



Mycophenolate mofetil sensor based on molecularly imprinted polymer/multi-walled carbon nanotubes modified carbon paste electrode

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ABSTRACT

Using square wave voltammetry, a carbon paste electrode modified by molecularly imprinted polymer (MIP) as a recognition element of mycophenolate mofetil (MMF) and multi-walled carbon nanotubes was used for MMF monitoring. To investigate the electrode during modification, electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV) were utilized. After optimization of the effective parameters, the anodic peak current of MMF was utilized for dynamic range study which was linear in 9.9 nM–87 μM range. The detection limit of the sensor was 7.0 nM. The capture ability of MIP to target was compared with that of non-imprinted polymer (NIP). The practical application of the sensor in biological fluid samples analysis demonstrates its selectivity, sensitivity, and stability.

Introduction

Mycophenolate mofetil (MMF, CellCept), as a morpholinoethyl ester of the antibiotic mycophenolic acid (MPA), is an efficient drug in preventing acute rejection in patients undergoing organ transplants [1,2]. After oral application, MMF is rapidly absorbed and hydrolyzed to its active metabolite (MPA) which inhibits the synthesis of guanosine monophosphate and thus inhibits purine synthesis [3] with potent cytostatic effects on lymphocytes. The half-life of MPA in plasma is approximately 16 h. Although MMF cannot prevent early events in the activation of human peripheral blood and mononuclear cells, it can obstruct the coupling of these events to DNA synthesis and proliferation. Due to clinical advantages of MMF, several analytical techniques such as chromatography [4–8], spectroscopy [9,10], and voltammetry [11,12] have been utilized for its determination. In comparison with chromatographic and spectroscopic methods, electrochemical techniques create a revolution in the analysis field because they are economical, sensitive, and have short analysis time. One of the disadvantages of electrochemical methods is the lack of enough selectivity, which is overcome by the electrode surface modification using modifiers with higher affinity toward the target molecule.

Development of molecularly imprinted polymers (MIPs) as key–lock pairs, with tailored high affinity and selectivity towards a pre-defined target molecule makes them very appealing candidates for fabricating novel sensors [13–18]. On the other hand, MIP as a synthetic polymer generates cavities around the target molecules. Removal of the target

from polymer matrices creates the recognition sites which match in size and shape with the target. Therefore, MIPs as low cost, stable, and robust materials with high affinity to the target [19] can be candidate as selective modifiers in sensors fabrication [13]. Low conductivity is one of the MIP drawbacks and thus mixing it with conductive compounds such as nano-materials reduces the above problem. In the present study, MIP was mixed with Multi-walled carbon nanotubes (MWCNTs) with excellent properties such as high adsorptive feature, great catalytic activities, high electrical conductivity, good biocompatibility, and high reactivity and then was utilized as a mediator for carbon paste electrode construction. The fabricated electrode was used for low level monitoring of MMF. Stability, selectivity, and sensitivity were the advantages of the MMF sensor. The practical applicability of the sensor was checked by determining MMF in real samples.

Experimental

Materials and instruments

Ethylene glycol dimethacrylate (EGDMA) and graphite were purchased from Fluka (Buchs, Switzerland). Methacrylic acid (MAA), mycophenolate mofetil (MMF) and 2, 2-azobisisobutyronitrile (AIBN) were supplied by Sigma–Aldrich (Munich, Germany). The other chemicals used were of analytical grade. 1 mM of MMF was prepared in 1:1 (v/v) of methanol-water mixture. Multi-walled carbon nanotubes (MWCNTs) with 95% purity (10 nm in diameters) and 1–2 μm length were gained

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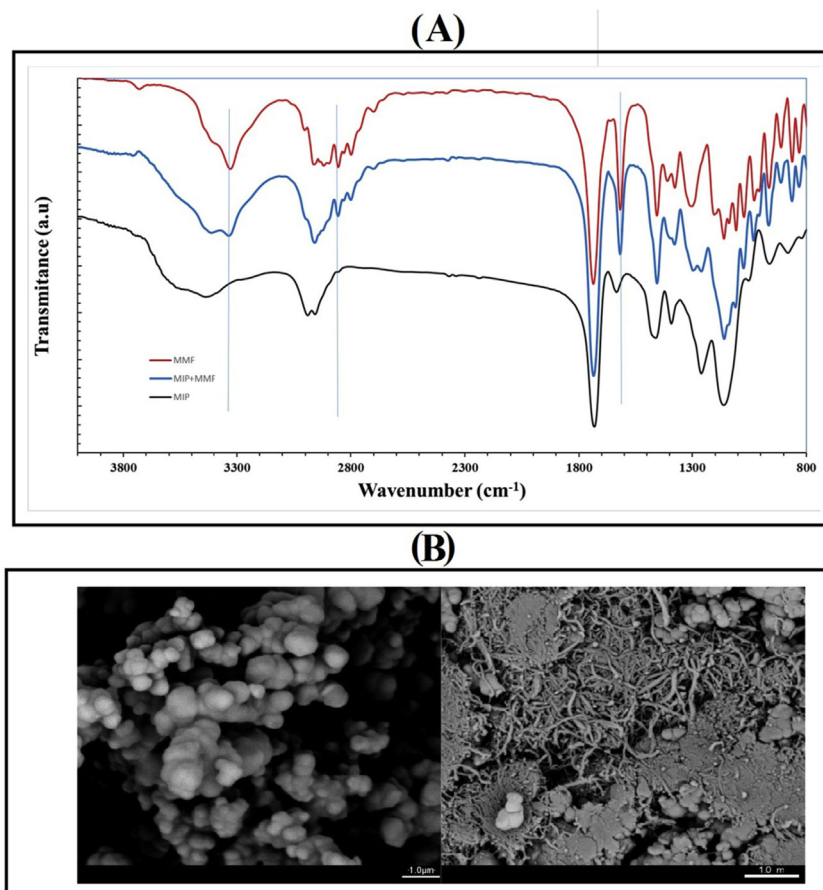


Fig. 1. (A) FTIR spectra of MMF, MIP + MMF and MIP. (B) SEM images of the pastes of MIP in the presence and absence of MWCNTs.

from Sigma–Aldrich. The phosphate buffer solutions with different pH were prepared from sodium salts of phosphoric acid and used as supporting electrolyte.

To collect the electrochemical data, a potentiostat/galvanostat (Autolab PGSTAT302 N) equipped with a three-electrode cell and Nova software version 1.11.1 was used. Metrohm pH-meter model 691 was applied for the pH measurements. The SEM images were taken by a Quanta 200 machin (FEI), and FT-IR spectra were recorded using a ALPHA spectrometer (BRUKER).

The prepared MIP or NIP based carbon paste sensors were applied as a working electrode. An Ag/AgCl and a platinum wire were applied as reference and the counter electrodes respectively.

MIP preparation

The MIP was synthesized according to previous report [20]. 0.8 mmol of MMF as template was added to 3.9 mmol of MAA as monomer in a glass tube and then the mixture was kept in contact for 12 h. After adding 8.5 mL of methanol to the resulting mixture under stirring, 19.5 mmol of EGDMA and 0.3 mmol of AIBN, (0.3 mmol) as cross linker and reaction initiator respectively, were added and the mixture was degassed with pure nitrogen for 10 min. The tube was sealed and kept in a thermostated water-bath at 60 °C for 24 h. The white polymer as product was filtered and dried and then was powdered to pass through a 25 mm sieve. The template was Soxhlet extracted from polymer particles with acetic acid– methanol (1:9 v/v). The template removal was checked by differential pulse voltammetric method. The MIP particle was washed with acetone for three times and then dried. A control polymer, non-imprinted polymer (NIP), was also prepared by the same procedure in the absence of template.

Preparing the electrodes

The carbon pastes were prepared by mixing different amounts of graphite powder, paraffin oil, MWCNTs, and MIP. Each paste was packed at the end of a Teflon holder equipped with a copper rod for electrical contact. The best cyclic voltammetric response was obtained in MMF sensor with ingredients of 60:22:7:11 (w/w %) of graphite powder, paraffin oil, MWCNTs, and MIP respectively. Instead of MIP, the similar paste with NIP was utilized for construction of the reference non-imprinted polymer sensor. To fabricate bare carbon paste electrode, 65:35 (w/w %) of graphite and paraffin oil were utilized.

Analytical procedure

The cell containing 10 mL of supporting electrolyte (phosphate buffer with pH = 7) with an open circuit accumulation potential, 40 s accumulation time, and 500 rpm stirring rate was subjected to anodic stripping voltammetry. After preconcentration and a 10 s rest by stopping the stirring, its square wave voltammogram was recorded at the scan rate of 50 mVs⁻¹ in the potential window of 0.0 to –1.3 V and used for background correction. The same procedure was utilized for recording and achieving the required data for calibration curve plot in solution with different amounts of MMF.

After each experiment, regeneration of the MIP/MWCNTs/CP electrode was carried out by cycling the electrode in the potential range of 0.3–1.3 V.

Real samples preparation

Serum and urine were collected as real samples from healthy volunteers. 10 mL of methanol as protein coagulant was added to 10.0 mL

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