



## Original Article

Graphene quantum dot modified glassy carbon electrode for the determination of doxorubicin hydrochloride in human plasma <sup>☆</sup>Nastaran Hashemzadeh <sup>a,b</sup>, Mohammad Hasanzadeh <sup>c,d,\*</sup>, Nasrin Shadjou <sup>e,\*\*</sup>, Jamal Eivazi-Ziaei <sup>a</sup>, Maryam Khoubnasabjafari <sup>f</sup>, Abolghasem Jouyban <sup>d</sup><sup>a</sup> Hematology-Oncology Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran<sup>b</sup> Faculty of Pharmacy, Students' Research Committee, Tabriz University of Medical Sciences, Tabriz 51664, Iran<sup>c</sup> Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran<sup>d</sup> Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran<sup>e</sup> Department of Nanochemistry, Nano Technology Research Center and Faculty of Chemistry Urmia University, Urmia 57154, Iran<sup>f</sup> Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran

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## ABSTRACT

Low toxic graphene quantum dot (GQD) was synthesized by pyrolyzing citric acid in alkaline solution and characterized by ultraviolet–visible (UV–vis) spectroscopy, X-ray diffraction (XRD), atomic force microscopy (AFM), spectrofluorimetry and dynamic light scattering (DLS) techniques. GQD was used for electrode modification and electro-oxidation of doxorubicin (DOX) at low potential. A substantial decrease in the overvoltage ( $-0.56$  V) of the DOX oxidation reaction (compared to ordinary electrodes) was observed using GQD as coating of glassy carbon electrode (GCE). Differential pulse voltammetry was used to evaluate the analytical performance of DOX in the presence of phosphate buffer solution (pH 4.0) and good limit of detection was obtained by the proposed sensor. Such ability of GQD to promote the DOX electron-transfer reaction suggests great promise for its application as an electrochemical sensor.

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## 1. Introduction

Graphene quantum dots (GQDs) are nanometer-sized fragments of graphene. GQDs are a kind of 0D material with characteristics derived from both graphene and carbon dots (CDs) [1]. Taking advantages of the electrochemical properties similar to those of graphene, GQDs are widely used as a kind of suitable electrode material, not only in fuel cells [2], supercapacitors [3,4] and photovoltaic cells [5], but also in the field of electrochemical sensors [6,7]. Furthermore, GQDs of tunable sizes, i.e.,  $2.2 \pm 0.3$ ,  $2.6 \pm 0.2$ , and  $3 \pm 0.3$  nm, can act as multivalent redox species using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) measurements, and present exciting opportunities for building electrochemical sensors [8]. More recently, GQDs have been used in the area of bioanalysis [6,7,9]. However, their applications in the analytical field have not been explored until now.

Due to their unique properties, sensors based on GQDs can achieve a high level of performance.

Toxicity of nanomaterials is one of the major challenges of their applications in science and biotechnology. GQDs have the potential to be remarkably successful in the field of nanobiotechnology due to their excellent opto-electrical properties and extremely low cytotoxicity [10–14]. Currently used quantum dots (CdS, PbS, ZnS, ZnSe, HgTe, Ag<sub>2</sub>S, Ag<sub>2</sub>Se, CuInS<sub>2</sub>, CuInSe<sub>2</sub>, InAs and InP) are composed of toxic metals which may cause problems for their use in biological systems. However, GQDs are increasingly being employed to provide more efficient and less toxic alternatives than currently used quantum dots [15–17]. Studies on human breast cancer have shown that GQDs can easily find their way into the cytoplasm and do not interfere with cell proliferation, which indicates that they are non-toxic materials [15–17].

Furthermore, GQDs expand contact area with the analyte, which increases the electrochemical active surface area to interact with some electroactive analytes. Since geometric surface area is a very important parameter in electrochemistry, modification of different substrates (such as glass, carbon, graphite etc.) by GQDs can increase the rate of electrochemical reaction.

Herein, we developed a highly sensitive electrochemical sensor based on GQD in order to determine low concentration of doxorubicin (DOX) in biological samples. To the best of our knowledge,

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this is the first report on the determination of DOX based on its direct electrochemical oxidation by graphene quantum dot-glassy carbon electrode (GQD-GCE). Using this system, the detection of low quantities of DOX was realized using differential pulse voltammetry (DPV). The electrode has an ultra-low detection limit during DOX electrooxidation. The electrode for DOX electrooxidation has demonstrated its excellent performance. Furthermore, the proposed sensor (GQD-GCE) was successfully used to detect DOX in human plasma, cerebrospinal fluid, and urine samples.

## 2. Experimental

### 2.1. Chemicals and reagents

All chemicals were purchased from Merck (Darmstadt, Germany) and used without further purification. Alumina slurry was purchased from Beuhler (Illinois, USA) and DOX was purchased from Exir Nano Sina Company (Tehran, Iran). All solutions were prepared with deionized water. The stock solution of DOX (0.18 M) was prepared by dissolving an accurate amount of DOX in an appropriate volume of 0.02 M phosphate buffer solution (PBS), pH=4.0 (which was also used as supporting electrolyte), and then stored in the dark place at 4 °C. Additional dilute solutions were prepared daily by accurate dilution just before use. Also the other stock solutions were prepared by dissolving an accurate amount equal to molecular weight of each one in 1000 mL deionized water and then all stored in the dark place at 4 °C.

### 2.2. Preparation of human plasma samples

Human plasma samples were obtained from the Iranian Blood Transfusion Research Center (Tabriz, Iran) and aliquots were transferred into microtubes and frozen at -4 °C until analysis. Human plasma samples frozen at -4 °C were thawed at room temperature daily and vortexed to ensure homogeneity. After thawing the samples gently, an aliquot of 2 mL of this sample was spiked with DOX, and then acetonitrile with the volume ratio of 2:1 (acetonitrile:plasma) was added to precipitate plasma proteins. The mixture was centrifuged for 10 min at 6000 rpm to separate residues of plasma proteins. Approximately, 2 mL of supernatant was taken and added into supporting electrolyte to reach a total volume of 10 mL.

### 2.3. Apparatuses and methods

Electrochemical measurements were carried out in a conventional three-electrode cell (from Metrohm) powered by an electrochemical system comprising of AUTOLAB system with PGSTAT302N (Eco Chemie, Utrecht, The Netherlands). The system was run on a PC using NOVA 1.7 software. Saturated Ag/AgCl was used as the reference electrode and the counter electrode (also known as auxiliary electrode), which is usually made of an inert material, platinum. All potentials were measured with respect to the Ag/AgCl which was positioned as close to the working electrode as possible by means of a luggin capillary. GCE (Azar electrode Co., Urmia, Iran) was used as the working electrode. Atomic force microscopy (AFM) experiments were performed in a contact mode by Nanowizard AFM (JPK Instruments AG, Berlin, Germany) mounted on Olympus Invert Microscope IX81 (Olympus Co., Tokyo, Japan). The transmission electron microscope (TEM) images were obtained on Leo 906, Zeiss (Germany). UV-vis spectroscopy was performed by Spectro UV-vis 2502 (Cecil, Cambridge, UK). X-ray powder diffraction (XRD) measurements were performed using Siemens, D500 (Germany). Dynamic light scattering (DLS)

was obtained using Malvern 3500 ZS. Spectrofluorimetry test was performed using Jasco, FP-750 (Tokyo, Japan).

## 3. Results and discussion

### 3.1. Synthesis of GQDs

An easy bottom-up method was used for the preparation of GQDs. At first, GQDs were synthesized by pyrolyzing citric acid and dispersing the carbonized products into alkaline solutions [18]. Briefly, 2 g of citric acid was put into a beaker and heated to 200 °C by a heating mantle until the citric acid changed to an orange liquid. Then, for preparing GQDs, 100 mL of 10 mg/mL NaOH solution was added into the orange homogenous liquid dropwise with continuous stirring. The obtained GQD solution was stable for at least one month at 4 °C. It is important to point out that the time of synthesis process of GQD was 30 min.

### 3.2. Characterization of GQDs

Fig. 1A shows the AFM image of synthesized GQDs. The corresponding AFM image shows a single GQD monolayer thin film. As can be seen in Fig. 1B, 90% of the particles represented dark brown color, which was assigned to a size range below 10 nm. Furthermore, the DLS study represented hydrodynamic sizes of GQDs with size distribution of  $(5 \pm 4)$  nm (Fig. 2A) confirming the AFM results.

The XRD pattern of GQD (Fig. 3A) shows a broad peak centered at around  $25\theta$  (0.36 nm), suggesting that the electrochemical process has more active sites along the surfaces of GQD, and the shifted peak to a higher degree, compared with the graphene, indicated that carbonization of citric acid produced graphite structures which had a more compact interlayer spacing than the original graphene.

The UV-vis absorption spectra of GQD (Fig. 2B) illustrate typical absorption of graphene derivatives in the UV region (200–300 nm) with an intensive peak at 340 nm and also a peak at 210 nm. Fig. 3B shows fluorescence spectra of the GQD dispersed in water at room temperature. The GQDs have a broad absorption from 400 to 600 nm. The maximum emission of ~480 nm was obtained with an excitation wavelength of 400 nm. Also when the excitation wavelength changed from 340 to 420 nm, the maximum peaks were constant. This could be explained by the uniformity both in the size and the surface state of those  $sp^2$  clusters contained in GQD which was responsible for the fluorescence of GQD.

### 3.3. Preparation of bare and GQDs modified electrodes

GCE (2 mm in diameter) was polished to a mirror-like finish with 0.3 and 0.05  $\mu$ m alumina slurry and then thoroughly rinsed with double distilled water. Then it was successively sonicated in acetone and double distilled water and was allowed to dry at room temperature. A total of 30  $\mu$ L of GQDs with the concentration of 3 mg/mL was dropped on the surface of electrodes pretreated and allowed to dry for 24 h at 4 °C in a dark place. Then the modified electrodes were rinsed with double distilled water 2 or 3 times and the GQDs modified electrodes were obtained and stored at 4 °C until use.

### 3.4. Electrochemical behavior

In order to verify the electrocatalytic activity of the modified electrode (GQD-GCE) for determination of DOX, the electrochemical experiments in the presence of DOX were carried out. Fig. 4 shows cyclic voltammograms (CVs) of bare GCE and

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