Designing and fabrication of new molecularly imprinted polymer-based potentiometric nano-graphene/ionic liquid/carbon paste electrode for the determination of losartan

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ABSTRACT

In this study, a novel losartan molecularly imprinted polymer was synthesized and used as a sensing agent in a sensing layer of the new modified potentiometric nano-graphene/carbon paste electrode incorporated with graphite powder, synthesized graphene nano-sheets and an ionic liquid, as the conducting binder, for the selective determination of losartan. Methacrylic acid as functional monomer, ethylene glycol dimethacrylate as a cross linker, 2-2′-azoisobutyronitrile as an initiator and chloroform as polymerization solvent were used. The characteristic of the synthesized molecularly imprinted polymer were investigated by Fourier transform infrared analysis and scanning electron microscopy. The molecularly imprinted polymer-modified electrode exhibited a Nernstian response (59.64 ± 0.20 mV decade^{-1}) in a wide linear dynamic range of 3.00×10^{-9} to 1.00×10^{-2} M with a lower detection limit of 1.82×10^{-9} M. The suggested potentiometric sensor demonstrated a fast response time of ~6 s, a high performance, fairly high selectivity over some interfering compounds and a satisfactory long-term stability (more than 3 months). It was successfully applied for the highly sensitive determination of losartan in pharmaceutical products and urine samples with satisfactory results.

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1. Introduction

Drug determination is an important branch of analytical chemistry. Determination of drugs in biological and pharmaceutical samples such as serum, urine and pharmaceutical industry products and wastewater is a very important topic for many applications (*e.g.*, clinical, forensic science, quality control and environmental protection) [1–3]. The presence of high levels of interfering compounds responsible for non-specific detecting makes the quantification of the analytes difficult, imprecise and prone to false positive and negative signals. Therefore, the fabrication of analytical tools for accurate quantification of drug species in these samples is very challenging [3–5]. In this context, electrochemical sensors can offer the straightforward advantage of being able to distinguish one specific species in complex mixtures. Also, they are considered to have technical simplicity, high sensitivity and easy adaptability for *in situ* analysis with relatively cheap instrumental setups [1–14].

Losartan (LOS) is the prototype of a new generation of effective and orally active pharmaceutical products used for the treatment of arterial hypertension [15–17]. LOS has been demonstrated to be superior to previous peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors because of its enhanced specificity, high selectivity, tolerability and long-lasting effect on the renin–angiotensin system [15–17]. Various instrumental techniques, including high-performance liquid chromatography (HPLC) [18], capillary electrophoresis (CE) [19], supercritical fluid chromatography (SFC) [20], fluorimetry [21], UV spectrophotometry [22] and colourimetry [23] have been used for the determination of LOS at low concentrations. However, most of these common techniques are too expensive that are not applicable for *in-situ* analysis. So, the development of convenient and direct methods for the assay of LOS in different real samples is an urgent need. Ion-selective electrodes (ISEs) are established tools that are capable of directly determining the activities of many analytes. Because the latest advances in the fundamental understanding of the ISE response mechanism gave rise to drastic improvements of the sensitivity and selectivity, many efforts have been focused on the development of novel potentiometric sensors for the detection of ions in aqueous solutions [24–52].

Among these sensors, potentiometric carbon paste electrodes (CPEs), due to the ease of their construction, easy renewability of the surface, inexpensive techniques, chemical inertness, robustness, stability of response, low ohmic resistance, no need of internal solution and compatibility with various types of modifiers, have been widely used as suitable tools for the determination of the various species [3,42–49]. As we know, the target-sensing properties of the

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potentiometric sensors largely depend on the nature of the employed sensing layer. Modifications can improve the surface state of the carbon paste sensor, which may lead to a significant increasing the target signals. Recently, research activities are related to the optimization and rational design of both modifiers and matrices targeted to particular applications [3,42–49].

The recent emergence of nano-materials has opened new horizons in designing integrated electrochemical systems, thanks to significant advances in materials science for developing new generations of chemically modified electrodes [3,42–51]. The main motivation relies on the possibility offered by nano-structured electrodes, or porous materials held at electrode surfaces, to enhance the surface area/volume ratio by several orders of magnitude. Graphene nano-sheet, a new class of promising carbon material, is of great interest. In addition, it exhibits high electrical conductivity and optical properties, is lightweight, and has a large specific surface area, strong mechanical strength and chemical stability [46,47]. However, the main challenge of how to improve the selectivity of the electrochemical sensors is remained. In order to meet this requirement, the inducing of a selective modifier onto the electrode with the desired properties is particularly attractive.

In the past years, as a new "green" media, room temperature ionic liquids (RTILs) have emerged as a frontier and novel area of research due to their excellent chemical and physical properties such as high chemical and thermal stability, ionic nature, good extraction ability, ion-exchange properties, low equilibrium vapor pressure, high conductivity and wide electrochemical windows [42–45,47].

Molecularly imprinted polymers (MIPs), as a new class of intelligent polymers have proven to be a powerful modifier in electrochemical sensors for some pharmaceuticals, owing to their predetermined selectivity for target analyte, high affinity and robustness [47–52]. They are the synthetic materials with an artificially generated three-dimensional network that is able to specifically rebind a target molecule. MIP has the advantages to be cost-effective, chemically and thermally stable, capable of molecular recognition and compatible with all solvents. It is generally used for the designing of resources with unusual identification capability towards target molecule [47–52].

In this study, we introduced a potentiometric nano-graphene/carbon paste electrode composed of a novel synthesized MIP as a selective sensing element, synthesized graphene nano-sheets (GNSs) and an air and water-stable ionic liquid 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide, as the conductive binder, for the determination of LOS in pharmaceutical and urine samples. By substituting non-conductive organic binders (e.g. paraffin oil) with suitable conductive binder (e.g. RTILs), low cost and easy to fabricate electrodes have been produced, with the advantages of high conductivity and sensitivity and high antifouling ability for electroanalysis compared to traditional oil-based electrodes. It was concluded with this combination of constituents in fabrication process of sensor, the response was enhanced significantly.

2. Experimental

2.1. Instrumentation

The glass cell in which the potentiometry was carried out into contained an Ag/AgCl electrode (Azar electrode, Iran) as a reference electrode and fabricated CPEs for LOS determination sensor as the working electrode. Both the electrodes were connected to a digital milli-voltmeter (HIOKI 3256.50, Japan). A Metrohm pH-meter (CRISON GLP 22, Swiss) with a combined glass electrode was used for pH controlling, and a Heidolph type of stirrer (MR 2000, Germany) was used for stirring the solutions. The morphology and structure of the synthesized GNSs and polymers were characterized by scanning electron microscopy (SEM–EDX, XL30, Philips Netherland). Transmission electron microscopy (TEM, Philips, CM10 and 100 kV) was performed to assay the morphology and structure of the synthesized GNSs. Fourier transform infrared (FT–IR) spectra of grounded polymer were recorded on a PERKIN ELMER-Spectrum GX, using KBr pellets in the range of 400–4000 cm^{-1}.
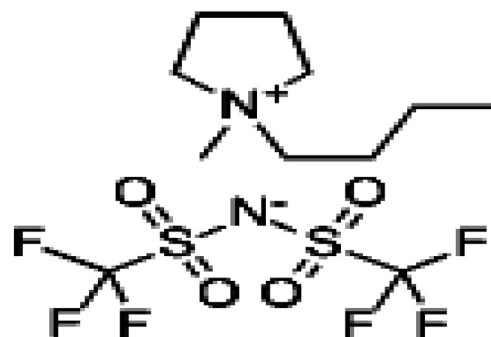
2.2. Reagents and materials

Natural graphite flakes (98%, 50 mesh, and 2–5 mm in lateral size) were obtained from Hyundai Coma Ind. Co., Korea. The ionic liquid 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide, [BMP]Tf$_2$N, (Scheme 1) (Darmstadt, www.merck.de), and high-purity paraffin oil (Aldrich, USA) were used for the preparation of carbon pastes. Methacrylic acid (MAA), Ethylene glycol dimethacrylate (EGDMA), 2-2′-Azoisobutyronitrile (AIBN) and LOS from Merck (Darmstadt, Germany) were used. Chloride and nitrate salts of the cations were also purchased from Merck (Darmstadt, www.merck.de). Distilled deionized water (DDW) was used throughout all experiments.

2.3. Preparation of GNSs

First, the graphene oxide (GO) was prepared with Hummer's method [53,54] and then, the GNSs was prepared by the reduction of GO according to the literature [47] as follow: GO (about 100 mg) was transferred into a 250 mL round bottom flask and then 100 mL of water was added, yielding an inhomogeneous yellow-brown dispersion. This dispersion was sonicated until it became clear with no visible particulate matter. Then 1.00 mL of 32.1 mmol hydrazine hydrate was added and the solution was heated in an oil bath at 100 °C under a water-cooled condenser for 24 h over which the reduced GO gradually precipitated out as a black solid. This product was filtrated and isolated, washed copiously with appropriate volume of water and methanol, and dried on the funnel under a continuous air flow through the solid product cake. Fig. 1a shows the TEM image of prepared GNS.

2.4. Synthesis of the host-tailored polymers

The MIP for LOS was synthesized from a reagent mixture obtained by mixing 2.0 mmol of MAA as the monomer, 13.6 mmol of EGDMA as the crosslinker, 0.2 mmol of the LOS, as the template molecule and 0.76 mmol of AIBN as the initiator in 30 mL chloroform. The mixture was uniformly dispersed by sonication. After sonicating, it was purged with N$_2$ for 20 min and the glass tube was sealed under this atmosphere. Then it was stirred in a water bath maintained at 60 °C for 24 h. Then, the synthesized MIP was washed with DDW and the resulting polymers were dried under vacuum oven at 50 °C for 12 h. In order to extraction of the template molecules from the polymer network, polymers were washed with the methanol-(acetic acid) mixture (9:1, v: v). The template extraction of the polymer created the cavities, leading to the specific sorption of the template. In addition, the removal of other materials from the polymer took place (e.g. residual monomers or oligomers and initiator fragments). The solid imprinted polymer was washed with DDW and dried again in a vacuum oven at 50 °C. The

Scheme 1. Structure of [BMP]Tf$_2$N.