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An electrically controlled drug delivery system based on conducting poly(3,4-ethylenedioxypyrrole) matrix

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ABSTRACT

As numerous therapeutic agents are not well tolerated when administrated systemically, localized and controlled delivery can help to decrease their toxicity by applying an optimized drug concentration at extended exposure time. Among different types of drug delivery systems, conjugated polymers are considered as promising materials due to their biocompatibility, electrical conductivity and ability to undergo controllable redox reactions. In this work poly(3,4-ethylenedioxypyrrole), PEDOP, matrix is described for the first time as a reservoir of a model drug, ibuprofen (IBU). Drug immobilization process is performed in situ, during the electrochemical polymerization of 10 mM EDOP in the presence of 5–50 mM IBU. The loading efficiency of polymer matrix is dependent on IBU concentration and reaches 25.0 ± 1.3 μg/cm^2. The analysis of PEDOP-IBU chemical structure based on Raman spectroscopy, energy dispersive spectroscopy and surface morphology data provided by scanning electron microscopy shows that IBU is accumulated in the structure of matrix and evidently influences its morphology. IBU is then released in a controlled way under the influence of applied potential (−0.7 V vs. Ag/AgCl). It is demonstrated that the judicious choice of the synthesis conditions leads to a tailored loading efficiency of PEDOP matrix and to a tunable drug release.

1. Introduction

The conventional methods of anti-inflammatory drug delivery involve systemic administration, commonly via oral or intravenous routes. While many drugs are well tolerated, numerous therapeutic agents, including non-steroidal anti-inflammatory drugs (NSAIDs), may cause significant adverse effects [1]. The systemic exposure to NSAIDs at inappropriate or excessive concentrations may lead to severe consequences, such as gastrointestinal ulcers [2], congestive heart failure [3] or renal impairment [4]. Localized and controlled delivery of therapeutics can help decrease their toxicity by optimization of their concentrations during extended drug exposure.

Among different types of drug delivery systems, conjugated polymers are considered as promising materials due to their biocompatibility and switchable states based on their reversible redox reactions and electrical conductivity [5–6]. Several literature reports describe the utilization of conjugated polymers as carriers of anti-inflammatory drugs, e.g. salicylate and naproxen in polypyrrole (PPy) [7], ibuprofen in poly(3,4-ethylenedioxythiophene) (PEDOT) [8] as well as dexamethasone in PPy [9] and PEDOT [10]. When electrically stimulated, these conductive carriers are able to release immobilized biomolecules in a highly controlled way [11]. Both PPy and PEDOT are biocompatible and do not cause adverse effects, such as inflammation or immune response, when introduced into tissues [12–14]. Still they exhibit some drawbacks: low electrochemical and mechanical stability for PPy [15] and limited solubility of EDOT, especially in aqueous environment. Therefore, still a need to elaborate on new materials exists that will combine advantages of PPy and PEDOT, and devoid of their defects.

Poly(3,4-ethylenedioxypyrrole), PEDOP, is a promising material for biomedical applications. PEDOP belongs to a group of poly(3,4-alkylenedioxypyrrole)s, PXDOPs, which are known for their low oxidation potentials, multi-color electrochromism, high level of stability, especially its resistivity to overoxidation [16]. They were synthesized for the first time by Merz et al. in 1992 [17–18], and soon became an area of research for Reynolds' group, who explored new routes of synthesis and examined their fundamental properties [16,19–21]. The unique combination of physicochemical properties, like low polymerization potential and improved stability, makes PXDOPs ideal candidates for applications such as sensors [22–24], biosensors [25–26] and bioengineering materials [27].

In this study, the application of PEDOP as a matrix for drug delivery is presented for the first time. As a drug of interest, we have chosen α-

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methyl-4-(isobutyl)phenylacetic acid, also known as ibuprofen (IBU) — a non-steroidal anti-inflammatory and analgesic drug showing the ability to enhance wound healing. Due to the fact that IBU is an anionic drug, its immobilization and release are based on the ion-exchange properties of conjugated polymer. The processes of drug immobilization and release from PEDOP matrix were realized with the use of electrochemical techniques, cyclic voltammetry and chronoamperometry. The efficiency of IBU release was studied in-situ by means of UV/Vis spectrophotometry. Raman spectroscopy, EDS elemental analysis and scanning electron microscopy were used to analyze structural and surface properties of drug-loaded PEDOP matrices.

2. Materials and methods

2.1. Materials

3,4-ethylenedioxypyrrole, EDOP, was synthesized according to the method described by Merz et al. [18]. Ibuprofen sodium salt, IBU (Sigma-Aldrich, ≥98%), potassium chloride (Sigma Aldrich, BioReagent, ≥99.0%), sodium chloride (Sigma Aldrich, BioReagent, ≥99.0%), disodium hydrogen phosphate (Sigma Aldrich, BioReagent, ≥99.0%), and potassium dihydrogen phosphate (Sigma Aldrich, 99.0%) were used as received. Grade 1 ($R > 10\ M\Omega \cdot cm^{-1}$) deionized water was employed as solvent for all prepared solutions.

2.2. Methods

2.2.1. Drug immobilization

Electrochemical immobilization was carried out by means of CH Instruments 620a Electrochemical Workstation in a standard three-electrode setup, employing a platinum foil working electrode (1 cm^2, 0.5 mm thickness, 99.99% trace metals basis), Ag/AgCl reference electrode and a platinum foil counter electrode. The incorporation of drug during the process of matrix synthesis involved the electrochemical polymerization of monomer (10 mM EDOP) in aqueous solution of 0.1 M KCl and the model drug — ibuprofen sodium salt (IBU). Deposition of the drug-loaded matrix was achieved in the range of −0.6 V ÷ 0.8 V (vs. Ag/AgCl), at a scan rate of 0.1 V/s.

2.2.2. Material characterization

The chemical structure of polymer matrices was characterized by means of Raman spectroscopy using Renishaw InVia confocal microRaman system equipped with laser operating at 633 nm, and a CCD detector. Raman spectra were acquired in the range between 600 cm^{-1} and 1900 cm^{-1}. The surface morphology of polymer matrices was studied by means of Phenom Pro-X scanning electron microscope operating at 10 kV. Elemental analysis was performed by means of EDS detector integrated in Phenom Pro-X operating at 15 kV. Charge storage capacity (CSC) was calculated from CV curves as the current integrated along the potential axis recorded for the polymer-coated electrode.

2.2.3. Drug release studies

The release of IBU from PEDOP matrix was conducted in phosphate buffer saline solution (PBS, pH = 7.4) containing 0.15 M NaCl, 0.0025 M KCl, 0.01 M Na_2HPO_4 and 0.002 M KH_2PO_4, in a 2 mm quartz cuvette (Hellma Analytics, type no. 100-QS) and monitored in situ by time-resolved UV/Vis spectroscopy (Hewlett Packard 8453 UV/Vis Diode Array Spectrophotometer). Spontaneous (passive) release was carried out under open circuit conditions, while electrically-triggered (active) drug release was performed by applying a reduction potential −0.7 V (vs. Ag/AgCl). IBU concentration was determined through calibration curve (Fig. S1) plotted for absorbance at $\lambda_{max} = 222$ nm versus drug concentration. A linear relationship was observed between 0.02 and 1 mM IBU satisfying the equation $y = 1.6474 \times (R^2 = 0.995)$. Drug concentration achieved during release was expressed as the mass of IBU in respect to the active area of the electrode covered with polymer layer (1 cm^2). The sink condition was maintained, i.e. the volume of dissolution medium was at least 10 times greater than the volume at the drug saturation point.

The experiments were performed in triplicates and the data are presented as the average of all the samples analyzed. Relationships between experimental data were investigated using regression methods, with the significance of the Pearson product–moment correlation coefficient.

3. Results and discussion

3.1. Drug immobilization

The process of electrochemical immobilization of biomolecules in conjugated polymer matrix is based on ionic interactions between negatively charged drug molecules and positive polymer matrix. When subjected to oxidation potential, molecules like EDOP extend their conjugated bond system and form positively charged polymer chain. Anions present in the electrolyte solution of monomer are used to stabilize growing polymer in the process known as doping.

Performing electrochemical polymerization by means of cyclic voltammetry is a convenient approach because of the fact that the process can be monitored in-situ. A set of cyclic voltammetric (CV) curves of EDOP (Fig. 1a) reveals an irreversible oxidation peak at

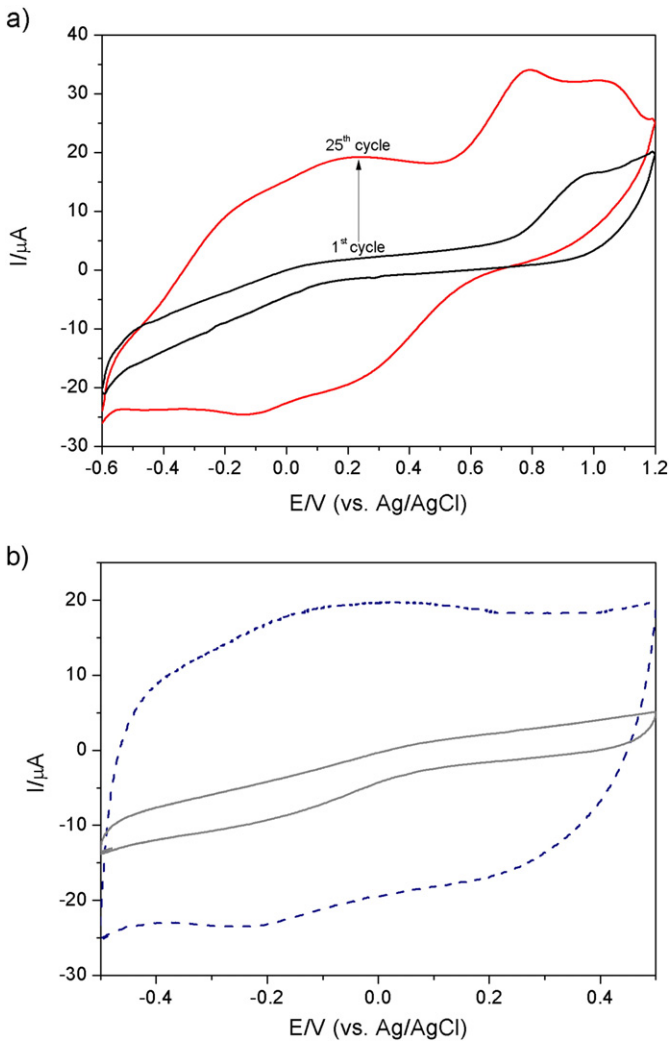

Fig. 1. Cyclic voltammograms recorded during the process of electrochemical polymerization of 10 mM EDOP in 0.1 M KCl aq (a); cyclic voltammograms of PEDOP (- - -) and bare Pt electrode (——) in 0.1 M KCl aq (b).