Materials Science and Engineering C 77 (2017) 790–802

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Electrochemical sensing of doxorubicin in unprocessed whole blood, cell lysate, and human plasma samples using thin film of poly-arginine modified glassy carbon electrode

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ARTICLE INFO

Article history:
Received 28 November 2016
Received in revised form 24 March 2017
Accepted 26 March 2017
Available online 28 March 2017

Keywords:
Doxorubicin
Electrochemistry
Biological fluids
Poly-amino acid
Whole blood
Cell lysate

ABSTRACT

A thin film of poly-arginine fabricated on glassy carbon electrode by one step electrodeposition method is applied for detection of doxorubicin hydrochloride in whole blood, cell lysate, and untreated-plasma samples. Cyclic voltammetry results indicated that the doxorubicin is oxidized *via* two electrons and two protons at physiological pH (pH = 7.4) using poly-arginine thin film modified glassy carbon. More importantly, electrostatic repulsion takes place between the prepared polymer film-modified electrode and selected drug resulting in the signal amplification on oxidation of doxorubicin and lowering its over potential and thereby selective detection of doxorubicin in real samples. The apparent electron transfer rate constant and transfer coefficient were determined by cyclic voltammetry and were approximately 10.1 s^{-1} and 0.82, respectively. Also, using differential-pulse voltammetric technique for sensitive detection of doxorubicin in whole blood and plasma samples, the lower limit of quantification was 69 nM and 103 nM, respectively. Also, application of this amino acid based biocompatible polymeric electrode was tested to the determination of doxorubicin in unprocessed whole blood and the results show that this sensor could be applied in online and real time monitoring of this anti-cancer drug in real samples which is important for clinical research.

1. Introduction

Doxorubicin (DOX) is a clinically important anti-cancer agent which is extensively used in treatment of a broad variety of cancers. However, long-term clinical use of DOX is limited due to its cytotoxic effects on neoplastic cells through the accumulation of reactive oxygen produced by scavenger enzyme activities [1,2]. Therefore, monitoring of the level of this drug in biological fluids of patients during their therapy period is vital. A number of analytical methods such as high performance liquid chromatography [3–5], fluorescence spectroscopy [6,7], electrochemical sensors [8,9] and capillary electrophoresis [10–12] have been developed for determination of DOX in biological samples.

But each method has its drawbacks as well such as time consuming, laborious, expensive and low sensitivity. The possibility to selectively, analyze biological samples directly without fractionally pre-treatment, inexpensive equipment, simple manipulation and simple model system for calibration are the advantages of electrochemical methods [13–21]. Also, several electrochemical methods have been reported as simple and inexpensive methods for DOX determination in biological fluids [22–26]. These methods present satisfactory sensitivity and selectivity. Electroanalytical methods are appropriate alternative to the above mentioned methods, because of simple sample pretreatment procedures. Based on this fact that DOX contains electroactive groups, some electroanalytical methods based on the use of various working electrodes have established for analysis of DOX [22–26]. Hasanzadeh and Shadjou [27] and Soleymani et al. [28] reviewed the reported electrochemical and spectroscopic sensing and biosensing methods in whole blood media, where the reported methods along with their advantages and disadvantages were discussed in depth.

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http://dx.doi.org/10.1016/j.msec.2017.03.257
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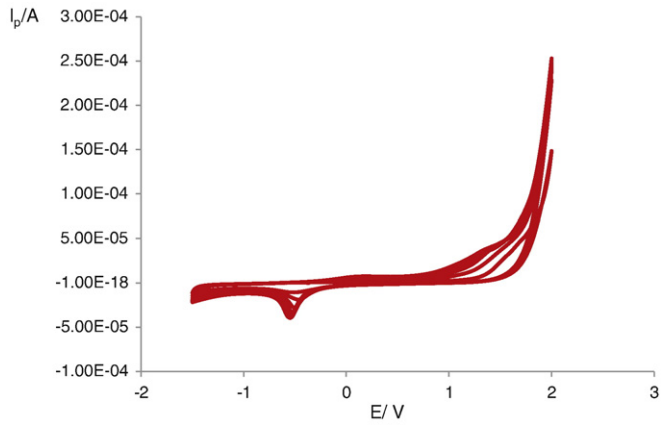
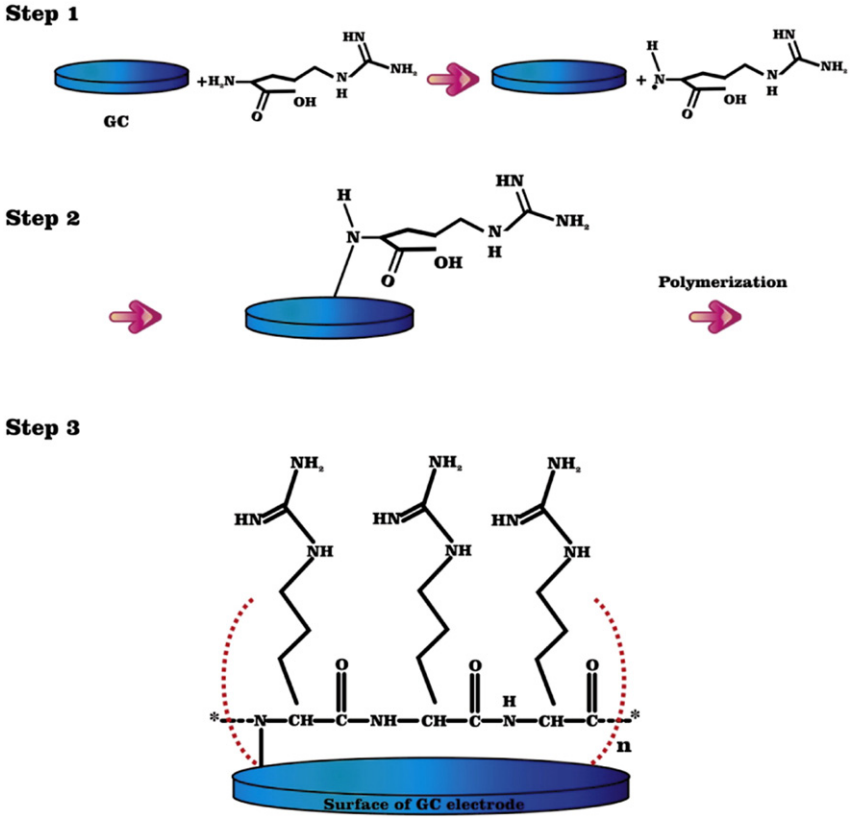


Fig. 1. Cyclic voltammograms for the electrochemical polymerization of 2.5mMARG on a GCE at the scan rate 100 mV/s.

The modification of polymeric species by adsorption or coating on to the surfaces of electrode gives extensive flexibility as polymers containing a range of functional groups which can achieve extremely high surface coverage using thick multilayer coatings [29]. This property helps attach relatively some of the compound to the polymer matrix-coated electrodes and subsequently mediate the oxidation of electroactive analytes. Among the different methods for preparing polymeric-modified electrode, electropolymerization has appeared as a versatile and efficient approach because of its advantages in terms of strong adherence to electrode surface and chemical stability of the film analysis, high sensitivity, selectivity and homogeneity in electrochemical deposition, reduced costs and *etc.* [30–32]. The electropolymerization of organic molecules with suitable functional groups, (—NH_2, —COOH —OH, —SH *etc.*) has exhibited to be a very convenient means for preparing functionalized and electroactive polymers at electrodes, because the procedure can be conveniently controlled by adjusting the electrochemical parameters. Accordingly, the charge transport, permeation, and thickness characteristics of the modified electrodes by polymer films can be enhanced. In addition, the electropolymerization of some organic molecules allows the production of new electrochemical sensors [33–35].

The —NH_2 and —COOH groups of amino acids play a key role in the electro-polymerization process on the electrode surface [36]. Owing to the excellent electrocatalytic properties of amino acids, different types of poly amino acids (polypeptide) have been prepared by chemical and electrochemical methods for electrochemical sensor applications [37]. Among different monomers, bio-inspired research has found that arginine is able to undergo an oxidative polymerization reaction in marine condition and form strong adhesion on the substrate on which it is grown. In contrast to other well established techniques, such as monolayer self-assembly, surface modification by poly-arginine (PARG) is carried out in an *in-situ* process. The PARG coating on the surface of substrates is typically thin and offers highly robust structure at a wide range of pH. Intrigued by the dormant potential of PARG, thus far it has been implemented as an electrochemical sensing platform for a myriad of substances. Therefore, PARG has been used for the modification of electrodes and applied for electrochemical determination, owing to its versatility and ease of preparation. However, only a few reports of the application of PARG for the development of modified electrodes have been recognized. Past studies have shown that the arginine exhibits high biocompatibility, high adsorption ability and the biological activity of redox proteins [38,39].

In this work, the first attempt to prepare ultra-thin film of PARG as electrochemical sensor *via* a facile electropolymerization process for selective and sensitive recognition of DOX in some real samples is made. An electropolymerized film of L-arginine was prepared on the surface of glassy carbon electrode (GCE) by cyclic voltammetry (CV). The polymer film has high concentration of negatively charged functional groups (COO^-). Therefore, electrostatic repulsion takes place between the



Scheme 1. Proposed mechanism of the preparation of PARG on the GCE.