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Voltammetric Understanding of Ionizable Doxorubicin Transfer Reactions across Liquid/liquid Interfaces and Sensor Development

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ABSTRACT

The transfer characteristics of the ionizable anticancer drug doxorubicin (DOX) across a polarized interface between two immiscible electrolyte solutions (ITIES) were investigated using voltammetry. Aqueous buffer solutions at different pH with a controlled ionic strength were interfaced with 1,2-dichloroethane in order to understand the nature of charged DOX. Following voltammetric investigation, an ionic partition diagram was established which can be correlated to the lipophilicity of DOX and further used for predicting specific charged forms of DOX in the aqueous phase at a certain pH value. Thermodynamic properties including the formal transfer potential, partition coefficient and Gibbs energy of DOX transfer processes at the water/1,2-DCE interface were also evaluated. At a buffer solution of pH 7 the peak current responsible for protonated DOX ($HDOX^+$) transfer across the ITIES gave a good linear relationship with the DOX concentration enabling a DOX sensitive voltammetric sensor to be developed. As a sensing demonstration for practical applications, a microhole supported water/organic gel interface was fabricated and used in conjunction with differential pulse stripping voltammetry (DPSV) to quantitatively analyze $HDOX^+$ in buffer followed by applying to local river water and human serum sample solutions. The results from the $HDOX^+$ sensor were then compared to those obtained using conventional high-performance liquid chromatography (HPLC).

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1. Introduction

Doxorubicin (DOX), also known as adriamycin, is regarded as one of the most potent Food and Drug Administration (FDA) approved chemotherapeutic drugs limited only by its toxicity on noncancerous cells in the human body [1]. DOX produces a potentially fatal cardiotoxicity that is dependent on the total cumulative dose administered [2]. Understanding the nature of DOX in an ionized form could thus be important to provide information about the pharmacokinetics of this drug and its behavior in biological systems [3].

One of the most useful tools to characterize lipophilicity and partitioning behavior of ionized and neutral forms of drug molecules alongside its pKa values is the voltammetric investigation of drug ion transfer processes across a polarized interface between two immiscible electrolyte solutions (ITIES) [4–9]. The transfer potential of the ionized drug at ITIES can be associated with the lipophilicity of the drug and thus its biological and pharmacological activity, providing further information about transfer behavior through the cell membrane, toxicity, and interaction with other biomolecules [4]. There have thus been extensive efforts on understanding transfer processes of various ionizable drug molecules across ITIES [7,9–14]. For example, Pereira's group investigated the electrochemical behavior of a similar anthracycline derivative anticancer drug, daunorubicin, at a micro-liquid/liquid interface [9]. In this article, we focused on utilizing ITIES for understanding the transfer process as well as thermodynamic and lipophilicity properties of the DOX molecule, which has the same dihydroxyanthraquinone ring and daunosamine moiety as daunorubicin but differs only in the C9 substituent [15]. Such relatively small differences lead to significant changes in the lipophilicity and also pKa values of both drugs [15,16]. It is thus important to separately investigate DOX in addition other derivatives from the same family in order to elucidate their distinct properties in a biological system.

In addition, ion transfer reactions across the ITIES can be a powerful basis for the development of a wide range of selective and sensitive sensors of ionic species such as DNA [17], proteins [18], food substances [19], carbohydrates [20], and ionized drug molecules [9,10,12–14]. However, still yet to be investigated

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considering little availability for drug sensitive sensing platforms [9,10,12–14]. Most common methods to quantitatively analyze drugs including doxorubicin are high-performance liquid chromatography (HPLC) [21–23], ultraviolet-visible (UV-Vis) [24] and Raman spectroscopies [25], capillary electrophoresis [26], flow injection chemiluminescence [27], and electrochemical methods [28,29].

In this paper, we characterized the voltammetric behavior of DOX in an aqueous solution at controlled pH values and ionic strengths interfaced with 1,2-dichloroethane in order to understand the charge properties of DOX. The aqueous pH was changed from 4.0 to 9.5 and the ionic strength was fixed at 0.02 mol/L to promote the drug molecule stability in an aqueous environment as DOX can self-associate [8,30]. Cyclic and differential pulse voltammetric investigation of DOX transfer behavior at different pH solutions enabled the establishment of a partition diagram. Since the interfacial transfer of positively charged $HDOX^+$ species at pH 4.0 and pH 7.0 showed a linear current response as a function of DOX concentration, a sensing platform utilizing a microhole supported liquid/gel interface was developed. A linear dynamic range from 5 μM to 80 μM of DOX was obtained using differential pulse stripping voltammetry. The selectivity of the DOX sensor was also studied in the presence of various potential interfering anthracycline-derived anticancer drugs, such as daunorubicin and epirubicin. The sensors applicability for real sample analysis was also demonstrated by determining DOX concentration levels in two very different sample matrices: (i) Sincheon river water flowing through Daegu City (S. Korea) and (ii) human serum solution. In each case, a series of known concentrations of DOX spiked into sample aliquots were assessed. The results were then compared to those using a conventional HPLC method.

2. Experimental

2.1. Materials

The chemicals listed were all used as received. Acetic acid (CH_3COOH, Duksan pure and chemical Co. Ltd), albumin from human serum (HSA, Sigma-Aldrich), boric acid (H_3BO_3, Sigma-Aldrich), bovine serum albumin (BSA, Affimetrix), calcium(II) chloride ($CaCl_2$, Duksan pure and chemical Co. Ltd), copper(II) chloride ($CuCl_2$, Sigma-Aldrich), 1,2-dichloroethane (1,2-DCE, Sigma-Aldrich), daunorubicin hydrochloride hydrate (daunorubicin HCl, Sigma-Aldrich), doxorubicin hydrochloride hydrate (doxorubicin HCl, Sigma-Aldrich), epirubicin hydrochloride hydrate (epirubicin HCl, Sigma-Aldrich), hydrochloric acid (HCl, OCI company Ltd), lithium chloride (LiCl, Fluka), lithium tetrakis(pentafluorophenyl)borate etherate (LiTB, Boulder Scientific Co.), magnesium(II) chloride ($MgCl_2$, Junsei Chemical), 2-nitrophenyloctylether (NPOE, Sigma-Aldrich), normal human serum (Millipore), polyvinylchloride (PVC, high molecular weight, Sigma-Aldrich), sodium acetate ($C_2H_3NaO_2$, Sigma-Aldrich), sodium chloride (NaCl, Sigma-Aldrich), sodium hydroxide (NaOH, Sigma-Aldrich), sodium dihydrogen phosphate-monohydrate ($NaH_2PO_4{\cdot}H_2O$, Sigma-Aldrich), di-sodium hydrogen phosphate-heptahydrate ($Na_2HPO_4{\cdot}7H_2O$, Sigma-Aldrich), tetrapropylammonium chloride (TPrACl, Sigma-Aldrich), tetraoctylammonium bromide (TOABr, Sigma-Aldrich), tetraoctylammonium chloride (TOACl, Sigma-Aldrich), trifluoroacetic acid (Sigma-Aldrich), and tris (hydroxymethyl)-aminomethane (Tris, Sigma-Aldrich), zinc(II) chloride ($ZnCl_2$, Sigma-Aldrich). All aqueous solutions were prepared using Millipore-filtered water. The aqueous supporting electrolyte solution with different pH values for doxorubicin analysis was prepared as follows: acetate buffer for a chosen pH between 4.0 and 5.5, phosphate buffer for pH 6.0 to 7.5, and borate buffer for a pH between 8.0 and 9.5. An organic supporting electrolyte, tetraoctylammonium tetrakis(pentafluorophenyl) borate (TOATB), was prepared using a previously reported method [31].

2.2. Electrochemical Set-up for Water/1,2-DCE Interface

Ionized doxorubicin transfer reactions across a water/1,2-DCE interface with the diameter of 1.13 cm^2 were investigated using a custom made circular glass cell in a four electrode configuration [31]. Two Ag/AgCl reference and two Pt counter electrodes were used where the current flow was circulated via two Pt electrodes each immersed in the water and 1,2-DCE phases. The reference electrodes placed in each phase through individual Luggin capillaries were used to polarize the interface.

2.3. Electrochemical Set-up and Fabrication Method for a Microhole Supported Interface between Water and PVC-NPOE Gel

A microhole supported liquid/gel interface was created using the previously reported method [32]; briefly, a sharp needle was used to pierce a microhole in a 12 μm thick polyethylene terephthalate (PET) film. Eight microliters of the NPOE solution containing 3% PVC and 10 mM tetraoctylammoniumtetrakis(pentafluorophenyl) borate (TOATB) were hot casted at around 80 °C on the back side of the microhole in PET film. The PVC-NPOE gel was then formed by leaving it overnight at room temperature.

2.4. Electrochemical Measurements

A potentiostat from Autolab PGSTAT30 (Ecochemie) was used for all electrochemical measurements. For cyclic voltammetry (CV), a scan rate of 20 and 100 mV s^{-1} were used throughout the measurement at microhole-liquid/gel and water/1,2-DCE interfaces, respectively. Differential pulse voltammetry (DPV) parameters were applied as follows: step potential = 3 mV, pulse amplitude = 50 mV, and scan rate = 8 mV s^{-1}. Whilst for differential pulse stripping voltammetry (DPSV), preconcentration time = 30 s at 1 V, step potential = 3 mV, pulse amplitude = 50 mV, pulse duration = 50 ms, and scan rate = 8 mV s^{-1} were used. An aqueous buffer solution with an ionic strength of 0.02 mol/L (adjusted with NaCl) with different pH values for doxorubicin analysis was used and 5 mmol/L acetate, phosphate or borate buffer was used to adjust the pH of the aqueous solution [8]. All experiments were performed at room temperature unless otherwise specified.

3. Results and Discussion

3.1. Characterization of Doxorubicin Transfer Reaction across a Water/1, 2-DCE Interface

Transfer behaviors of ionized DOX molecules across ITIES were investigated using the electrochemical Cell 1 in conjunction with CV and DPV techniques. Different concentrations of DOX molecules dissolved in an aqueous solution at different pH values with an ionic strength of 0.02 mol/L were interfaced with 1,2-DCE.

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