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Conducting Polymer Microcontainers for Biomedical Applications

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Abstract

Advancement in the development of metallic-based implantable micro-scale bioelectronics has been limited by low signal to noise ratios and low charge injection at electrode-tissue interfaces. Further, implantable electrodes lose their long-term functionality because of unfavorable reactive tissue responses. Thus, substantial incentive exists to produce bioelectronics capable of delivering therapeutic compounds while improving electrical performance. Here, we have produced hollow poly(pyrrole) microcontainers (MCs) using poly(lactic-co-glycolic) acid (PLGA) as degradable templates. We demonstrate that the effective surface area of the electrode increases significantly as deposition charge density is increased, resulting in a 91% decrease in impedance and an 85% increase in charge storage capacity versus uncoated gold electrodes. We also developed an equivalent circuit model to quantify the effect of conducting polymer film growth on impedance. These MC-modified electrodes offer the potential to improve the electrical properties of implantable bioelectronics, as well as provide potential controlled release avenues for drug delivery applications.

I. Introduction

The development of responsive, durable, and selective implantable bioelectrodes is of considerable interest for biosensor and bioelectronics applications. [1] The fundamental requirements of such devices include recording signals with high signal-to-noise ratio for

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precise time intervals ranging from seconds to years. [2] Current electrodes are comprised of conventional metallic materials, which are generally mechanically hard, electronically based, dry, and static in nature. These characteristics are mismatched with those of biological tissue that is soft, ionically based, wet and dynamic, often resulting in reactive tissue responses and electrode encapsulation. Further, these electrodes often exhibit low surface area, owing to their planar microscale geometry, resulting in low signal-to-noise ratio, high impedance, and low charge injection capacity at electrode-tissue interfaces. [3] Strategies to address these challenges have included optimizing size, shape, and material of the substrate, adding bioactive coatings, and delivering anti-inflammatory drugs. [4]

Conducting polymers (CP) have attracted considerable attention for applications in biosensors and bioelectronics due to their excellent biocompatibility, as well as superb mechanical and electrical properties. [5] Poly(lactic-co-glycolic acid) (PLGA) is an attractive material for soft templating of CP microstructures. PLGA is biocompatible and biodegradable, making it an ideal matrix for drug encapsulation, and as a degradable template. [6] We previously demonstrated that electrospun PLGA nanofibers and electropolymerized PEDOT could be effectively combined to produce conductive nanotubes that dramatically decrease the impedance of microelectrodes while exhibiting tunable drug release kinetics. [5] In this study, we have produced hollow, organic conducting polymer microcontainers (MCs) from template PLGA microspheres (MS). These MCs have large surface areas, yielding low impedance values and high charge storage capacities for micro-scale electrodes, as well as controlled release avenues for potential drug delivery applications. We have also constructed an equivalent circuit model (ECM) to analyze the effect of film growth on electrode impedance of the PPy MCs.

II. Materials And Methods

A. Materials

Poly(D,L lactide-co-glycolide) 85:15 DLG 7E with an inherent viscosity of 0.6–0.8 dL/g was purchased from Evonik Industries (Birmingham, AL). Benzyltriethyl ammonium chloride (BTEAC) and pyrrole (Py, MW 67.09g/mol) were purchased from Sigma-Aldrich. Poly (sodium-p-styrenesulfonate) (MW 70kg/mol) was purchased from Acros-Organics. Chloroform was purchased from SupraSolv Company. N-type Si wafers coated with SiO₂ were purchased from University Wafer Company. All other materials and reagents were used as purchased.

B. Fabrication of Conductive Substrates

Gold electrodes were fabricated on Si wafers (two circles with diameters 1.5mm and 5.0mm connected with a 1mmx10mm rectangle) using electron beam evaporative deposition and laser-cut adhesive masks. A thin (10nm) layer of titanium was deposited first to facilitate adhesion of the (100nm) Au layer to the Si wafers.

C. Fabrication of Template PLGA Microspheres

A homogeneous solution of 4% (w/w) PLGA and 2% BTEAC (w/w PLGA) was prepared by dissolving 0.617g of PLGA and 0.0123g BTEAC in 10ml of chloroform at room

temperature for 12 hours. The mixture was electrosprayed for 25s using an applied field of 100kV/m (8kV applied potential and 8cm syringe-substrate separation distance), a spinneret gauge of 22, and a flow rate of 500 μ l/hr. Temperature and humidity were controlled at 22°C and 30–34% respectively. The resulting BTEAC-loaded PLGA MS were deposited onto the 1.5mm circle of the conductive substrate.

D. Fabrication of hollow CP MCs

Electrochemical polymerization was performed using an Autolab PGSTAT 302N (USA METROHM Company) in galvanostatic mode with a two-electrode configuration at room temperature. PLGA MS were coated with PPy using a solution of 0.2M Py (0.2M PSS as dopant) and applying a 0.5mA/cm² current density over 4 different deposition charge densities: 30mC/cm², 60mC/cm², 120mC/cm², and 180mC/cm². The working electrode was applied to the 5mm circle of the substrates while the counter electrode was connected to a platinum wire in the Py-PSS solution. The PLGA microspheres within the PPy coating were dissolved in chloroform overnight to create hollow PPy MCs.

E. Electrical Characterization

Impedance spectroscopy (IS) and cyclic voltammetry (CV) were performed using the Autolab PGSTAT 302N and Nova frequency response analyzer software in potentiostatic mode. A solution of 0.1M phosphate-buffered saline (PBS, pH=7.4) was used as the electrolyte in a three-electrode configuration. The Ag/AgCl reference electrode, Pt-foil counter electrode, and PPy-coated microspheres were immersed in the electrolyte solution. For impedance spectroscopy, a sinusoidal AC signal (10mV rms amplitude) was imposed to measure the impedance magnitude over a frequency range of 1–10⁴Hz. For cyclic voltammetry, the potential on the working electrode was swept between –0.8 to 0.4 V vs. the reference electrode at a scan rate of 30mV/s, using a staircase CV method. In order to calculate the charge storage capacity, the third cycle was used since the readings were observed to be consistently stable after the second cycle. The integrated surface area contained within the CV curve was determined using OriginLab software.

III. Results and Discussion

A. Fabrication of Hollow PPy-MCs

Fig. 1 outlines the fabrication route for the electrodes that were modified by PPy MCs. The process includes (1) fabrication of customized Au substrates with consistent 1.5mm diameter working areas, (2) electrospraying of PLGA MS onto the working area of those gold substrates, (3) electrochemical deposition of PPy on the electrodes bearing the PLGA MS at designated deposition charge densities, and (4) dissolution of PLGA templates by chloroform. This process consistently produces controllable hollow PPy MCs.

B. Morphology of Hollow PPy MCs

The morphology of the PLGA MS and PPy MCs was characterized using scanning electron microscopy (SEM). Fig. 2a–d shows progressive growth of PPy around PLGA MS as the deposition charge density was varied (30mC/cm², 60mC/cm², 120mC/cm², and 180mC/cm²,

respectively). PPy MCs after the removal of PLGA template MS are shown in Fig. 2e–h at the same deposition charge densities.

C. Electrical Performance of PPy MCs

Electrochemical impedance spectroscopy (IS) was used to investigate the conductivity of the PPy MCs at various deposition charge densities. Fig. 3a shows the IS for the PPy MCs at all deposition charge densities over a frequency range of 1–10⁴Hz. As the deposition charge density increases, the impedance of the PPy MC-modified electrodes decreases. Table 1 shows the impedance of PPy MCs at 10Hz. The impedance decreases from 1.38e4Ω for bare gold electrodes to 8.10e2Ω at 180mC/cm², a decrease of over 91% for this particular sample.

Cyclic voltammetry (CV) was used to investigate the charge storage capacity of the PPy MCs. The CV was performed with a scan voltage between –0.8 and 0.4V at 30mV/s. The integrated surface area of the CV curves is proportional to the charge storage capacity of the electrodes. [7] Fig. 3b shows that the surface area of the CV curve increases with deposition charge density. Table 1 shows a steady increase in the derived charge storage capacity up to 42.7mC/cm² at 180mC/cm² deposition charge density versus 6.38mC/cm² for bare gold; an 85% increase. Impedance and charge storage capacity are highly dependent on the surface area of the electrodes. The addition of PPy MCs increased the effective surface area of the electrodes (Table 1). As deposition charge densities increased from 30mC/cm² to 180mC/cm², the conducting polymer surface area contributed by the MCs significantly increased from 0.24±0.09mm² to 6.62±0.3mm², respectively.

D. Modeling

Impedance characterization of the electrode-electrolyte interface provides useful insight into the physical processes contributing to the impedance and their dependence on the underlying structure of the bioelectrode. The IS measurements of electrodes characterized by different electrochemical polymerization deposition charge densities suggest that impedance decreases as the CP deposition charge density (and hence the CP film area) increases. In order to quantify the effect of CP film growth on electrical property of the electrode, an equivalent circuit model was developed to describe the observed reduction in interface impedance.

As shown in Fig. 4A, the model circuit considers impedance of the bare gold at the base of the hollow CP MCs (see Fig. 2) to be in parallel with that of the CP film, together in series with solution resistance. The contributions of bare gold and CP to the equivalent impedance of the parallel circuit are weighted by the surface coverages of the two materials on the electrode surface, respectively. For all deposition times reported here, approximately 60% of the electrode surface was covered by CP.

For each deposition charge density t_d , the planar surface coverage of CP was augmented by a factor of $\alpha(t_d)$ to account for the contribution of the CP layer formed on the outer surface of the MCs. Hence, the CP resistance $R_{f0}/[1 + \alpha(t_d)]$ was allowed to decrease, and the CP capacitance $C_{f0}[1 + \alpha(t_d)]$ was allowed to increase, with deposition charge density at a rate that was estimated from the best fit of the model to experimental measurements. Comparison of model predictions of impedance with experimental measurements is shown in Figure 4B

for different deposition charge densities. The values of model parameters corresponding to the model predictions shown in this figure are presented in Table 2.

For these parameter values, the equivalent circuit model is capable of quantitatively capturing the measured frequency-dependence of impedance. The circuit parameters for the contribution of bare gold to impedance were held fixed. Aside from the constant phase element parameter Y_q , which exhibits a monotonically increasing trend with deposition charge density, the remaining model parameters are nearly the same for different deposition times, with a maximum variation of about 12% from the mean.

It is interesting to note that the deposition charge density dependence $\alpha(t_d)$ of the CP resistance and capacitance (shown in the last row of Table 2) is found to be qualitatively similar to that measured for the growth of the CP film on the outer surface of MCs.

IV. Conclusion

We successfully demonstrated (1) electrochemical deposition of PPy around the electrosprayed PLGA microspheres, (2) dissolution of PLGA microspheres to fabricate hollow PPy microcontainers, and (3) improvement of electrical properties of Au electrodes by decreasing impedance and increasing charge storage capacity. This study demonstrates the potential of our PPy MCs for implantable bioelectronics applications including neural interfacing and neural regeneration. The impedance modeling showed that the CP resistance (capacitance) decreased (increased) with deposition charge density at a rate that correlated with the measured growth rate of the CP film on the outer surface of MCs. Future studies will focus on the incorporation of bioactive compounds such as nerve growth factor and antitumor agents for controlled drug delivery using electrical actuation of PPy microstructures as demonstrated with nanotubes. [5]

Acknowledgments

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Figure 1. Schematic for the fabrication of PPy microcontainers. A) Au electrodes with 1.5mm diameter working areas are fabricated, B) PLGA MS are electrospayed onto the circular electrodes, C) PPy is electrochemically deposited on Au electrodes and around the PLGA MS templates at specified charge deposition densities, and D) PLGA MS are dissolved.

Figure 2. Scanning electron micrographs of PPy microcontainers with (a–d) and without (e–h) PLGA template microspheres. As deposition charge density increases, progressively more of the PLGA templates are coated. Scale bars = 1μm.

Figure 3.

Electrical properties of Au electrodes modified with PPy MCs: bare gold (black squares), 30mC/cm² (red circles), 60mC/cm² (blue triangles), 120mC/cm² (magenta inverted triangles), and 180mC/cm² (green diamonds). A) Impedance spectrum over a frequency range of 1–10⁴ Hz. B) Cyclic voltammetry; the potential swept from –0.8 to 0.4V with a scan rate of 30mV/s.

Figure 4.

(A) Equivalent circuit model of CP-coated electrode-electrolyte interface; The circuit elements are: solution resistance (R_s), coating capacitance (C_f), coating resistance (R_f), coating constant phase element impedance (CPE_f), gold charge transfer resistance R_{ct_g} , and gold constant phase element (CPE_g). (B) Measured (markers) and modeled (fitted lines) impedance modulus as a function of frequency for PPy MCs coated with 30 mC/cm² (red circles), 60 mC/cm² (blue triangles), 120 mC/cm² (magenta inverted triangles), and 180 mC/cm² (green diamonds) deposition charge density.

TABLE I

Poly(pyrrole) Conducting Microcontainer Properties

Properties	Bare gold	30 mC/cm ²	60 mC/cm ²	120 mC/cm ²	180 mC/cm ²
Impedance (kΩ) ^a	13.8	2.79	1.93	0.97	0.8
Charge Storage Capacity (mC/cm ²) ^a	6.38	9.91	14.87	32.04	42.70
CP Surface Area (mm ²) ^b	0.00	0.24±0.09	0.45±0.18	6.10±0.3	6.62±0.3

^aData from one sample

^bArea of microcontainer surface only

TABLE II

Summary of the parameter values obtained from the best fit of the circuit model to measured impedance data for Deposition Charge Density of 30mC/cm², 60 mC/cm², 120 mC/cm², and 180 mC/cm²

Parameters	$t_d = 30\text{mC/cm}^2$	$t_d = 60\text{mC/cm}^2$	$t_d = 120\text{mC/cm}^2$	$t_d = 180\text{mC/cm}^2$	Mean Value
$R_{tg} \text{ (k}\Omega\text{)}^a$	280	280	280	280	280
n_g	0.965	0.965	0.965	0.965	0.965
$Y_{dlg} \text{ (}\mu\text{S.s}^{n_g}\text{)}$	1.35	1.35	1.35	1.35	1.35
$R_s \text{ (}\Omega\text{)}^b$	400	380	370	380	382
$Y_{t1} \text{ (}\mu\text{S.s}^{n_1}\text{)}$	3.4	6.5	9.8	10.2	-
n	0.66	0.60	0.66	0.66	0.65 ± 0.03
$R_{t0} \text{ (}\Omega\text{)}^c$	179	169	167	174	172 ± 5.4
$C_{t0} \text{ (}\mu\text{F)}^d$	0.83	0.68	0.80	0.94	0.81 ± 0.10
$\alpha \text{ (}t_d\text{)}$	1.2	1.7	2.6	3.0	-

^a gold charge transfer

^b solution resistance

^c CP resistance

^d CP film capacitance