



Full length article

An interpenetrating, microstructurable and covalently attached conducting polymer hydrogel for neural interfaces



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ABSTRACT

This study presents a new conducting polymer hydrogel (CPH) system, consisting of the synthetic hydrogel P(DMAA-co-5%MABP-co-2.5%SSNa) and the conducting polymer (CP) poly(3,4-ethylenedioxythiophene) (PEDOT), intended as coating material for neural interfaces. The composite material can be covalently attached to the surface electrode, can be patterned by a photolithographic process to influence selected electrode sites only and forms an interpenetrating network. The hybrid material was characterized using cyclic voltammetry (CV), impedance spectroscopy (EIS) and X-ray photoelectron spectroscopy (XPS), which confirmed a homogeneous distribution of PEDOT throughout all CPH layers. The CPH exhibited a 2.5 times higher charge storage capacity (CSC) and a reduced impedance when compared to the bare hydrogel. Electrochemical stability was proven over at least 1000 redox cycles. Non-toxicity was confirmed using an elution toxicity test together with a neuroblastoma cell-line. The described material shows great promise for surface modification of neural probes making it possible to combine the beneficial properties of the hydrogel with the excellent electronic properties necessary for high quality neural microelectrodes.

Statement of Significance

Conductive polymer hydrogels have emerged as a promising new class of materials to functionalize electrode surfaces for enhanced neural interfaces and drug delivery. Common weaknesses of such systems are delamination from the connection surface, and the lack of suitable patterning methods for confining the gel to the selected electrode site. Various studies have reported on conductive polymer hydrogels addressing one of these challenges. In this study we present a new composite material which offers, for the first time, the unique combination of properties: it can be covalently attached to the substrate, forms an interpenetrating network, shows excellent electrical properties and can be patterned via UV-irradiation through a structured mask.

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1. Introduction

Neural interfaces are gaining in importance as a methodology to treat, restore or investigate neurological dysfunctions based on both the recording of neural activity and the electrical stimulation of neuronal cells. Clinical applications include the treatment of paralysis, Parkinson's disease or the restoration of hearing with cochlear implants [1–4]. A major challenge to assure the long term functionality of such implantable devices consists in improving the

integration of the implant into the neural tissue, for example by reducing the neuro-inflammatory response of the host. Persistent inflammation can lead to degradation or corrosion of the implant material, the loss of healthy neurons in the surrounding tissue, or the formation of an encapsulating layer – the glial scar. These mechanisms ultimately result in electrical insulation of the implant from the tissue and consequently a malfunctioning device [5–7]. To address this challenge, material-based strategies are urgently needed. Promising strategies involve the chemical modification of the implant surfaces using polymer coatings based on CPs or CPHs [5,8–11]. CP coatings such as PEDOT or polypyrrole (PPy) enhance the tissue-electrode communication by improving the electrical performance of the electrode. Furthermore, they have

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the potential to facilitate better tissue integration by immobilization of biomolecules on their surface or the release of drugs from their matrix through electrochemical switching [5,10,12,13]. Building on this idea, CPHs are material networks that consist of CPs grown within a hydrogel matrix. Hereby, the combination of both components opens up new possibilities to engineer smart and multifunctional materials. A wide range of CPH systems have been developed for applications in the field of neuroprosthetic devices [14–16], biosensors [17], drug-release devices [18–20] tissue engineering [21,22] and bioelectronics [23]. The hydrogel component provides a highly hydrophilic and porous network which can be filled with the CP in order to increase its electrical conductivity. The formation of a hybrid increases the storage volume accessible for the release of drugs and further facilitates the incorporation of biological components and cells into the electrode material [19,24]. As a result of its soft mechanical properties, it was proposed that the hydrogel can reduce the mechanical mismatch between the tissue and the electrode material and can act to stabilize the otherwise brittle CP [9,25]. The hydrogel itself can furthermore serve as an anti-biofouling surface preventing unwanted adhesion of proteins or inflammatory cells [26,27].

To successfully integrate CPHs as coating materials on neuroprosthetic devices, there are several design criteria that have to be met apart from the overall electrochemical performance and the biocompatibility of the material. Firstly, the CPH complex must be chemically and electrochemically stable, which is facilitated by a fairly homogenous integration of the CP into the hydrogel matrix. The deposition of a CP is typically performed by means of electrochemical polymerization, which requires the addition of an anionic dopant such as polystyrene sulfonate (PSS) or paratoluenesulfonate (pTS). Green et al. developed a strategy to achieve a true integration of the CP into the hydrogel by chemically attaching the anionic dopant to the hydrogel backbone [8]. The CP is then forced to grow along the hydrogel network forming a so called interpenetrating network (IPN).

Secondly, it is essential to ensure stable adhesion of the coating to the substrate electrode in order to avoid delamination of the CPH during the implantation procedure or during repeated CPH swelling and deswelling. The ideal way to achieve this is to establish covalent chemical bonds between the CPH and the substrate. A variety of different strategies have been developed to this end. For example, Guiseppi-Elie et al. have addressed this challenge by covalently attaching a poly(hydroxyethyl methacrylate) and PPy based CPH to a gold surface using a functionalization with 3-(aminopropyl) trimethoxysilane [28]. Prucker et al. have developed a different strategy by developing a procedure to covalently bind polymers to solid surfaces using benzophenone monolayers [29].

Thirdly, a critical part in making CPHs truly useful for microelectrode coatings is the opportunity to deposit and microstructure the material exclusively at selected sites on the probe. Commonly used electrodes for neural applications can have diameters as small as 20–150 μm [30–32]. Consequently, it is of great importance to establish a fabrication process which allows the patterning of CPHs within this size range. A study reported by Pan et al. showed the micropatterning of a phytic acid gelled and doped polyaniline hydrogel using ink-jet printing or spray coating methods [23]. Although CPHs meeting the single design criteria have been presented in previous studies, a CPH system offering a combination of the listed requirements has, to our knowledge, not been reported yet.

In this work, we present a CPH, which can be patterned with a photolithographic process, forms an IPN and can be covalently attached to the substrate electrode via ultraviolet light (UV)-reactive 4-(3-triethoxysilyl)propoxybenzophenone (3-EBP) silane. The CPH is composed of the synthetic hydrogel P(DMAA-co-5% MABP-co-2,5%SSNa) (PDMAAp) and the CP PEDOT (Fig. 1). The

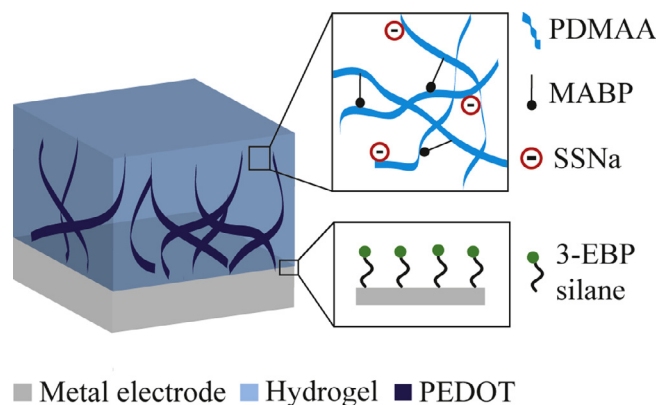


Fig. 1. Schematic depiction of the CPH composition. The hydrogel component PDMAAp consists of the PDMAA backbone, the MABP crosslinker and the SSNa units, which serve as counterions during the deposition of PEDOT. The hydrogel is covalently attached to the surface with 3-EBP silane.

hydrogel component is a copolymer consisting of dimethylacrylamide (DMAA), sodium 4-styrenesulfonate (SSNa), which serves as the anion for the deposition of PEDOT, and the UV-reactive 4-methacryloyloxy benzophenone (MABP). Hydrogels based on PDMAA have already been investigated for several biomedical applications and have shown to serve as protein-repellent coating materials [27,33–36]. In general, a synthetic hydrogel offers high control and reproducibility of its chemical composition, mechanical properties, microstructure, and degradation rate. It can be produced at low costs and is at low risk for immune responses since it does not contain biological impurities [37,38]. This indeed holds true also for the PDMAAp which, for example, can be tuned with respect to its chemical, mechanical and electrochemical characteristics and be modified with bioactive agents [33]. The choice to use PEDOT as CP component is based on its superior electrochemical stability in comparison to PPy [39]. In this work, the CPH was characterized using CV, EIS, XPS and water contact angle measurements. In addition, non-toxicity was verified using an elution toxicity test with a neuroblastoma cell line.

2. Materials and methods

2.1. Sample fabrication

Two types of test samples were designed and fabricated for this work. The first type, as illustrated in Fig. 2a was used for the electrochemical characterization and the XPS analysis. Each sample consists of a single electrode site (2,0 mm in diameter) realized on a Pyrex substrate (0,5 × 5,0 × 30,0 mm). The image reversal resist AZ 5214E (Microchemicals GmbH, Ulm, Germany) was used to form the tracks for the deposition of the metal layers. Sputter deposition with a Leybold Univex 500 sputter device (Oerlikon Leybold Vacuum GmbH, Germany) was applied to deposit a layer of titanium (Ti, 50 nm), platinum (Pt, 150 nm) and iridium oxide (IrO_x, 800 nm). The IrO_x layer was deposited selectively onto the electrode site and the interconnection line by reactively sputtering iridium in an oxygen plasma. The metals were patterned with a lift-off process. The samples were insulated with a 30 μm thick negative photoresist (SU-8 3025, MicroChem. Corp., USA). The relatively large electrode dimensions of this test sample were chosen to facilitate the exploration and development of the CPH.

The second type of test samples, as illustrated in Fig. 2b, served as a test platform for the cell culture study and the water contact angle measurements. For these experiments, a large electrode area was required to obtain a high ratio of exposed electrode material to

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