Materials Science & Engineering C 84 (2018) 248–253

Contents lists available at ScienceDirect

Materials Science & Engineering C

journal homepage: www.elsevier.com/locate/msec

Free standing PEDOT films prepared by vapour phase polymerisation as electrically tuneable barriers to drug permeability

Mahima Bansal[a], Manisha Sharma[a], Chris Bullen[b], Darren Svirskis[a,*]

[a] School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand
[b] National Institute of Health Innovation, The University of Auckland, New Zealand

ARTICLE INFO

Keywords:
Conducting polymers
Electrically responsive
Drug delivery
Controlled release
Rate controlling membrane
Size exclusion

ABSTRACT

We report the fabrication of PEDOT films using vapour phase polymerisation with Fe(III)tosylate as the oxidant and to provide the doping ion. Multiple polymerisation steps resulted in the formation of free-standing PEDOT films. The PEDOT films were highly conductive, a single layer was 1840 ± 50 S/cm with a small decrease in conductivity for the five layered films to 1550 ± 60 S/cm. The five-layered films were flexible and freestanding in air with a thickness of 1.66 ± 0.06 μm. The ability of the freestanding PEDOT films to act as electrically tuneable rate controlling membranes was determined for nicotine (MW 162.2 Da), dexamethasone phosphate (MW 516.4 Da) and bovine lactoferrin (MW 80 kDa), using a customised Franz cell. The membranes were highly permeable to nicotine and dexamethasone phosphate, however, the large lactoferrin molecules could not diffuse through the PEDOT membranes. The permeability of dexamethasone phosphate could be controlled electrically with an increase in flux observed when the membranes were maintained in the oxidised state compared to the reduce state. This is the first report where free standing PEDOT films were prepared by vapour phase polymerisation; these films were capable of electrically modifiable permeation of small drug molecules. The free standing and highly conductive PEDOT membranes are exciting materials to explore for molecular separation and drug delivery applications.

1. Introduction

Conducting polymers (CPs) such as poly(3,4-ethylenedioxythiohene) (PEDOT) and polypyrrole (PPy), have been widely explored as synthetic materials for biomedical applications as biosensors [1,2], bioactuators [3,4], neural electrode coatings [5,6], tissue engineering [7,8] and electrically tuneable drug delivery [5,9]. For tuneable drug delivery, release rates from CP matrices or through CP membranes can be controlled through reversible oxidation and reduction reactions driven by the application of electrical stimuli which alters polymer charge, conductivity, volume and porosity [10–12]. These types of drug delivery systems support the promise of individualised dosing which can be externally tuned to treat conditions with changing dosing requirements such as diabetes, addiction problems and the management of post-surgical pain [10,13,14].

CP matrices have been demonstrated to control the release of drugs such as dopamine [15] and risperidone [16,17]. However, only limited amounts of drugs can be delivered from CP matrices due to low drug loading capacity [18]. The ability of CP based drug delivery systems to release higher amount of drugs have been demonstrated using controllably porous membranes over drug reservoirs [18]. Jeon et al. reported the pulsatile release of fluorescin isothiocynate-labeled bovine serum albumin for 600 s through nanoporous membranes of uniform pore size [10]. The electrically tuneable membrane was fabricated by polymerising PPy/dodecylbenzenesulonate over an anodised aluminium oxide nanoporous membrane [10]. The pore size could be controlled by altering the electrochemical state resulting in smaller pores in the reduced state (140 nm) compared to the oxidised state (190 nm) [10]. The change in the pore size was attributed to the morphological changes due to swelling and de-swelling of the CP coating which lines the pores [13]. Similarly, Magnus et al. fabricated electrically responsive nanoporous membranes by coating anodized alumina with PEDOT and PPy. They reported a three times increase in the flux of a neutral dye when the membranes were maintained in the oxidised state compared to that in the reduced state [19]. To date, these porous membranes have only been used to control the movement of large drugs or model drugs including proteins and natural dyes [10,19]. The electrically tuneable delivery of smaller drug molecules still remains challenging. In this study we demonstrated the use of continuous membranes to achieve a level of control over the diffusion of small drug

* Corresponding author at: School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.
E-mail address: d.svirskis@auckland.ac.nz (D. Svirskis).

https://doi.org/10.1016/j.msec.2017.12.002
Received 16 August 2017; Received in revised form 19 September 2017; Accepted 13 December 2017
Available online 14 December 2017
0928-4931/

molecules.

We propose continuous and mechanically robust PEDOT films are appropriate to function as rate controlling membranes due to their biocompatibility [20–22], high electrical conductivity [23], reversible electro activity and performance stability [24]. PEDOT films can be prepared by chemical, electrochemical and vapour phase polymerisation (VPP) methods [25]. The VPP method has been demonstrated to produce thin flexible films with the highest reporting conductivity for PEDOT with values exceeding 1500 S/cm [26–28]. The previously reported PEDOT films have a thickness of < 200 nm and while free standing in a solvent, require a substrate to support the membrane in air [23,29]. Free standing PEDOT films would be suitable to explore as rate controlling membranes to achieve tuneable drug delivery of smaller drug molecules.

The focus of this study was to investigate and optimise various VPP conditions in an effort obtain free standing PEDOT films, with the ability to act as electrically responsive rate controlling membranes. The free standing PEDOT films were characterized for conductivity, surface morphology, intermolecular interactions and reversible electro-activity. The ability of the PEDOT films to act as rate controlling membranes was investigated by studying the permeability of three differently sized drugs; nicotine (MW 162.2 Da), dexamethasone phosphate (dexP) (MW 516.41 Da) and lactoferrin (LF) (MW 80 KDa), with and without electrical stimulation.

2. Experimental Section

2.1. Materials

EDOT (97%) and the triblock polymer PEG-PPG-PEG (Mw = 5800 Da) were obtained from Sigma Aldrich. Fe(III)tosylate was purchased from Watson International, China. L-Nicotine (99 + %) was obtained from Thermo Fisher Scientific New Zealand Limited. DexP was purchased from Jai Radhe Sales (India) and bovine lactoferrin (bLF) was donated by Fonterra (New Zealand). Phosphate buffered saline (PBS) tablets were purchased from Sigma Aldrich. Water used in the formulation of buffers was obtained from a Millipore system by the process of reverse osmosis (0.22 μm Millipore). Ag/AgCl electrodes were purchased from Bioanalytical Systems, Inc. (BASi., USA). Polydimethylsiloxane (PDMS) was purchased from Electropar, NZ.

2.2. Vapour phase polymerisation

The polymerisation method for PEDOT was adopted and modified from previous work [26,30–32]. The films were prepared on either glass or acrylic slides. The slides were washed with a mild detergent, followed by rinsing with ethanol and milli Q water and finally dried. The composition of the oxidant solution was modified from the literature [26,31] comprising PEG-PPG-PEG (23% *w*/w), Fe(III)tosylate (15.4% w/w) and ethanol (61.5% w/w). The oxidant solution was spin coated on glass or acrylic substrates using a spin coater (Laurell Technologies, WS-650MZ-8NPPB, US). The oxidant coated substrate was kept at 70 °C for 30 s and then transferred to a vacuum oven (Jiotech Inc., US) maintained at 40 °C. EDOT monomer was placed in a petri dish kept inside the vacuum oven. The vacuum oven was pumped down to 40 mbar. The samples were removed from the oven after 3 h and then rinsed in ethanol to remove unreacted EDOT and residual Fe(III) tosylate. The samples were air dried. To obtain films with sufficient mechanical strength to hold a drug reservoir, multi-layered PEDOT films were constructed by sequential polymerisation with additional layers polymerised over the previous PEDOT layers using the process described above. The process of sequential polymerisation was repeated until free standing films were obtained.

2.3. Characterization

2.3.1. Electrochemical characterization

Electrical conductivity of PEDOT films was determined at room temperature using a Jandel Multi Height Probe (RM2 Model), Resistivity Test Unit with a four-point linear probe (1.0 mm tip space). The conductivities were measured directly on the surface of the films. Measurements were taken by application of a constant current between the outer electrodes and the potential drop across the two inner electrodes measured. Three replicate measurements were taken for each value of current applied.

A three-electrode set up was utilised to determine the redox behaviour and reversible electro activity of PEDOT films via cyclic voltammetry. The PEDOT films were cycled between − 1.0 V and + 1.0 V at 100 mV/s in PBS using steel mesh as a counter electrode and Ag/AgCl as a reference electrode. Measurements were taken using a potentiostat (Model EA161 and *E*-corder 410 with E-Chem software, eDAQ Pty Ltd. Australia).

2.3.2. Physical characterization

A Bruker Contour GT-K Optical profiler equipped with Vision software (Vision 64, Germany) was used to investigate the thickness of PEDOT films. PEDOT films were placed on a clean glass slide and measurements were made using an objective lens of 5 × and zoom lens of 0.55 × magnification. The scan range was 25 μm in total which included a back scan of 15 μm.

The surface morphology of PEDOT films was investigated by using a Philips XL30S field emission gun scanning electron microscope. The samples for SEM were mounted on aluminium studs using adhesive graphite tape. These mounted samples were sputter coated with platinum using a Polaron SC 7640 sputter coater.

Fourier transform infrared (FTIR) spectra of PEDOT films were recorded in ATR mode using a germanium (Ge) crystal on a Bruker Tensor 37 FTIR spectrometer, with OPUS spectroscopic software (OPUS 6.5, Germany). Measurements were recorded between 400 and 4000 cm^{-1} with a resolution at 4 cm^{-1}.

2.4. Drug diffusion through PEDOT films

The permeability of selected drugs through PEDOT films acting as rate controlling membranes was investigated by using a customised Franz cell set up (Fig. 1) (Logan FDC-6, Logan Instruments Corp, USA). Customised donor chambers for the Franz cells were designed and fabricated using a 3D printer (UP plus 3D printer, 3D printing systems, NA) allowing for electrical connections to be made with the PEDOT membranes. A lid for the customised donor chamber was fabricated to hold counter and reference electrodes in place. The rate controlling membranes were tested after the PEDOT films were sealed between the clamped donor and receptor chambers with the help of PDMS rings. The area of PEDOT membranes available for diffusion was 1.77 cm^2.

The percentage permeability of nicotine, bLF and dexP through PEDOT membranes was investigated without electrical stimulation and when stimulation was used to achieve different redox states of the polymer, either + 0.5 V to oxidise or − 0.5 V to reduce the PEDOT. Drug solution (nicotine 30 mg/mL; bLF 5 mg/mL; or dexP 50 mg/mL) was placed in the donor chamber and freshly prepared PBS was placed in the receptor chamber (volume 12 mL) with a magnetic stirrer bar to maintain homogenous drug distribution. Sampling was performed at regular intervals and media was replaced with an equal volume of fresh PBS. Electrical stimulation was provided using a BioLogic Potentiostat equipped with EC-Lab software (Bio-Logic Science Instruments, France).

In addition, the electrically tuneable flux of dexP through PEDOT membranes was investigated by periodic bursts of oxidative stimulation compared with flux without electrical stimulation. To probe the effect of periodic electrical stimulation, + 0.5 V was applied for 1 h after 1, 3