Electrochimica Acta 132 (2014) 49–57

Contents lists available at ScienceDirect

Electrochimica Acta

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

Voltammetric behavior of doxorubicin at a renewable silver-amalgam film electrode and its determination in human urine

Olga Vajdle, Jasmina Zbiljić, Bojan Tasić, Danica Jović, Valéria Guzsvány*, Aleksandar Djordjevic

Department of Chemistry, Biochemistry and Environmental Protection, Faculty of Sciences, University of Novi Sad, Trg D. Obradovića 3, 21000 Novi Sad, Serbia

ARTICLE INFO

Article history:
Received 3 December 2013
Received in revised form 26 January 2014
Accepted 16 March 2014
Available online 1 April 2014

Keywords:
Renewable silver-amalgam film electrode
AdSWV
doxorubicin
urine
trace level determination

ABSTRACT

Voltammetric characterization of doxorubicin (DOX) and its determination using a renewable silver-amalgam film electrode (Hg(Ag)FE) was performed by direct cathodic square-wave voltammetry (SWV) and by the highly sensitive adsorptive square-wave voltammetry (AdSWV) in aqueous Britton-Robinson buffer solutions as supporting electrolyte (pH 2.0-8.0). The Hg(Ag)FE response of DOX was monitored in the potential range between -0.20 and -0.80 V. For the trace level analysis the method optimization showed that the optimal conditions were: the pH 6.0, the accumulation potential -0.20 V, and the accumulation time 140 s. In the model solutions, DOX was determined in the concentration range of 4.99-59.64 ng mL^{-1}. The developed AdSWV method was applied for the determination of DOX in spiked human urine sample. The lowest concentration of DOX of 9.89 ng mL^{-1} was determined with the relative standard deviation less than 6%.

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1. Introduction

Doxorubicin, DOX, (7S,9S)-7-[(2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7H-tetracene-5,12-dione, Fig. 1) is an anticancer (antineoplastic) chemotherapy drug classified as an anthracycline antiobiotic, commercialized in the form of chloride salt and sold as Adriamycin [1]. The pharmacological effects of this drug have been ascribed to the interaction with double helix of DNA and the anthracycline moiety which causes inhibition of replication and transcription of DNA in cancer cells [2,3]. However, clinical use of DOX is still limited for its cardiotoxicity that is usually caused by oxidative stress. Like all anthracyclines, DOX primarily works by intercalating DNA, but the mechanism of toxicity is also based on cells damage induced by reactive oxygen species, a mechanism in which free iron plays an important role. This opens a new field for the application of antioxidants (free radical scavengers and/or iron-chelating agents) in the potential protection of heart and other organs from DOX toxicity without impairing its antitumour efficacy [4]. It was reported that fullerenol $C_{60}(OH)_{24}$ nanoparticles in the presence of DOX exhibit such protective chelating and antioxidative properties in both, *in vitro* and *in vivo* models [4–6].

So, it is unequivocal that the development of sensitive and reliable analytical tools for the determination of DOX is a basic requirement for the study of this analyte in different types of samples with complex matrices. For this purpose, different analytical techniques have been used, and the most common among them is high performance liquid chromatography coupled with different detectors such as UV-Vis [7], tandem MS [8,9], chemiluminescence [10], fluorimetric [11], and electroanalytical [12] detectors. The capillary electrophoresis coupled with laser induced fluorescent detector [13–15] is noted as another powerful hyphenated measurement technique for the separation and trace level determination of DOX and its intermediates from complex biological matrices. Besides, UV-Vis spectrophotometry [16], fluorimetry [17,18], Raman spectroscopy [19], immuno assay analysis [20], and electroanalytical measurement techniques [21–44], have also been used for the determination of DOX in different samples.

Electroanalytical methods represent an appropriate alternative to the above mentioned techniques, because of low cost of instrumentation, fast and sensitive performance of analysis, and simplier sample pretreatment procedures. Voltammetric methods, based on the use of different working electrodes, have proven to be convenient for the determination of this drug, thanking to the fact that its structure contains electroactive groups [21–44]. Generally,

* Corresponding author.
E-mail address: valeria.guzsvany@dh.uns.ac.rs (V. Guzsvány).

http://dx.doi.org/10.1016/j.electacta.2014.03.124
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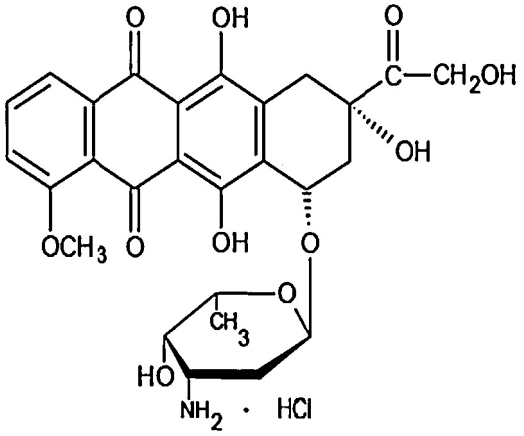

Fig. 1. Moleculare structure of doxorubicin hydrochloride.

the electroanalytical signals of DOX are characterized by two main pairs of peaks of analytical importance. According to the literature data, these peaks correspond to the reduction of quinone (around -0.6 V vs. SCE) and oxidation of hydroquinone (around 0.5 V vs. SCE) functional groups and their counterparts [21]. The determination of DOX is usually carried out using mercury-based electrodes [21–25] as well as different types of carbon based electrodes [26–30]. It is well known that DOX is strongly adsorbed on different electrode materials such as mercury [21–25], carbon paste [26–28], different types of graphite [25,29], and glassy carbon [30]. This property has been utilized for electroanalytical determinations of DOX at trace levels [21–30]. Besides, DOX was monitored by different electrodes in complex biological matrices, e.g. to assess its efflux from monolayers of cancer cells [31], and later, from single isolated cells of the same cell lines [32], and in a case study on assessing transport at live cell preparations [33]. Finally, electrochemical methods have been used in the exploratory investigation concerning the interaction of DOX and DNA [34–44].

It is well known that mercury is a favorite electrode material for voltammetric determinations based on cathodic reduction. However, because of the fears of mercury toxicity, there is a tendency to replace it with other nontoxic materials or minimize its amount. Among the promising alternatives to mercury electrodes, besides "metal-film" electrodes as bismuth particle-based [45] and antimony particle-based [46] electrodes, one should mention different solid amalgam electrodes [47–68], especially the renewable silver-amalgam film electrode, (Hg(Ag)FE) [52–68]. The reservoir of this electrode contains a small drop of saturated silver amalgam, so that the required amount of hazardous mercury (in its amalgam form) is reduced [52,54,68]. Such configuration of the Hg(Ag)FE can be considered as environmental friendlier than the classical Hg-based electrodes, which are hazardous to human health and environment. The Hg(Ag)FE has been successfully applied for the determination of several elements such as Cr(VI), Ni(II), Co(II), Mn(II), [53,56–58,68]. One of the first application of this electrode for assaying organic compounds was the determination of B_1 and B_6 vitamins by square-wave voltammetry (SWV) [60]. Further, there are reports concerning the determination of Proguanil and Blasticidin S compounds in model solutions and their traces in different samples like water, urine and spiked rice [63,65]. Recently, the Hg(Ag)FE-based SWV method have been successfully applied to monitor different insecticides from the group of neonicotinoids in the samples with different complex matrices such as honey in the case of thiamethoxam [62], solar photocatalytic degradation of imidacloprid [59], clothianidin from the Poncho formulation from the surface of corn seed samples [66], dinotefuran in carrot juice [64], clothianidin, thiacloprid, and nitenpyram in spiked Danube water samples [67].

The aim of this work was to expand the area of electrochemical application of the renewable Hg(Ag)FE in pharmaceutical analysis. To this end, a detailed study was performed to characterize the voltammetric behavior of DOX at Hg(Ag)FE, concerning primarily the influence of the pH of the supporting electrolyte and DOX adsorption on the electrode, with a final goal to develop a method for the determination of DOX. The developed Hg(Ag)FE-based highly sensitive adsorptive square-wave voltammetry (AdSWV) method was applied for the first time for the determination of DOX in spiked human urine samples.

2. Experimental

2.1. Chemicals

All chemicals used were of analytical reagent grade. The stock solution of DOX of the concentration of 0.1 mg mL^{-1} was prepared from doxorubicin hydrochloride (Pfizer, New York City, New York, USA) in bidistilled water. All solutions were stored in a refrigerator in the dark at 4°C, not longer than two weeks.

Britton-Robinson buffer solutions, used as the supporting electrolytes, were prepared from a stock solution containing 0.04 mol L^{-1} phosphoric (Merck, Darmstadt, Germany), boric (Merck) and acetic (Merck) acids, respectively, by adding 0.2 mol L^{-1} sodium hydroxide (Merck) to obtain the required pH values, covering the pH range 2.0-8.0.

2.2. Apparatus

Voltammetric experiments were performed on an AUTOLAB PGSTAT12 electrochemical analyzer operated via GPES 4.9 software (Ecochemie, The Netherlands). The cell stand included a three-electrode system with a renewable Hg(Ag)FE (MTM Anko Instruments, Cracow, Poland) [52,68], of a 12-mm^2 surface area as working, a saturated calomel electrode (SCE) (Amel, Italy) as reference, and a platinum (Amel) auxiliary electrode. All potentials are quoted vs. SCE reference electrode.

The pH measurements were made using a combined glass electrode (Jenway, UK), on a previously calibrated pH-meter (Radiometer, The Netherlands).

2.3. Voltammetric determination of doxorubicin

Characterization and determination of DOX in model solutions. Voltammetric measurements were carried out in the presence of Britton-Robinson buffer solutions pH 2.0-8.0. In the case of model solutions of DOX, the analyte was added with a micropipette to the supporting electrolyte consisting of bidistilled water (5.0 mL) and the appropriate Britton-Robinson buffer (5.0 mL). As it was mentioned earlier, the Hg(Ag)FE surface required special pretreatment before use [54,59,62,67]. Briefly, it was cleaned with 2% HNO_3 for about 5 minutes, and then covered again with amalgam by dipping it into the attached amalgam pool. In the case of DOX, before each set of measurements, the Hg(Ag)FE was activated electrochemically by cycling its potential in the range from -0.20 to -1.60 V in the corresponding supporting electrolyte.

Determination of DOX in spiked urine sample. Morning midstream human urine samples were collected daily from a healthy young female (aged 25) volunteer. To investigate possible interferences caused by urine matrix, 5.0 mL of Britton-Robinson buffer (pH 6.0) and between 1.0 ml and 100.0 μL of urine were placed into the voltammetric cell, and at the end 5.0 mL of bidistilled water was added. Every day, a fresh urine sample was analyzed without any conservation or other sample preparation steps. The quantitation was performed by the standard addition method as follows: to the solution consisting of 5.0 mL of bidistilled water and

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