



# Preparation and application of a carbon paste electrode modified with multi-walled carbon nanotubes and boron-embedded molecularly imprinted composite membranes

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## ABSTRACT

An innovative electrochemical sensor was fabricated for the sensitive and selective determination of tinidazole (TNZ), based on a carbon paste electrode (CPE) modified with multi-walled carbon nanotubes (MWCNTs) and boron-embedded molecularly imprinted composite membranes (B-MICMs). Density functional theory (DFT) calculations were carried out to investigate the utility of template-monomer interactions to screen appropriate monomers for the rational design of B-MICMs. The distinct synergic effect of MWCNTs and B-MICMs was evidenced by the positive shift of the reduction peak potential of TNZ at B-MICMs/MWCNTs modified CPE (B-MICMs/MWCNTs/CPE) by about 200 mV, and the 12-fold amplification of the peak current, compared with a bare carbon paste electrode (CPE). Moreover, the coordinate interactions between trisubstituted boron atoms embedded in B-MICMs matrix and nitrogen atoms of TNZ endow the sensor with advanced affinity and specific directionality. Thereafter, a highly sensitive electrochemical analytical method for TNZ was established by differential pulse voltammetry (DPV) at B-MICMs/MWCNTs/CPE with a lower detection limit ( $1.25 \times 10^{-12}$  mol L<sup>-1</sup>) (S/N = 3). The practical application of the sensor was demonstrated by determining TNZ in pharmaceutical and biological samples with good precision (RSD 1.36% to 3.85%) and acceptable recoveries (82.40%–104.0%).

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## 1. Introduction

Tinidazole (TNZ), an anti-parasitic drug, has been used in the treatment of various amoebic [1] and parasitic infections [2]. Its action mechanism involves interference with DNA by a metabolite containing a nitro group being reduced to a free nitro-radical, which may be responsible for cytotoxicity [3]. In addition, TNZ has also been effective against giardiasis [4] and susceptible protozoal infections [5], and has been applied in the management of the eradication of *Helicobacter pylori* [6,7]. On one hand, an overdose of TNZ in plasma causes bad side effects, such as rash, prurigo and angioneurotic edema [8]. Moreover, intermediates, by-products and other impurities may be brought into pharmaceuticals for the synthesis of TNZ [9]. Therefore, the pharmaceutical quality control of TNZ is crucial in determining toxicity and guiding withdrawal of other anti-parasitic drugs, and there is an urgent need for the development of an effective and sensitive method to detect TNZ in pharmaceutical and biological samples [10].

To date, several analytical methods including spectrophotometric [11] and chromatographic [12] methods have been used for the quantification of TNZ. Despite requiring simple instrumentation and

equipment, the sensitivity of spectrophotometric methods is poor. Compared with spectrophotometric methods, chromatographic methods can offer the required sensitivity and selectivity but they are limited by the need for expensive instrumentation and high degree of user expertise. Electrochemical approaches, especially molecularly imprinting-based electrochemical sensor, have emerged as the preeminent analytical tools by virtue of their fast-response, cost-effectiveness and high efficiency [13–16]. Moreover, the possession of reduction nitro group makes it attractive to employ electroanalytical techniques to determine TNZ [17–19].

Multi-walled carbon nanotube (MWCNT), a rapidly rising star in the field of materials, shows exceptional electrical conductivity and large specific surface areas with potential applications in modifying sensors [20,21]. Molecularly imprinted polymers (MIPs) with specific binding sites were used as recognition elements due to their predetermined selectivity and chemical stability [22]. Generally, MIP-based sensors recognize target molecules in non-covalent ways [23,24], but non-covalent interactions alone including hydrogen-bonding and van der Waals forces are limited for the formation of selective recognition sites [25]. Thus, the introduction of coordination interactions offers a greater promise for producing more highly defined recognition sites [26,27].

In the present work, we developed a highly sensitive and selective sensor for the determination of TNZ, based on a carbon paste electrode

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(CPE) modified with B-MICMs and MWCNTs. The as-constructed B-MICMs/MWCNTs/CPE could not only implement direct signal transformation between imprinting cavities and sensing elements, but also provide enhanced imprinting recognition capability towards template TNZ. Quantum chemical calculations (QCC) combined with density functional theory (DFT) calculations were employed to model molecular interactions and screen appropriate functional monomer by calculating binding energy difference ( $\Delta E$ ) between monomer and template. The as-prepared sensor was successfully applied to analyze real samples with satisfactory results, which were further validated by using liquid chromatography.

## 2. Experimental

### 2.1. Instruments and reagents

All electrochemical measurements were performed on a CHI 660C electrochemical workstation (ChenHua Co. Ltd. China). A standard three-electrode cell assembly composed of a B-MICMs/MWCNTs/CPE (3.5 mm) as working electrode, a platinum electrode as counter electrode and a standard hydrogen electrode (SHE) as reference electrode. Scanning electron microscopy (SEM) was performed on a JSM-6700F with an energy-dispersed spectral (EDS) unit (Czech Republic).

Multi-walled carbon nanotubes were obtained from Sinopharm Chemical Reagent Ltd. Tinidazole, metronidazole (MNZ), ronidazole (RNZ), dimetridazole (DTZ), aminopropyltrimethoxysilane (APTMS) and tetraethyl orthosilicate (TEOS) were purchased from Aladdin Reagent Company (Shanghai, China). Phenylaminopropyltrimethoxysilane (PAPTMS) and aminophenylboronic acid (APBA) were purchased from Bide Pharmatech Ltd. (Shanghai, China).

### 2.2. Computational design of B-MICMs

Systematic density functional theory (DFT) calculations were carried out to probe the utility of B-MICMs sensing template at molecular level and appropriate monomers were selected on the basis of the energy difference of complexes compared with uncomplexed template and monomers [28]. Gauss View 5.0 software was employed to set up complexes and stabilization energies for complexes were obtained by DFT at the B3LYP/6-31+G level with Gaussian 09 software. The energy difference of template-monomer complexes was calculated using the following equation [28]:

$$\Delta E = E(\text{template-monomer complexes}) - E(\text{template}) - \Sigma E(\text{monomer}) \quad (1)$$

In addition, solute dipole may induce a dipole moment in the surrounding solvent, resulting in a change in the charge distribution of the solvent [29]. Thus, the binding energies of TNZ with individual monomers or mixtures of monomers (PAPTMS, APBA, and APTMS) were performed using polarizable continuum model (PCM) in ethanol.

### 2.3. Fabrication of B-MICMs/MWCNTs/CPE

A bare carbon paste electrode (CPE) was fabricated by mixing and grinding paraffin oil with graphite powder in a ratio of 20:80 (wt paraffin oil/wt graphite powder) in an agate mortar until a homogeneous paste was obtained, then pressing the paste into a Teflon tube with an inner diameter of 3.5 mm and smoothing on weighing paper to obtain a uniform surface. A pencil core inserted into the tube served as electrical contact.

The steps for the construction of B-MICMs/MWCNTs/CPE are shown in Scheme 1. Firstly, both aminophenylboronic acid (APBA) and phenylaminopropyltrimethoxysilane (PAPTMS) were co-electro polymerized on the surface of MWCNT-coated CPE to form a boron-

embedded conductive copolymers layer. Then trimethoxysilyl groups ( $\text{Si}(\text{OCH}_3)_3$ ) linked to the conductive copolymer were hydrolyzed and condensed with monomer aminopropyltrimethoxysilane (APTMS), cross-linking agent tetraethyl orthosilicate (TEOS) and template TNZ, forming a molecularly imprinted polymers layer over the conductive copolymers layer via sol-gel process. Thereafter, the boron-embedded molecularly imprinted composite membranes (B-MICMs) were established, which consisted of boron-embedded conductive copolymers layer and a molecularly imprinted polymers layer. Subsequently, template TNZ was removed from the cavity of boron-embedded molecularly imprinted composite membranes (B-MICMs). The detailed preparation process are presented in Supplementary information (SI).

As a control, the boron-embedded molecularly imprinted composite membranes (B-MICMs)-modified CPE (B-MICMs/CPE) (no MWCNTs), the trisubstituted boron atom-free molecularly imprinted composite membranes (MICMs)-modified MWCNTs/CPE (MICMs/MWCNTs/CPE) (no boron) and the boron-embedded non-molecularly imprinted composite membranes (B-NICMs)-modified MWCNTs/CPE (B-NICMs/MWCNTs/CPE) (no template TNZ) were fabricated by using the same procedures mentioned above without MWCNTs, APBA or template TNZ, respectively. A CPE that was only modified with MWCNTs (MWCNTs/CPE) (no B-MICMs) was constructed as well.

### 2.4. Electrochemical measurements

A three-electrode cell linked to an electrochemical workstation was employed to perform electrochemical measurements. A working electrode was first immersed in 5.0 mL of test sample or standard solution for 20 min to equilibrate with TNZ and then put into 5.0 mL of supporting electrolyte containing  $0.1 \text{ mol L}^{-1}$  KCl and  $0.04 \text{ mol L}^{-1}$  Britton-Robinson (pH 5.0). A differential pulse voltammetry experiment was performed in the potential interval from 0 V to  $-1.0 \text{ V}$  with pulse width of 120 ms, potential increment of 20 mV, pulse amplitude of 50 mV, and scan rate of  $25 \text{ mV s}^{-1}$ . All measurements were carried out in triplicate.

### 2.5. Preparation of sample solution

Commercial tinidazole tablets (Zhejiang Kelian pharmaceutical co. LTD 250 mg; Hubei sihuan pharmaceutical co., LTD 250 mg) were obtained at a local drugstore. Human serum and urine samples were kindly received from two healthy volunteers who were not taking any medicines. Ethical approval to undertake this study was examined by Human Research Ethics Committee of University of South China. Besides, the informed consent for participation in this study was obtained from the two participants. Ten tablets were pulverized with a pestle and dissolved in 20 mL acetone with ultra-sonication for 15 min. After filtration through a  $0.22 \mu\text{m}$  syringe filter, the filtrate was transferred to a 10 mL volumetric flask and diluted to the mark with acetone. Subsequently, 100  $\mu\text{L}$  of the obtained solution was spiked into 5.0 mL BR buffer (pH 5.0) and subjected to further detection. The corresponding spiked samples were prepared by adding known concentrations of TNZ into serum and urine samples. Prior to detection, serum or urine sample (2.0 mL) was mixed with 2.0 mL of methanol, vortexed for 60 s, and centrifuged at 10,000 rpm for 10 min to remove proteins. The supernatant was then diluted to 5.0 mL with BR buffer (pH 5.0) to reduce the matrix effect and used as the test solution.

## 3. Results and discussion

### 3.1. Theoretical selection of a suitable functional monomer

For theoretical calculations, phenylaminopropyltrimethoxysilane (PAPTMS), anilinomethyltriethoxysilane (AMTEOS), aminopropyltrimethoxysilane (APTMS) and aminophenylboronic acid (APBA) were selected as potential functional monomers. Density

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