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Simultaneous determination of mycophenolate mofetil and its active metabolite, mycophenolic acid, by differential pulse voltammetry using multi-walled carbon nanotubes modified glassy carbon electrode

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ABSTRACT

A highly sensitive electrochemical sensor for the simultaneous determination of mycophenolate mofetil (MPM) and mycophenolic acid (MPA) was fabricated by multi-walled carbon nanotubes modified glassy carbon electrode (MWCNTs/GCE). The electrochemical behavior of these two drugs was studied at the modified electrode using cyclic voltammetry and adsorptive differential pulse voltammetry. MPM and MPA were oxidized at the GCE during an irreversible process. DPV analysis showed two oxidation peaks at 0.87 V and 1.1 V vs. Ag/AgCl for MPM and an oxidation peak at 0.87 V vs. Ag/AgCl for MPA in phosphate buffer solution of pH 5.0. The MWCNTs/GCE displayed excellent electrochemical activities toward oxidation of MPM and MPA relative to the bare GCE. The experimental design algorithm was used for optimization of DPV parameters. The electrode represents linear responses in the range 5.0×10^{-6} to 1.6×10^{-4} mol L^{-1} and 2.5×10^{-6} mol L^{-1} to 6.0×10^{-5} mol L^{-1} for MPM and MPA, respectively. The detection limit was found to be 9.0×10^{-7} mol L^{-1} and 4.0×10^{-7} mol L^{-1} for MPM and MPA, respectively. The modified electrode showed a good sensitivity and stability. It was successfully applied to the simultaneous determination of MPM and MPA in plasma and urine samples.

1. Introduction

Mycophenolic acid (MPA), the active metabolite of mycophenolate mofetil (MPM), is an antiproliferative immunosuppressive agent. It is increasingly used after solid organ transplantation and also proposed for therapy of several autoimmune diseases [1,2]. Its immunosuppressive action resides in the noncompetitive, selective and reversible inhibition of inosine monophosphate dehydrogenase, thereby suppressing the de novo synthesis of guanosine nucleotides in T and B lymphocytes. Due to the rapid and extensive metabolism of MPM to the active plasma metabolite, pharmacokinetic investigation following the administration of the prodrug-MPM has been based principally on the kinetics of MPA. Since MPM is at the moment, at a relatively early stage of the drug development process, the full pharmacokinetic characterization in recipients of kidney transplantation, in conjunction in with pharmacokinetics (clinical efficacy) is essential for optimization of drug therapy [3]. It has also been tried for the prophylaxis of graft-versus-host disease after bone marrow transplantation [4]. Due to the clinical advantages of MPM, there has been an increase in the number of MPM formulations in the market in recent years [5]. Several analytical methods namely, HPLC [6–8], LC-MS [9], spectrophotometric [10], and micellar electrokinetic chromatographic [11] methods have been reported for the determination of MPM and MPA in bulk, pharmaceutical formulations, and biological samples. The reported chromatographic and spectroscopic methods were found to be time consuming. This prompted us to develop a simple, rapid, and cost effective analytical method for simultaneous analysis of MPM and MPA.

Multi-walled carbon nanotubes (MWCNTs) are molecular-scale wires that have attracted considerable attention due to their extraordinary structural, mechanical, electrical, and electrochemical properties as well as their promise in the field of material science [12]. It has been shown that application of MWCNTs results in extraordinary advantages over conventional electrodes, including enhanced mass transport (via thin layer diffusion besides the semi-infinite planar diffusion), catalysis, highly effective surface areas, high porosity, more adsorption, and reactive sites. Furthermore, control over the electrode macro environment can provide an important and feasible platform for electroanalysis, particularly in the design of the modified electrodes for electrochemical sensing [13–17].

In the present study, a glassy carbon electrode modified with multi-walled carbon nanotubes (MWCNTs/GCE) was constructed and applied to the simultaneous determination of MPM and MPA. The experimental results indicate that modification caused a significant increase in electroactive surface area of the GCE. As a consequence, the oxidation peak current of MPM and MPA remarkably enhanced at the modified electrode compared to bare GCE. We reported a simple, precise, accurate, and economically viable electrochemical method for the simultaneous

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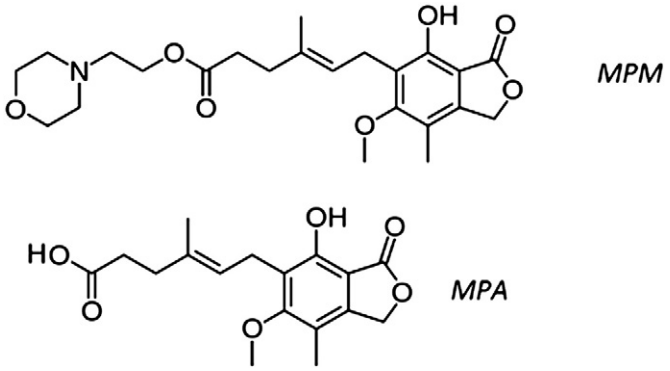

Scheme 1. Structural formula of mycophenolate mofetil (MPM) and mycophenolic acid (MPA).

determination of MPM and MPA in biological samples using MWCNTs/GCE. Statistical tests were performed for validation of data.

2. Experimental

2.1. Chemicals

MPM and MPA were obtained from Nokam Mamotir pharmaceutical Company (Saveh, Iran). Scheme 1 shows the structures of MPM and MPA. All chemicals used were of analytical regent grade purchased from Merck Company (Darmstadt, Germany) unless otherwise stated. Doubly distilled water was used throughout. Stock solutions of MPM (1.0×10^{-2} mol L^{-1}) and MPA (1.0×10^{-2} mol L^{-1}) were prepared in a 50:50 (v/v) mixture of water and methanol and stored in a refrigerator at 4 °C. In the present study, phosphate buffer (sodium dihydrogen phosphate, sodium hydrogen phosphate and sodium hydroxide, 0.1 mol L^{-1}) solutions of different pH values were used. Multi-walled carbon nanotube (MWCNT) with purity more than 90%, outer diameter between 70 and 90 nm and inner diameter between 5 and 9 nm was from Neutrino Company (Iran) and used without any purification as the substrate for the modification of the GCE. A plasma sample was prepared from a healthy volunteer.

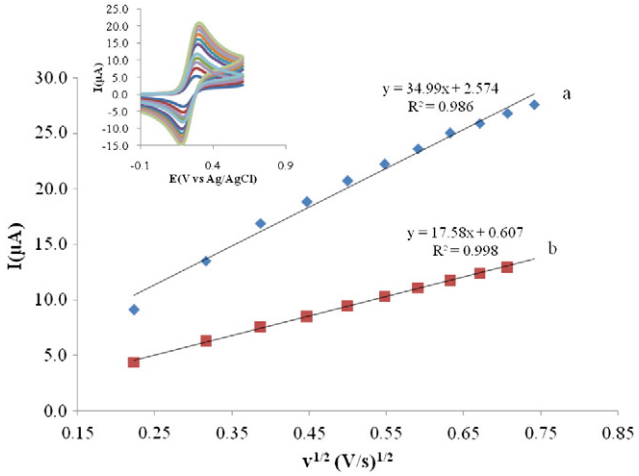

Fig. 2. Plot of I_{pa} versus $v^{1/2}$ for the oxidation of $K_4Fe(CN)_6$ (1.0 mmol L^{-1}) (a) MWCNT/GCE, (b) GCE, insert shows, cyclic voltammograms at different scan rates of 50, 100, 150, 200, 300, 400, 500, 600 and 700 mV s^{-1}, Electrolyte:0.1 mol L^{-1} KCl.

2.2. Apparatus

A Metrohm Model 827 pH lab (Herisau, Switzerland) pH-meter with a combined glass electrode was used for pH measurements. Voltammetric systems were conducted using a potentiostat/galvanostat (Autolab PGSTAT302 N) and it was controlled by a computer using Nova version 1.7 software. Three-electrode cell systems were used to monitor the cyclic and differential pulse voltammograms. A saturated Ag/AgCl electrode, a platinum wire and a modified GCE were used as the reference, auxiliary and working electrodes, respectively.

2.3. Preparation of the MWCNTs/GCE

Prior to modification, the glassy carbon electrode was polished using alumina slurry. Afterward, the electrode was sonicated thoroughly with ethanol and water then dried at room temperature. Then 20 mg of MWCNTs was dispersed in 10 mL of 1% SDS and ultrasonicated for 20 min until a homogenous suspension of MWCNTs was obtained. Then, 20 μL of the suspension was carefully cast on the surface of the

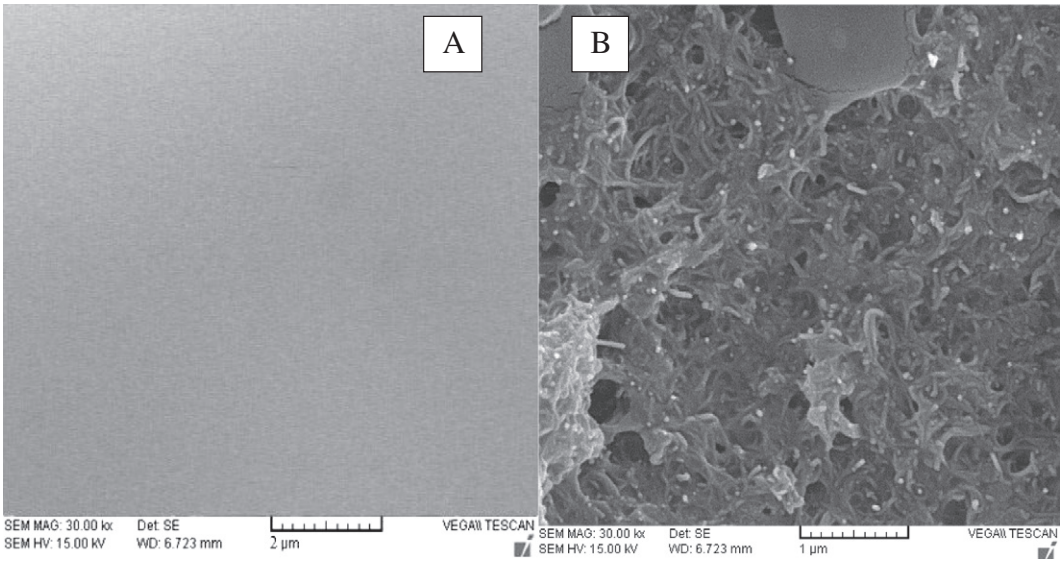

Fig. 1. SEM images of A) GCE, and B) MWCNTs/GCE.