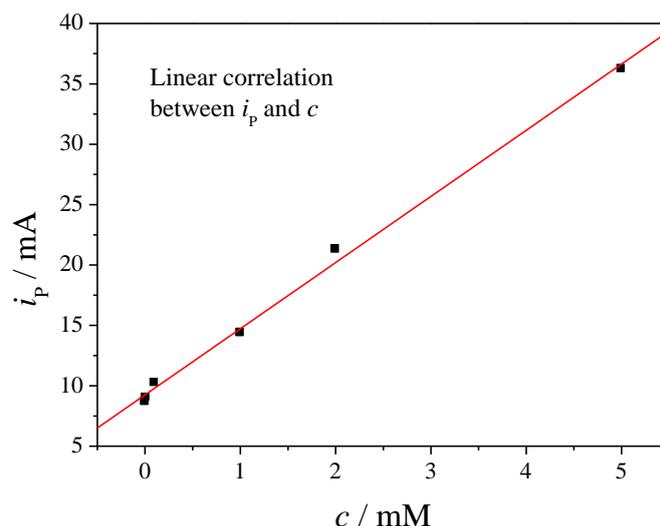


Figure 5. The correlation between the concentration of methimazole and the peak current.

Table 2. Comparison with the related methods of methimazole determination

Methods	Range of determination (mM)	Detection limit (mM)	Test condition	RSD
UV-visible Spectrophotometry[7]	0.01–0.5	Not provided	0.5 M HCl, 325 nm	Not provided
Potentiometric Titration[27]	0.001–0.7	5.0×10^{-4}	Tris-HCl buffer, pH 7.2	0.81%
Electrochemical sensor-Ag/grapheme[25]	0.001–0.08	6.8×10^{-4}	PBS, pH 4.0	Not provided
Electrochemical sensor-F-doped SnO ₂ [28]	0.006–0.24	1.98×10^{-3}	Britton-Robin buffer, pH 3.0	2.0%
Electrochemical sensor-Au@Ir/C [‘This work’ results]	0.001–5.0	4.6×10^{-4}	PBS, pH 7.2	0.73%

3.4. Sensitivity to methimazole concentration

In order to investigate the sensitivity of Au@Ir/C active material to methimazole concentration, amperometric (*i-t*) technique is employed to detect the methimazole concentration alternation. Figure 6a displays sensitivity response curve which is obtained under the potential of 0.56 V in 200 ml 1.0×10^{-4} mM methimazole initial solution along with 0.20 ml addition of 0.01 M concentrated methimazole solution at intervals of 600 s. As comparison the amperometric curve of PBS solution is also provided (Figure 6b) [29,30]. It is obvious that the *i-t* curve of PBS solution shows little current response and nearly no interference to methimazole. As to methimazole curve, a step jump of polarization curves is observed and an addition of 0.01 mM methimazole brings about a sharp increase in the current value, and then followed by a gradual degradation in current intensity. The statistical data for dependence of response current on methimazole concentration alternation is shown in table 3, where it clearly confirm that each change in methimazole concentration leads to a considerable alternation in average current. It can be concluded that the active material of Au@Ir/C has a high sensitivity to the change of methimazole concentration and supports precise methimazole determination.

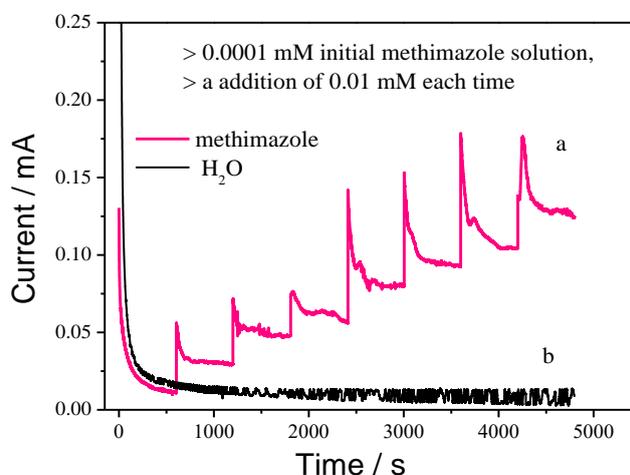


Figure 6. The amperometric (*i-t*) polarization curve of methimazole solution (25°C, potential=0.56V).

Table 3. The dependence of response current on methimazole concentration alternation.

No.	Addition of concentration (mM)	Detection concentration (mM)	Average current (mA)	Alternation of average current (mA)
1	—	0.0001	0.0163	—
2	0.01	0.0101	0.0305	0.0142
3	0.01	0.0201	0.0505	0.0200
4	0.01	0.0301	0.0630	0.0125
5	0.01	0.0401	0.0834	0.0204
6	0.01	0.0501	0.0958	0.0124
7	0.01	0.0601	0.110	0.0142
8	0.01	0.0701	0.129	0.0190

3.5. Stability test

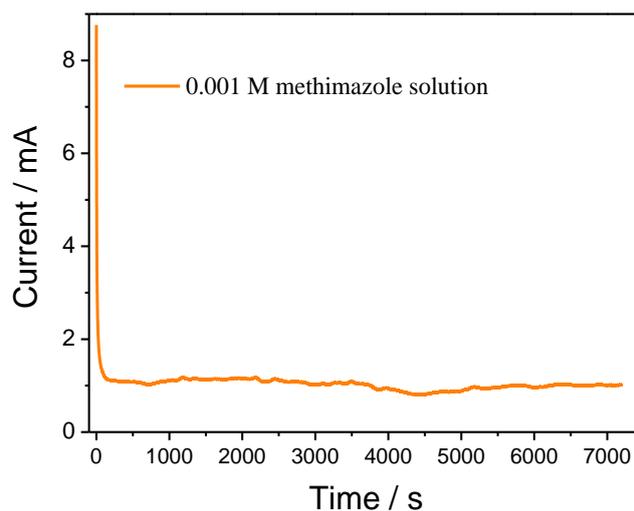


Figure 7. Stability test ($i-t$) for methimazole solution (25°C, potential=0.56V).

Stability is an important factor in electrochemical measurement that is associated with the long-term performance of a detection device [26,31]. For this purpose, stability measurement on methimazole was conducted under constant potential (0.56 V) for 2 h, and the result is shown in Figure 7. In this figure, a sharp degradation of the current appears at initial stage, which is resulted from the pulse current. And then it exhibits an approximately flat platform of the $i-t$ curve along with the time, although there is a slight fluctuation in the process. It is suggested that this method possesses a high stability for the determination of methimazole, and the experimental data has a high reliability.

4. CONCLUSIONS

Au@Ir/C nanocomposite as an electroactive material for methimazole detection has been synthesized via polyol reduction method. It is revealed that ultrafine nanoparticles of Au@Ir composite (2-4 nm) are evenly dispersed on carbon. This structure helps enhance its activity and stability. Electrochemical tests prove that the active material of Au@Ir/C has high response sensitivity to methimazole and well supports precise methimazole determination. Within the concentration range from 0.001 to 5.0 mM, methimazole concentration and peak current possesses a linear correlation, and the linear regression equation is expressed as: $i_p = 5.4775c + 9.2488$ ($R = 0.9987$, $P < 0.0001$). Also, chronoamperometry ($i-t$) result has proved the high stability of Au@Ir/C on methimazole measurement, suggesting a superior reliability for this method.

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