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Computational design as a green approach for facile preparation of molecularly imprinted polyarginine-sodium alginate-multiwalled carbon nanotubes composite film on glassy carbon electrode for theophylline sensing

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ABSTRACT

This paper reports on the synthesis of a novel molecularly imprinted composite film using the mathematical modeling. This composite was then used in the electrode modification for the determination of theophylline. The ratio of monomer to template in optimum condition was obtained to be 4. The modification of electrode was performed in the presence of theophylline through the electropolymerization of arginine on the composite of sodium alginate/multiwalled carbon nanotubes (SA-MWCNTs), which had been coated on glassy carbon electrode (GCE). The SA-MWCNTs composite with netlike morphology demonstrated high conductivity and electrocatalytic activity. Cyclic voltammogram of modified electrode (MIP/SA-MWCNTs/GCE) in the presence of theophylline showed a sensitive anodic peak in 1170 mV in buffer solution of phosphate (pH 7.0). The investigation and optimization of the effective factors on the response and electrochemical behavior of target theophylline were accurately done on the surface of the modified electrode. Theophylline response was linearly within the range of 0.01–60.0 μM with detection limit of 3.2 nM. Regarding the added standards, the recoveries were values between 93.4–105%. The function of this electrode was satisfactory in the determination of theophylline in real samples like theophylline tablet, theophylline oral solution and human plasma samples.

1. Introduction

Theophylline (1, 3-dimethyl-3,7-dihydro-1H-purin-2,6-dion) known as a class of methyl xanthine derivatives is widely available in nature. As a member of important natural alkaloids, it is found in large amount in tea and cocoa beans [1]. Theophylline antagonizes are found almost equally A1, A2 and A3 receptors, as a non-specific adenosine antagonist. For about one century, it is used as a treatment for adults' respiratory diseases such as asthma and chronic obstructive pulmonary disorder (COPD). In addition, in therapy for infant apnea and asthmatic acute phase in children, it has been effective as respiratory stimulators [2]. In order to be effective as bronchodilator, the accepted level of theophylline in plasma of adults, is 5–20 μg/ml. High dosage levels more than 20 μg/mL in blood serum can cause problems such as heartburn, anorexia, coma, and even cardiac or respiratory arrest. Accordingly, the determination of theophylline concentration via a simple, rapid, precise, and inexpensive method is important in medical affairs [2].

Hitherto, methods of analysis for theophylline assessment include liquid chromatography–mass spectrometry (LC–MS), spectrophotometry, GC coupled with mass spectrometry (GC/MS), high performance liquid chromatography (HPLC), electron capture gas chromatography, immunoassay, and capillary electrophoresis [3–9]. These methods, however, require tedious and time-consuming pretreatment stages, and skilled operators to handle the needed complicated and costly instruments. On the contrary, the electrochemical techniques have been developed due to their advantages including high sensitivity, good stability, simplicity, cost-effective equipment, being easy to use, and in situ analysis [10,11].

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Molecular imprinting is a technique which is used to molecular recognition via self-assembly of functional monomers around a template molecule through the interaction between their functional groups [12]. This technology has been developed for use in sensors since it can provide enhanced selectivity and/or sensitivity [13,14]. In addition, molecularly imprinted polymers (MIP) benefit from ease of preparation along with good stability in chemical, physical and mechanical properties [15]. Also, during preparation of MIP by electropolymerization, it is possible to control the morphology and thickness of the polymer through the changes in deposition conditions which is effective on the properties of the final sensors [14,15]. Polyarginine as a conductive polymer possesses unique properties such as high conductivity, nontoxicity, biocompatibility, and biodegradability. Owing to these properties, it has been used in the preparation of electrochemical sensors based on MIP.

In order to increase the sensitivity of MIP based sensors, nanomaterials are generally used in their constructions [16]. Multi-walled carbon nanotubes (MWCNTs) have attracted more attention compared with other nanomaterials. Moreover, MWCNTs are among the major nanomaterials which are being used in the modification of electrodes due to their huge cylindrical surface. In addition, MWCNTs are famous and attractive due to their exceptional properties including considerable electrical and thermal conductivity, chemical stability, high tensile strength, high elasticity, and in some cases, metallic conductivity and support of catalyst [17–19]. Moreover, the MWCNTs can be functionalized by various groups anchored on their surface such as hydroxyl, carboxyl, and carbonyl groups providing a suitable modifiable support [20]. The extensive surface and reasonable electrical conductivity make it suitable to construct a sensitive electrode. Sodium alginate (SA) is a polymer with polar side-chains functionalized MWCNTs solution noncovalently and can lead to having a stable homogeneous solution [21]. Accordingly, in comparison with traditional carbon electrodes, sensors based on MWCNTs-SA render higher sensitivity, lower detection limit, faster electron transfer kinetic, low background current, wide potential window, reduced overpotential, and resistance to surface fouling without the problem of dispersing MWCNTs and poor solubility. It has been revealed that the modification of electrodes by MWCNTs, demonstrates electrocatalytic behavior towards some of the biological species with excellent efficiency [19,21].

Herein, we introduce a new MIP-based electrochemical sensor for sensing of theophylline. The sensor was fabricated through the electropolymerization of arginine in the presence of theophylline on a modified GCE by SA-MWCNTs nanocomposite. The presence of theophylline imprinted polyarginine provides good recognition property, while the SA-MWCNTs nanocomposite increases significantly the surface area of electrode and the efficiency of electron transfer [21] which in overall lead to a sensor with high sensitivity and selectivity.

2. Experimental

2.1. Materials and apparatus

All the studied reagents, as well as theophylline, were purchased from Merck (Darmstadt, Germany) in analytical grade. MWCNTs were prepared from USA Research Nanomaterial's, Inc. with diameters ranging between 10–30 nm and purity above 90%. Moreover, NaH_2PO_4 and Na_2HPO_4 were used for the preparation of Phosphate buffer solution (PBS). Electrochemical analyses were performed using solutions with 0.03 M phosphate buffer (pH 7.0). Double distilled water was used in preparation of all the solutions. A milli-Q system from Millipore (Bedford, MA, USA) provided ultrapure water. A fresh stock solution of 25 mM theophylline was also used in all the experiments. In order to perform the electro analytical measurements, a 2 mM equimolar solution of ferro-ferricyanide was prepared which contained 0.1 M KCl ($[Fe(CN)_6]^{3-/4-}$. Adjustment of the pH of buffer solutions was done using a digital WTW Metrohm 827 Ion analyzer (Herisau, Switzerland) equipped with a combined glass-calomel electrode pH meter. The SEM images were taken by a scanning electron microscope (TESCAN vega3, Czech Republic). Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) studies were performed using electrochemical analyzer (Metrohm Ltd.CH-9101 Herisau 757 V A); the analyzer was equipped with a three electrode cell. The working, counter and the reference electrodes, were respectively MIP/SA-MWCNTs/GCE, Pt wire and a saturated Ag/AgCl electrode. All the measurements were reiterated three times in room temperature about 25 °.

3. Methods

3.1. Computational study

The monomers and the template were set up to perceive the characteristics of MIP and binding mechanism at molecular level. In order to obtain the most effective ratio for the construction of MIP at molecular level, the structure of monomers, template and ratios of monomer-template complexes were designed and then optimized by Gaussian 09 software [22]. Optimization was carried out for the aim of obtaining the most stable structure of the molecule which was in harmony with nature. The more the monomer and the template structure in consistent to reality, the more accurate calculations and ratios would be achieved. Designing the most selective MIPs was implemented by the ab initio computational method. The technique of ab initio owns the preferences of high accuracy and low cost computation. Quantum mechanical calculations were done based on DFT at level of B3LYP (Becker's three parameters functional with nonlocal correlation) and the basis set of 6–31 G (d) was employed for the optimization of all the conformations according to interaction energies. The different molar ratios of arginine (ARG), lysine (LYS) and phenylalanine (PHY) such as monomer to theophylline (template) were investigated to distinguish between the most stable complex of the monomers and template. Then, interaction energies were calculated using the Eq. (1), in which n represents the number of monomers in the monomer-template complexes.

At first, geometry of ARG, LYS, PHY and theophylline were optimized, followed by the calculation of the electronic energy of the isolated molecules. To analyze the possible sites of interactions, calculation of the atomic charges derived from the natural bond orbital (NBO) of the ARG, LYS, PHY and theophylline were done. Finally, in order to analyze the value of ΔE in each site of interaction, the energy calculations of the formed complexes between the ARG, LYS, PHY and each theophylline were calculated.

The ΔE calculation of theophylline was conducted with each molecule of ARG, LYS, and PHY were performed using the Eq. (1):

$$\Delta E = E(\text{template-monomercomplex}) - [E(\text{template}) + nE(\text{monomer})] \quad (1)$$

Where n indicates monomer number in the template-monomer complexes. A complex with higher ΔE value predicts the most stable conformation.

Molecular electrostatic potential (MEP) was performed as a useful method to predict possible sites of electrostatically-driven interactions. NBO [23] method was used to study orbital interactions, the localized orbital interactions involved in non-covalent interactions. These were then quantified using second order perturbation theory, in which the second-order energy ($E^{(2)}$) was used to measure the interaction strength.