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3-Dimensionally ordered macroporous PEDOT ion-exchange resins prepared by vapor phase polymerization for triggered drug delivery: Fabrication and characterization

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ABSTRACT

This paper reports a simple fabrication strategy towards 3-dimensionally ordered macroporous (3DOM) poly(3,4-ethylenedioxythiophene) (PEDOT) thin films via vapor phase polymerization (VPP) coupled with colloidal crystal templating. PEDOT was synthesized by VPP over a colloidal crystal thin film composed of monodisperse polystyrene colloids functionalized with a Fe(III) tosylate catalyst, after which the polystyrene template was selectively removed. The resulting 3DOM PEDOT films comprised a face-centered cubic array of 280–290 nm spherical macropores in a PEDOT matrix, around 5–6 μm thick. Cyclic voltammetry (CV) was used to probe electrochemistry and highlighted the merits of the fabrication strategy introduced here; the 3DOM PEDOT films exhibit a 2.9-fold increase in electrochemically available surface area compared to the non-templated PEDOT films. As a demonstration of functionality, ion-exchange of the dopant tosylate for the anionic drug dexamethasone phosphate ($dexP^-$) was explored. Loading by passive ion exchange was three-fold higher for 3DOM PEDOT compared with non-templated PEDOT. Notably, CV-driven ion exchange was more efficient to load drug into the polymer than passive ion exchange, and occurred to similar extents for both non-templated PEDOT and 3DOM PEDOT structures. Following loading, minimal $dexP^-$ release was observed in the absence of an electrical stimulus, while $dexP^-$ release was triggered upon application of a suitable electrical stimulus. 3DOM PEDOT prepared by VPP thus represents a promising material for use as an ion exchange resin with drug loading achieved subsequent to polymerization and electrically triggered drug release demonstrated.

1. Introduction

The concept of using ion-exchange for sustained drug delivery was first explored over five decades ago [1]. Ion-exchange resins have since been employed for the delivery of drugs which are ionic, with drug loading performed by means of exchanging ions bound to the resin structure with drug ions from solution. As drug binding is a reversible and competitive process, drug is released when the resin is exposed to another solution which contains ions that displace the drug from the resin, or where concentration gradients drive drug release [2].

Conducting polymers (CPs) are a group of organic biocompatible polymers which possess semi-conductive properties [3]. Anions are electrostatically bound, as dopants, within the CP structure in close proximity to positive charges residing on the conjugated backbone of the CP chains when in the oxidized state [4]. Ion-exchange in CPs can be electrically tuned by controlling the redox state of the

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polymer through electrochemical reduction or oxidation [5]. Therefore, the doping level within the CP using specific anions can be controlled by electrochemically shifting the redox state of the polymer in different solutions [6]. Poly(3,4-ethylenedioxythiophene) (PEDOT) is a robust CP whose environmental and electrochemical stability, as well as its biocompatibility, render it attractive for use in biomedical applications especially for biosensing and drug delivery [7–9].

Recent efforts have explored polymerization approaches to impart desired structure to PEDOT, often for the purpose of increasing both surface area and electroactive area [10–12]. Nanostructured PEDOT has been polymerized with the aid of templates using chemical, electrochemical and chemical vapor deposition techniques [13–16]. To date, these polymerization approaches have not been extended to include vapor phase polymerization (VPP). VPP involves monomer vapors, typically in a temperature controlled vacuum chamber, condensing onto a liquid oxidant film and undergoing oxidative polymerization to form a polymer [4,11,17–19]. VPP is an attractive approach as the monomer is in the gaseous state with high diffusivity (relative to its liquid state) promoting penetration into both simple and complex templates. In addition, VPP has minimal practical limitations (conductive substrates are not required and the size is only limited by the chamber dimensions). PEDOT films prepared via VPP have resulted in some of the highest reported conductivities for this material with thin films exceeding 3000 S/cm [11,20–23]. Fe^{3+} is the most widely used chemical oxidant for the purpose of VPP, usually in the form of ferric chloride or ferric tosylate [24]. The negatively charged counter ion (chloride or tosylate) is incorporated into the CP structure during polymerization as the dopant ion [25]. Given this, the opportunity presents to investigate ion-exchange for drug delivery applications by exchanging the chloride or tosylate using electrochemical processes for an anionic drug. Dexamethasone sodium phosphate ($dexP^-$) is a negatively charged corticosteroid which has been previously loaded as a dopant directly into PEDOT during electrochemical polymerization [26].

Previous reports have investigated passive ion-exchange from PEDOT where polymer is left to equilibrate in a solution [27]. The surface area at the polymer:solution interface facilitates ion-exchange [1]; hence an increase in surface area is hypothesized to increase the rate of ion-exchange. Colloidal crystal templating is a popular strategy for improving the specific surface area and porosity of solids, including polymeric materials. The strategy involves the self-assembly of monodisperse sub-micron sized polymer or silica colloids on a face-centered cubic lattice, followed by the filling of the interstitial voids in the resulting colloidal crystal template with a solid material. Selective removal of the colloidal crystal template by selective chemical dissolution (or calcination for polymer templates) yields a 3-dimensionally ordered macroporous solid where the macropores are of similar size to that of the polymer colloids in the templates. Porosities in 3DOM structures obtained via colloidal crystal templating are typically in the range 80–90%, offering an excellent platform for the development of high surface area conducting polymer drug release systems.

In this study, the successful fabrication of highly porous 3DOM PEDOT structures via VPP over a colloidal template is reported. The 3DOM PEDOT films exhibited a 2.9-fold increase in electrochemically available surface area over the non-templated PEDOT. We found the increase in surface area correlated with a three-fold higher level of passive ion-exchange of dexP- into 3DOM PEDOT compared with non-templated PEDOT. Moreover, CV-driven ion exchange, where PEDOT was repeatedly cycled between oxidized and reduced states was more efficient to load drug into the polymer than passive ion exchange, and occurred to a similar extent into both PEDOT structures. Following loading, minimal $dexP^-$ release was observed in the absence of an electrical stimulus, while $dexP^-$ release was triggered upon application of a suitable electrical stimulus, with ±1 V at 0.5 Hz the most efficient release stimulus.

2. Experimental section

2.1. Materials

Water was obtained from a MilliQ ultra-pure water producing system by reverse osmosis (Millipore, USA). EDOT monomer, N,N-dimethylformamide (DMF), lithium perchlorate, phosphate buffer saline (PBS) and PEG-PPG-PEG (mw: 5800 Da) were purchased from Sigma-Aldrich (USA). Dexamethasone phosphate (dexP) was purchased from Jai Radhe Sales (India). Ethanol was obtained from Merck Inc. (USA). Fe(III) tosylate (CB-40 V2) (40% w/v in butanol) was purchased from Heraeus Chemicals (Germany). Indium tin-oxide (ITO) coated glass slides were purchased from Delta Technologies (USA). Stainless steel mesh was purchased from Ted Pella Inc. (USA). Borosilicate glass slides were purchased from Paul Marienfeld GmbH & Co. KG (Germany).

2.2. Methods

2.2.1. Fabrication of porous PEDOT

Polystyrene (PS) colloids (diameter 285 ± 1 nm) were synthesized by the surfactant free emulsion polymerization of styrene at 75 °C, and self-assembled on glass substrates in the form of a thin colloidal crystal film by the falling meniscus method. Briefly, a dilute aqueous solution of the polystyrene colloids was prepared (500 mL, 2–3 wt%) and transferred into a glass petri dish of wall height 5 cm. Then, the glass microscope slides were immersed vertically in the polystyrene colloid solution. The petri dish and solution was then heated at ~40 °C on a hotplate. As the water in the colloid solution evaporated, a thin colloidal crystal film of about 5–6 μm thickness formed at the falling meniscus. The complete evaporation of the solution took approximately 2 days. The resulting colloidal crystal thin films, comprising 25–26 layers of colloids, were then used as sacrificial templates to fabricate porous PEDOT by VPP with three different polymerization durations (12.5, 25 and 50 min). The polystyrene colloidal crystals were first filled with a solution containing Fe(III) tosylate (12.3 wt%) and PEG-PPG-PEG (23.1 wt%) in butanol through spin coating at 1500 rpm for 25 s onto the PS coated glass substrates. The substrates were then placed in a 70 °C oven for 30 s and transferred into a vacuum chamber operating at 40 °C. A vacuum chamber contained EDOT monomer reservoir (vapor pressure: 0.37 mbar at 25 °C) and was pumped down to 45 mbar to facilitate polymerization process. To investigate the growth of PEDOT over the PS template over time, polymerization times of 12.5, 25 and 50 min were investigated. For subsequent experiments a polymerization time of 1 h was used. Immediately after polymerization, films were removed from the polymerization chamber, washed with ethanol to remove any remaining Fe(III) tosylate and PEG, and then immersed in DMF for 2 h to dissolve the polystyrene colloidal crystal template. At this point, the 3DOM PEDOT films could be transferred intact from the original substrate and onto ITO or any other planar substrate.

2.2.2. AFM characterization

The morphology of PEDOT surfaces in air was characterized using AFM in tapping mode. A MultiMode® 8 instrument with a Nanoscope V controller (Bruker, USA) was used to perform imaging in ScanAsyst modes in an air environment. The AFM base was placed on an active antivibration table (Vision IsoStation, Newport), and equipped with a vertical engagement scanner "J" (maximum scan range 125 μm in x and y directions, and nominal 5 μm in the z