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Anticancer drug detection using a highly sensitive molecularly imprinted electrochemical sensor based on an electropolymerized microporous metal organic framework

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ABSTRACT

A simple and highly sensitive approach for the detection of the anti-neoplastic drug gemcitabine is presented, based on a one-step electropolymerized molecularly imprinted microporous-metal-organic-framework. The sensitive layer was prepared by electropolymerization of the aniline moieties of *p*-aminothiophenol- gold nanoparticles on the surface of gold electrodes tethered with *p*-aminothiophenol, in the presence of gemcitabine as a template molecule. Experimental parameters that control the performance of the sensor were investigated and optimized. Under optimal conditions a calibration curve was obtained in the linear range from 3.8 fM to 38 nM with a limit of detection of 3 fM. The obtained imprinted sensor has the advantages of easy manufacture, high sensitivity and selectivity and good reproducibility. Furthermore the feasibility of the proposed technique has been investigated on spiked serum samples and infusion solution containing gemcitabine.

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1. Introduction

Given the rapid growth of the cancer research field, the development of new analytical methods for the detection of antineoplastic drugs is of great interest. Establishing personalized therapeutic schemes depending on the treatment response of each patient is extremely important for good chemotherapy management. Gemcitabine (GMT), 4-amino-1-(2-deoxy-2,2-difluoro-β-D-erythro-pentofuranosyl) pyrimidin-2(1H)-on (Fig. 1), is a nucleoside analog used for the treatment of various carcinomas, such as non-small cell lung cancer, pancreatic cancer, metastatic breast cancer and advanced recurrent ovarian cancer. Monitoring the concentration of antineoplastic drugs is important for the optimization of therapy and management of side effects, as at too low doses the effects can be reduced or even lost, while at too high doses side effects and toxicity can occur. Therefore, the determination of GMT in biological samples and pharmaceuticals is of paramount importance. Several methods have been reported for the quantification of GMT in plasma and serum, such as high performance liquid chromatography (HPLC) [1–3], HPLC–tandem mass spectrometry (HPLC–MS) [4] or liquid chromatography–tandem mass spectrometry (LC–MSMS) [5]. However, these methods are time consuming and require expensive instrumentation and complex sample pretreatment. Electrochemical sensors are attractive candidates to measure the concentration of antineoplastic drugs due to their high sensitivity, low cost and short analysis time. A differential pulse voltammetry method has been reported for the detection of GMT in pharmaceutical formulations based on its electrochemical oxidation on gold [6] and carbon electrodes [7]. Detection limits, in the range of 0.06–1 μM, were obtained.

The molecular imprinting technique has been widely used in recent years for the preparation of polymeric materials with special molecular recognition abilities [8–10]. The method consists in polymerizing functional monomers in the presence of template molecules and subsequently extracting the template from the resulting polymer matrix, which generates cavities complementary in shape and size with the template. A material with specific recognition properties towards template molecules is thus obtained, with the advantages of physical and chemical stability,

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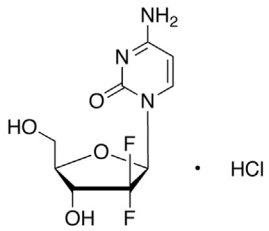

Fig. 1. Chemical structure of gemcitabine hydrochloride.

ease of preparation, low cost, and possibility of use in harsh environmental conditions [11]. The more elaborate preparation process and the lower-rate mass transfer and poor site accessibility associated with the conventional bulk method for the preparation of molecularly imprinted polymers (MIP) has focused attention on the electropolymerization technique for the deposition of imprinted films. Electrodeposition of polymers consists in the adsorption of an electropolymerized material at the electrode surface and, unlike bulk polymerization, eliminates the need for the rigorous synthesis and film preparation typically required by spin- or solvent-casting techniques [12]. Moreover it has the advantage of ease of control over the film thickness by controlling the electrochemical parameters.

Increasing interest has been given to microporous metal-organic frameworks (MMOF) as highly sensitive and selective platforms for the development of sensors. The assembly of organic linking units with metal ions or metal clusters in MMOF has exhibited high potential in a wide range of applications such as gas storage, separation and catalysis [13–15].

Through their unique properties gold nanoparticles have attracted attention as nanostructured materials for constructing sensing devices. Molecularly imprinting sensors with embedded gold nanoparticles have demonstrated high sensitivity, an enhanced number of accessible binding sites and fast equilibration with the analyte [16–18].

Here, a molecularly imprinted MMOF with recognition sites for gemcitabine was prepared through electropolymerization of *p*-aminothiophenol (PATP) functionalized AuNPS in the presence of the template molecule. Several parameters influencing the performance of the sensor have been carefully optimized and the resulting highly sensitive and selective sensing material has been applied to gemcitabine determination in spiked serum samples and pharmaceutical products. To our knowledge this is the first molecularly imprinted MMOF electrochemical sensor reported for the detection of gemcitabine.

2. Materials and methods

2.1. Chemicals and instrumentation

Gemcitabine hydrochloride (GMT), *p*-aminothiophenol (PATP), tetrachloroauric acid ($HAuCl_4$), sodium borohydride ($NaBH_4$), potassium ferrocyanide ($K_4[Fe(CN)_6]$), potassium ferricyanide ($K_3[Fe(CN)_6]$, calf serum and phosphate buffered saline (PBS) tablets were purchased from Sigma-Aldrich. All solutions were prepared using UHQ water. Gemcitabine Teva 1000 mg, powder for infusion, was obtained from TEVA Pharmaceuticals, Romania.

Electrochemical measurements were performed using a VOLTALAB-80 PGZ/301 potentiostat–galvanostat (Hach Lange, France), controlled by Voltamaster 4 software. All experiments employed an electrochemical cell containing 5 mL of electrolyte solution, with a gold working electrode (0.07 cm^2), a saturated calomel electrode (SCE) reference electrode and a platinum plate auxiliary electrode (0.17 cm^2).

2.2. Preparation of PATP functionalized AuNPs

The AuNPs were synthesized according to the procedure described in the literature [19]. For a typical preparation of gold nanoparticles, 31.6 mg (8×10^{-5} mol) of tetrachloroauric(III) acid trihydrate was dissolved in 30 mL of methanol in a round 0.1 L flask equipped with a condenser. A solution of *p*-aminothiophenol (1.6×10^{-4} mol) in 12 mL of a methanol/water (*v*/*v*) mixture was added dropwise under stirring to the gold salt solution, which changed color from yellow to dark brown. After 10 min, 30.4 mg of $NaBH_4$ (8×10^{-4} mol) dissolved in 2.2 mL of water was added dropwise to the mix under vigorous stirring. After 10 min, stirring was stopped and the solution was kept in darkness for 1 h. The suspension was then filtered through a polymer membrane and washed successively with water and ether. The resulting black powder was dried and stored either as a solid or dispersed in 0.1 N HCl solution. The UV–vis spectra of gold nanoparticle colloids display a small surface plasmon band centered around 535 nm. TEM observations show a mean diameter of around 5 nm with a narrow size distribution (data not shown).

2.3. Preparation of MIP and non-imprinted polymer (NIP)-modified electrodes.

Both MIP and NIP films were prepared on the surface of gold electrodes using cyclic voltammetry (CV), by electropolymerization of PATP self assembled on gold electrodes and PATP functionalized gold nanoparticles. Prior to SAM formation, the gold electrodes were cleaned by rinsing with ethanol and water followed by exposure to UV/ozone. An intermediate monolayer of PATP was firstly formed by immersing the gold electrodes in a 50 mM PATP ethanolic solution for 12 h at 4 °C. After rinsing with ethanol and water to remove the physically adsorbed PATP, the electropolymerization of MIP was carried out in a solution containing 0.1 mg/mL PATP functionalized AuNPs and 0.1 mg/ml gemcitabine in the supporting electrolyte (10 mM $[Fe(CN)_6]^{-3/-4}$ in PBS pH 7.2). The potential was cycled between −0.35 V and +0.80 V vs SCE, at a scan rate of 100 mV/s, for 10 cycles. A control non-imprinted film (NIP) was also prepared in every case, in the same manner, but without any additional gemcitabine.

The modified electrodes were then washed with PBS pH 7.2 for 30 min to remove the imprinted molecules and adsorbates on the surface of the film, triggering the formation of recognition cavities in the MIP film.

In order to facilitate the recognition and binding of template molecules the MIP electrode was left to incubate with gemcitabine solutions for 20 min. For the characterization of the MIP sensor at different steps of the preparation, electrochemical measurements were carried out in 10 mM $[Fe(CN)_6]^{-3/-4}$ in PBS pH 7.2 at room temperature. Linear sweep voltammetry was employed from 0.80 V to −0.35 mV at a scan rate of 50 mV/s.

3. Results and discussion

3.1. Electropolymerization of gemcitabine imprinted films

The fabrication of the MIP sensor was conducted in several steps as depicted in Fig. 2. The starting point for the preparation of the electrodes was the self-assembly of PATP on the gold surface of the electrode via Au–S bonds, and the subsequent deposition of an electropolymerized layer of polythioaniline/AuNPs/GMT. The GMT template was then removed from the matrix, generating cavities that can recognize and bind gemcitabine in the next step.

The electropolymerization was carried out by CV in a solution of 10 mM $[Fe(CN)_6]^{-3/-4}$ in PBS pH 7.2 and the film formation was

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