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The fabrication of a new electrochemical sensor based on electropolymerization of nanocomposite gold nanoparticle-molecularly imprinted polymer for determination of valganciclovir

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A new sensitive and selective electrochemical sensor was successfully developed for the determination of valganciclovir. It is based on one-step electropolymerization of the molecularly imprinted polymer composed from 2,2′-dithiodianiline, gold nanoparticles, and valganciclovir on a glassy carbon electrode modified with carboxyl-functionalized multiwalled carbon nanotubes via cyclic voltammetry. The gold nanoparticles were introduced into the polymer composite for the development of electrical response by facilitating charge transfer. The fabrication process of the sensor was characterized by cyclic voltammetry and electrochemical impedance spectroscopy. Under the optimized condition calibration curve of the imprinted sensor has two linear concentration ranges from 1.0 to 500.0 nM and 500.0 to 2000.0 nM, with the limit of detection of 0.3 nM. The relative standard deviation (RSD) for seven parallel determination of 1.0 μM valganciclovir at optimum conditions was found to be 2.9%. The imprinted sensor has the advantages of high porous surface structure, ease of preparation, good reproducibility, good repeatability and high selectivity and sensitivity. Furthermore, the proposed method was successfully intended for the determination of valganciclovir in real samples.

1. Introduction

Valganciclovir (VGCV) is an antiviral medication which is used for treatment of cytomegalovirus retinitis in patients with AIDS. VGCV is an L-valine ester of ganciclovir (GCV) that exists as a mixture of two diastereomers. Oral bioavailability is approximately 60%. It takes about 2 h to reach maximum concentration in the serum. Also VGCV is eliminated as GCV in the urine, with a half-life of about 4 h in people with normal kidney function. After oral administration, it is rapidly converted to GCV by the hydrolysis of the ester linkage by the esterase enzymes present in the liver and intestine, thus presenting the same mechanism of antiviral activity of its precursor [1,2]. The side effect of VGCV is decreasing the bone marrow function; its results are lowering the number of blood cells such as red cells, white cells, and platelets and decreasing the body's ability against infection. This side effect will be accompanied with bleeding problems such as anemia. So determination of this drug in real sample such as biological fluids and pharmaceutical formulation is very important. Therefore, several analytical methods have been described for the determination of VGCV, including chromatographic techniques [3–6] and UV spectrophotometric [7,8] and voltammetric methods [9,10]; while electrochemical sensor possessing the advantages of excellent sensitivity, rapid response, simplicity and low cost, has been applied in medical, biological and environmental analyses extensively [10,11]. Therefore, it is interesting to develop an electrochemical sensor for VGCV determination with high sensitivity and selectivity. One of the methods for improving the sensitivity and selectivity of the sensor is the combination of suitable nanoscale modifiers and an efficient recognition element.

Due to the ability to specific bind species, mechanical/chemical stability, low cost, and easy preparation, molecularly imprinted polymers (MIPs) have widely been used as efficient recognition element in various analytical methods [12–17], especially in electrochemical MIP based sensors, which are the combination of the significant characteristics of electrochemical determination and molecular imprinting techniques [18–20].

The discovery of carbon nanotubes (CNTs) by Iijima [21] added a new member to carbon family. Their novel and unique chemical and physical properties have attracted great attention in multidisciplinary areas such as nanotechnology, electronics, optics, water treatment, and other fields of materials science. The relatively large specific surface area (SSA) and high reactivity are another important properties of CNTs, which enable them to become candidate for adsorption of gas [22], metal ions [23] and organic compounds [24]. Therefore, CNTs not only increase the surface area and decrease the charge transfer resistance of the sensor [25–32], it can be as a suitable solid support material for assembling of an organic compound film such as MIP at the surface of the electrode.

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Among various methods for MIP preparation, electropolymerization is a potential technique to develop electrochemical sensors. This method can deposit a recognition film with spatial selectivity on the detector surface with no restriction to the choice of the analyte, even when small molecules have no functionality [33–36]. Although the deposited MIP increases the selectivity of sensor, it diminishes the conductivity of the resulted electrode and its response.

Nowadays, the combination of surface molecular assembly with nanostructure(s) in the imprinting technology, wherein template molecules are imprinted within the large surface area of nanoparticle, is very attractive. This yields hybrid nanocomposites which can easily be coated over a sensing platform via either physical adsorption or covalently binding [37–40]. The combination of nanoparticles such as gold nanoparticles in MIP was to enhance the conductivity of the composite that was homogeneously coated onto glassy carbon electrode surface.

Gold nanoparticles (AuNPs) have been widely used in fabrication of different kinds of sensors due to their unique properties such as strong adsorption ability, large specific surface area, good biocompatibility as well as conductivity. Therefore the use of AuNPs for fabrication of MIP-based nanocomposites can increase the amount of effective binding sites in the sensor and improve the conductivity of molecularly imprinted sensor. This is the simplest method to provide a higher surface area of the conductive polymer film. The MIPs doped with AuNPs can be simply fabricated by some approaches including covalent linking, direct electrostatic assembly, polymer entrapment, and electrodeposition methods [41–44].

By now, no research has been reported on using an electrochemical sensor based on MIP composed from 2,2′-dithiodianiline and AuNP film for VGCV detection. The MIP-based nanocomposites were synthesized on the surface of carboxyl-functionalized MWCNT, as the conductive supported material, on the glassy carbon electrode (GCE). The prepared electrochemical sensor (AuNP-MIP/MWCNT/GCE) was characterized by scanning electron microscopy (SEM), cyclic voltammetry (CV) and electrochemical impedance experiment in detail. The experimental parameters that affect the performance of the MIP sensor were studied and optimized. As expected, the electrochemical sensor not only can strikingly improve the sensitivity and selectivity of VGCV analysis, but also obtains good repeatability and thus can be potentially exploited for the detection of the VGCV in real samples.

2. Experimental

2.1. Materials

2,2′-Dithiodianiline was purchased from Sigma-Aldrich (Munich, Germany). N-hydroxysuccinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Carboxylated multiwalled carbon nanotubes with purity 95% were obtained from DropSens (Llanera, Spain). VGCV, GCV, acyclovir (ACV) and valaciclovir (VCV) were obtained from Merck (Darmstadt, Germany, www.merck.de) and their stock solutions (1.0 mM) were prepared by dissolving appropriate amounts of them in distilled water. All other chemicals were of analytical grade and were purchased from Merck (Darmstadt, Germany). Phosphate buffered solutions (PBSs) (0.01 M) at various pH values were prepared by 0.01 M H_3PO_4, 0.01 M KH_2PO_4 and 0.01 M K_2HPO_4 and then adjusting the pH with 0.2 M HCl or 0.2 M NaOH. All solutions were stored at 4 °C by light protection.

2.2. Instrumentation

Voltammetric measurements were carried out with a μAutolab III potentiostat/galvanostat (Eco Chemie B. V. Netherlands) electrochemical and electroanalytical instrument having NOVA 1.10 software. The electrochemical cell consisted of unmodified and modified GCE as working electrode, and Ag/AgCl and platinum wire as a reference and counter electrodes, respectively. A Metrohm pH-meter (model 691) was also applied for pH measurements. SEM images were obtained with a field emission gun scanning electron microscope (Philips XL 30, USA). All measurements were carried out at room temperature.

2.3. Preparation of the MIP modified electrode

Before the electropolymerization, the surface of the bare GCE was carefully hand-polished with 0.3 and 0.05 μm alumina–water slurry using a polishing cloth in sequence, afterward it was ultrasonically cleaned in HNO_3, ethanol, and doubly distilled water in sequence for 10 min. Then the electrode was immersed in 0.5 M H_2SO_4 solution and the potential was cycled between −0.5 and 2.0 V at 100 mV s^{-1} until a stable cyclic voltammogram was obtained. The functionalized MWCNT suspension was prepared by dispersing 1.0 mg of MWCNTs in 1.0 mL of dimethyl formamide (DMF) and then it was homogenized in an ultrasound bath for 30 min. 3 μL of the above MWCNT suspension was cast on the surface of GC electrode and dried in air. The MWCNT/GC electrode was immersed into phosphate buffer solution (PBS) containing 1.0 mM of EDC and NHS (pH 7.0) as a coupling agent for about 2 h to activate the carboxyl-terminated surface of the MWCNTs, and then the resulted electrode was washed with buffer solution and dried in the air. This electrode was immersed in a phosphate buffer solution (pH 3) containing 0.1 mmol L^{-1} 2,2′-dithiodianiline, 0.05 mmol L^{-1} $HAuClO_4$ and 0.1 mmol L^{-1} of VGCV as a template. Then, it was electrochemically polymerized via cyclic voltammetry (10 cycles) in the potential window of −1.0 to 1.0 V at a scan rate of 50 mV s^{-1}. The removal of the template (VGCV) was carried out by immersing the modified electrode (AuNP-MIP/MWCNT/GCE) in 0.01 M phosphate buffer solution (pH 3) and scanning the potential in the range of 0.3–1.2 V at a scan

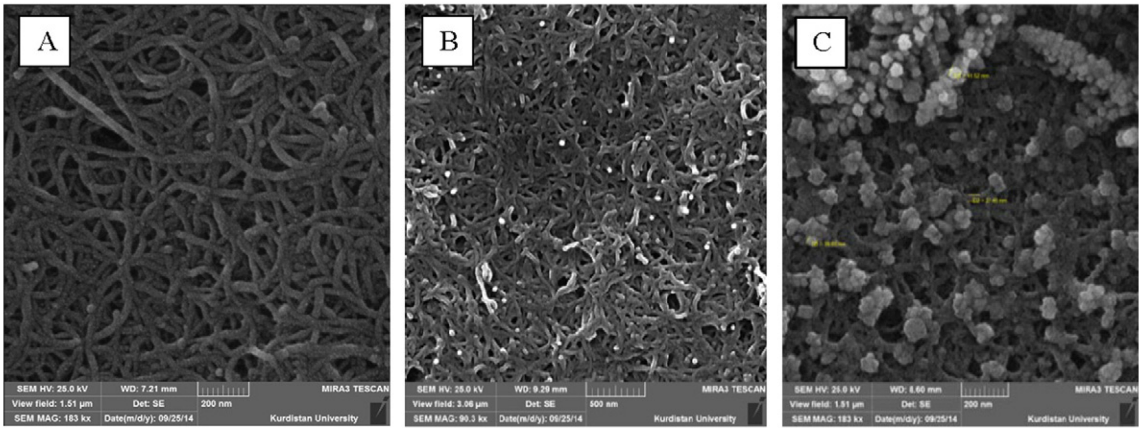

Fig. 1. SEM images of A) MWCNT/GCE, B) MIP/MWCNT/GCE and C) AuNP-MIP/MWCNT/GCE.