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Electrochemical Behavior and Determination of Salicylic Acid at Carbon-fiber Electrodes

Jinwoo Park*, Changsun Eun

Department of Biotechnical and Clinical Laboratory Sciences, University at Buffalo, State University of New York, Buffalo, NY 14214-3005, USA

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ABSTRACT

The loss of electrode activity (referred to as electrode fouling) caused by an electropolymerized passive film of salicylic acid (SA), a major hydrolysis product of aspirin, significantly decreases the accuracy and the precision of indirect electrochemical detection of aspirin. However, the electrode fouling problem for electrochemical determination of SA and ways to remove the fouling film have been sparsely discussed. In addition, the electrochemical behavior of SA on a carbon-fiber electrode (CFE), widely used for the study of neurochemicals *in vivo* and *in vitro*, has not yet been studied. Herein, we report the electrochemical behavior of SA at CFEs using cyclic voltammetry and differential pulse voltammetry. The irreversible and pH dependent electrochemical oxidation of SA produced dihydroxybenzoic acids, SA dimeric products and poly-SA films that strongly adhered to the electrode surface and passivated further reactions. The electrode fouling caused by the SA films on a CFE decreased electrode sensitivity and reproducibility for the indirect determination of aspirin. In this study, the fouling effects were characterized with $Fe(CN)_6^{4-/3-}$. Interestingly, we found that the poly-SA films on CFE can be removed by a strong base, undergoing the intramolecular base catalyzed hydrolysis of salicylate esters. This non-destructive cleaning method of poly-SA films on the electrode improved the linear dynamic range of SA as well as the accuracy and precision of SA measurements. This new cleaning method of CFEs was further applied to the indirect determination of aspirin in commercially available pharmaceutical tablets.

1. Introduction

For over 100 years, acetylsalicylic acid, commonly known as aspirin, has been one of the most used non-prescription medications in the world [1]. Approximately, one-fifth of Americans take aspirin on a daily basis [2] as a non-steroidal anti-inflammatory, anti-pyretic and anti-thrombotic agent [1,3]. Aspirin is rapidly hydrolyzed in the body to salicylic acid (SA), which is responsible for most of the pharmacological activities of the parent drug. Further oxidation and conjugation of SA in the body leads to its metabolites including 2,3-dihydroxybenzoic acid (2,3-DHBA), 2,5-dihydroxybenzoic acid (2,5-DHBA), 2,3,5-trihydroxybenzoic acid (2,3,5-THBA), glucuronide products and uric acid derivatives [3,4]. Recent studies reported that daily low doses of aspirin could also effectively prevent cancers and attenuate the effects of neurodegenerative disorders [5,6]. These new therapeutic applications of aspirin have sparked new investigations ranging from clinical studies to biochemical investigations [7,8]. Due to the many benefits of aspirin, the detection of SA has become increasingly important for the study of its many functions in the body.

Attributed to the acidic functional groups and conjugated π electrons, SA can be detected by titration, UV–vis spectrophotometry [9] and spectrofluorimetry [10], accompanied with various separation techniques such as electrophoresis [11] and chromatography [12,13]. In addition, the electrochemical determination of SA has received increased attention due to easy sample preparation, fast response, and relatively simple and inexpensive instrumentation. Various types of electrodes including glassy carbon electrodes [14], gold electrodes coated with copper nanoparticles [15], platinum electrodes [16,17] and others [18–21] have been reported for the electrochemical measurement of SA.

However, strong electrode fouling caused by an electropolymerized passive SA-film on electrodes is a major challenge for the electrochemical determination of SA. Although the

* Corresponding author at: Department of Biotechnical and Clinical Laboratory Sciences, 26 Cary Hall, 3435 Main Street, University at Buffalo, Buffalo, NY 14214-3005, USA. Tel.: +1 716 829 5186; fax: +1 716 829 3601.
E-mail address: jinwoopa@buffalo.edu (J. Park).

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electrochemical oxidation pathways of SA have not been reported in detail, Scheme 1 depicts the possible pathways based on the well-known electrochemical oxidation pathways of phenol [22–27]. Briefly, a SA radical formed by an irreversible one electron oxidation reacts with either water or SA molecules to produce 2,3- and 2,5-dihydroxybenzoic acids (DHBAs) (I) and dimeric products (II). With further coupling and crosslinking reactions, an electronically inactive porous poly-SA film (III) forms over the electrode surface. The thickness of the film ranges from 5 μm to 100 μm depending on different reaction media [28–32]. The passivation properties of the film are attributed to its electro-inactivity and small pore size, resulting in electrode fouling [31–33].

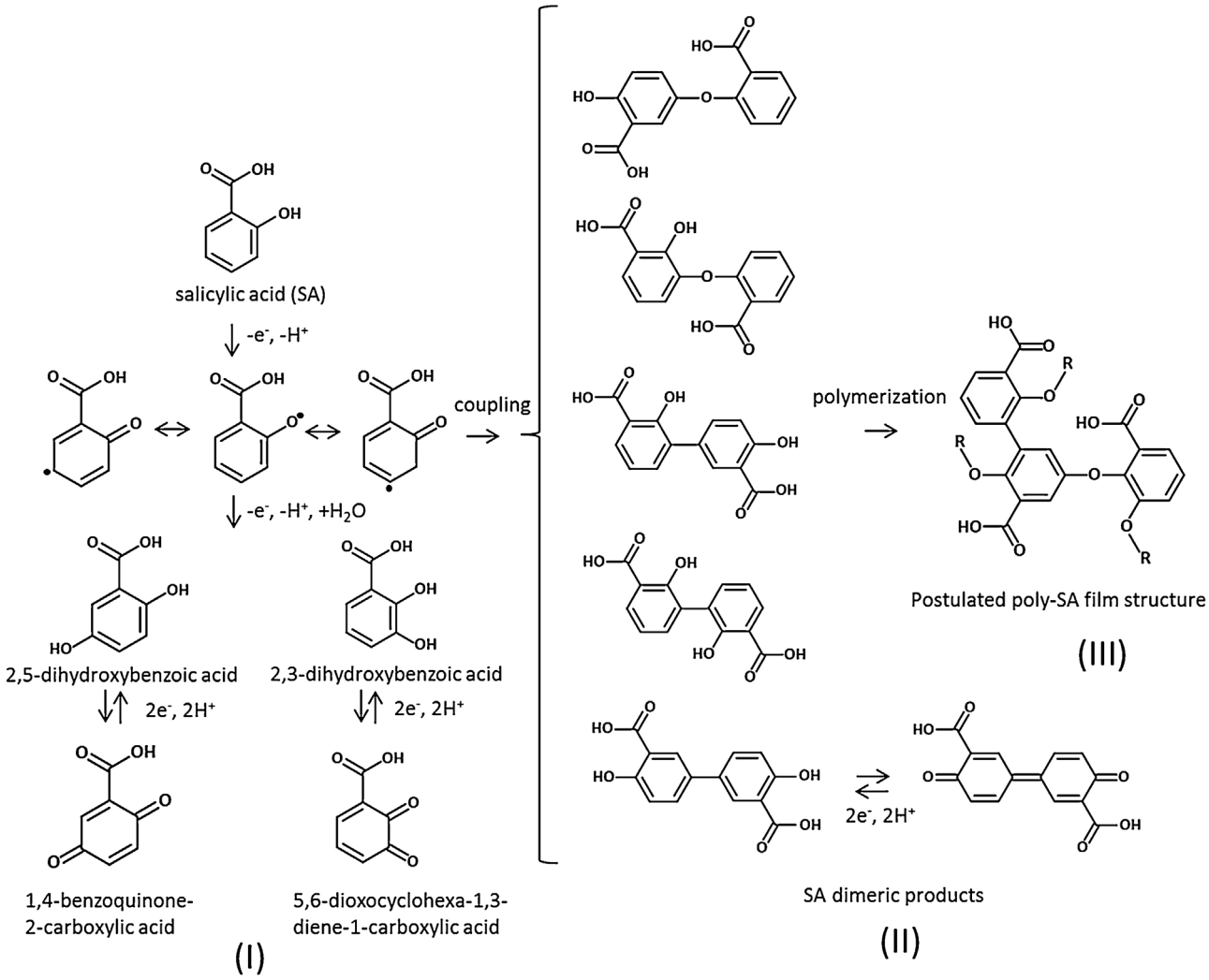
In order to inhibit electrode fouling caused by the films of phenolic compounds and their derivatives, different approaches have been reported such as solvent modification [34], anodic polarization of the electrode [27], and oxidation pathway alteration [35]. Although SA is one of the many phenolic compounds, unfortunately, the passive nature of the poly-SA film and its electrochemical oxidation products have been of little concern during the electrochemical determination of SA in previous studies. Therefore, the fouling effects and the context of the fouling processes caused by these poly-SA films must be appropriately addressed for assessing the accurate and precise electrochemical measurements of SA.

In this study, we investigated the electrochemical properties of SA at carbon-fiber electrodes (CFEs) using cyclic voltammetric and differential pulse voltammetric methods for our future application of CFEs to study effects of SA on neurochemicals in the brain. The CFEs are widely used for the *in vivo* and *in vitro* study of neurochemicals including monoamines in the body [36–39]. We also characterized the passivating kinetics of the poly-SA film with ferrocyanide(II)/ferricyanide(III) ($Fe(CN)_6^{3-/4-}$) redox couple and demonstrated that the poly film on the CFE was removed in a strong base, NaOH, by the reaction of intramolecular base catalyzed hydrolysis of salicylate esters. This non-destructive cleaning of the SA film on the electrode significantly improved the accuracy and the precision of repeated measurements of SA. Finally, the electrochemical detection of SA with CFE was used to indirectly determine both acetylsalicylic acid from Sigma-Aldrich and commercial aspirin tablets after hydrolysis of the compounds to SA.

2. Experimental

2.1. Chemicals and materials

Sodium salicylate (SA), methyl salicylate (MeSA), 2,3-dihydroxybenzoic acid (2,3-DHBA), 2,5-dihydroxybenzoic acid (2,5-DHBA), potassium hexacyanoferrate(II) trihydrate ($K_4Fe(CN)_6{\cdot}3H_2O$), and



Scheme 1. Electrochemical oxidation pathways of salicylic acid (SA).