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# NANO-FIBER SCAFFOLD ELECTRODES BASED ON PEDOT FOR CELL STIMULATION

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## ABSTRACT

Electronically conductive and electrochemically active 3D-scaffolds based on electrospun poly(ethylene terephthalate) (PET) nano-fibers are reported. Vapour phase polymerization was employed to achieve a uniform and conformal coating of poly(3,4-ethylenedioxythiophene) doped with tosylate (PEDOT:tosylate) on the nano-fibers. The PEDOT coatings had a large impact on the wettability, turning the hydrophobic PET fibers super-hydrophilic. SH-SY5Y neuroblastoma cells were grown on the PEDOT coated fibers. The SH-SY5Y cells adhered well and showed healthy morphology. These electrically active scaffolds were used to induce  $\text{Ca}^{2+}$  signalling in SH-SY5Y neuroblastoma cells. PEDOT:tosylate coated nano-fibers represents a class of 3D host environments that combines excellent adhesion and proliferation for neuronal cells with the possibility to regulate their signalling.

## KEYWORDS

Polyethylenedioxythiophene (PEDOT); electrospinning; Poly(ethylene terephthalate) (PET); cell stimulation; SH-SY5Y neuroblastoma cells; nano-fibers.

## 1. INTRODUCTION

Traditionally, *in vitro* cell studies are performed using planar and rigid Petri dishes comprising the cell culture and the associated aqueous culture medium. Cellular responses upon exposure to various drugs and biomolecules are studied by adding these in solution to the media. This is far different from the *in vivo* situation where cells grow in a complex 3D environment. They receive chemical and electrical signals from neighbouring cells and from the extracellular matrix which is the scaffold that organises cells into tissues.

In order to mimic the complex *in vivo* 3D environment several artificial surfaces and scaffolds have been developed, including micro- and nanostructured surfaces [1-5], biomolecular coatings [6], gels [7], and nano-fibrous scaffolds [8-10]. Planar electronically active cell seeding surfaces based on conjugated polymers have been used to control the cell adhesion and proliferation of various cell systems [11-13]. In addition, these materials have been successfully utilized to induce and record signalling in neurons [3, 14-16].

Electrospun 3D nano-fibrous structures provide a suitable engineered 3D surface similar to the extracellular matrix, which is characterized by a wide range of pore diameters, high porosity, and high mechanical endurance [17-19]. Adding an electroactive coating would result in enhanced functionality over the present, passive 3D-scaffolds.

Here, 3D-scaffolds that are electrically conductive and electrochemically switchable, based on electrospun Poly (ethylene terephthalate) (PET) nano-fibers are presented. To achieve uniform coatings, vapour phase polymerization (VPP) of poly(3,4-ethylenedioxythiophene) doped with tosylate (PEDOT:tosylate) was employed. These surfaces were used to stimulate  $\text{Ca}^{2+}$  signalling in SH-SY5Y neuroblastoma cells.

## 2. EXPERIMENTAL

### 2.1 SAMPLE FABRICATION

The electrospinning solution contained 10% poly(ethylene terephthalate) (PET, Wellman Int. Ltd) (w/w) dissolved in a 1:1 (v/v) mixture of trifluoroacetic acid and dichloromethane (Sigma-Aldrich, analytical grade without further purification). Electrospinning of the PET nano-fiber was carried out at room temperature at a voltage of 25kV (HV Power Supply, Gamma High Voltage Research, Ormond, FL). The syringe used had a capillary tip with a diameter of 0.9 mm. A copper wire was mounted within the capillary tip and served as the positive electrode. A grounded aluminium foil was used as the counter electrode and was mounted at a distance of 20 cm away from the outlet of the capillary tip. Continuous PET fibers were collected on the aluminium foil in the form of a fibrous mat. After completing the electrospinning processing, the nano-fiber mats were transferred to a vacuum chamber for at least 24 hours in order to remove any organic solvent.

The PET fiber mat on Al foil was attached to a glass substrate, which served as a rigid carrier during the remaining processing steps. The fibers were spin coated with an oxidation solution comprising 40% Fe(III)tosylate in butanol (Baytron C, Bayer AG) and 0.028 g/ml pyridine (Sigma-Aldrich) diluted 1:1 with butanol (Sigma-Aldrich), at 1300 rpm for 120 s. Hereafter, the substrates were exposed to the monomer ethylenedioxythiophene (EDOT) vapour at 60 °C for approximately 6 hours resulting in conformal PEDOT coated fibers [20].

In addition to the vapour phase polymerization, PET fibers were coated using chemical polymerization. A 1:25 mixture (v/v) of the EDOT monomer and oxidation solution was spin coated at 1300 rpm for 120 s, onto the fibers and heated at 40 °C for approximately 20 minutes to favour polymerization and to evaporate remaining solvents. After polymerization the Al foil was peeled off from the fiber mats. Planar polymer films were bar coated on flat PET foil using the same mixture of oxidation solution and EDOT and an automatic film applicator (BYK Gardner) at a speed of 150 mm/s and heated at 40 °C for 10 minutes. In all

three coating procedures, the finished samples were washed in butanol, isopropanol, and DI water consecutively.

## 2.2 Characterization

Scanning electron microscope (SEM) images were recorded with a JSM-6330F Field Emission Scanning Electron Microscope. A 10 nm thick gold layer was evaporated onto the uncoated PET fibers to create a conducting surface. The conductivity of the PEDOT coated fibers was high enough to facilitate SEM measurements without requiring any further surface processing. Fiber samples were positioned on a 30° tilted holder to get 3-D pictures of the substrate.

The sheet resistances of VPP-PEDOT coated fiber was measured with the standard four-point technique using a Jandel Multiposition Probe connected to a Keithley 2400 source meter. Polymerization times of 1 h through 6 h were investigated.

Electrochemical switching of the PEDOT fiber electrodes was performed using a two electrode set-up. Two equally sized, physically separated substrates of VPP-PEDOT coated fibers were switched using a 0.1 M NaCl aqueous or gelled electrolyte (Fig. 1b). The PEDOT fibers were contacted using silver tape and care was taken to avoid contact of the tape with the electrolyte.

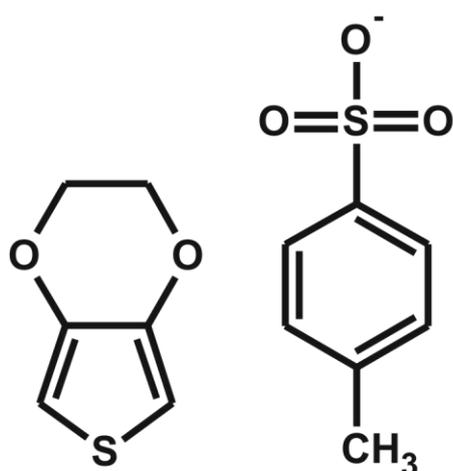
A potential difference between the two electrodes of 1.5-3.0 V was used to investigate redox switching of the VPP-PEDOT nano-fiber electrodes and 3.0 V was used in the cell stimulation experiments.

Static water–air contact angles were measured to investigate the wettability of the surfaces using a goniometer (CAM 200, KSV) by adding a droplet of water on uncoated and VPP-PEDOT coated PET fibers. As a reference to the properties of fiber topography even bar coated PEDOT on flat PET foil was used.

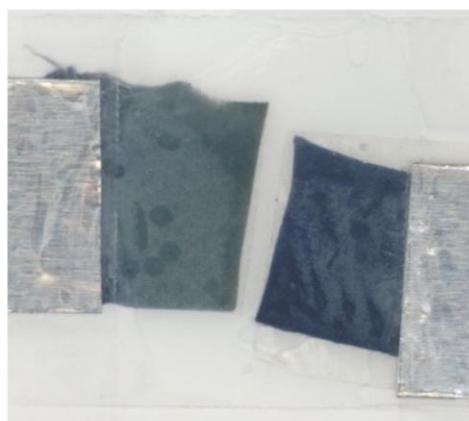
## 2.3 CELL STIMULATION

Undifferentiated SH-SY5Y human neuroblastoma cells (ATCC nr: CRL-2266, passage 10-14) were cultured in a 1:1 mixture of Minimal Essential Media Eagle (Sigma) and Hams mixture (Sigma) supplemented with 10% Fetal Bovine Serum (FBS, Sigma), 1% GlutaMAX (Gibco), 1% non-essential amino acid solution (Sigma), 1% Hepes buffer (Sigma), and penicillin/streptavidin (final concentration 100 U/ml;100g/ml, Sigma).

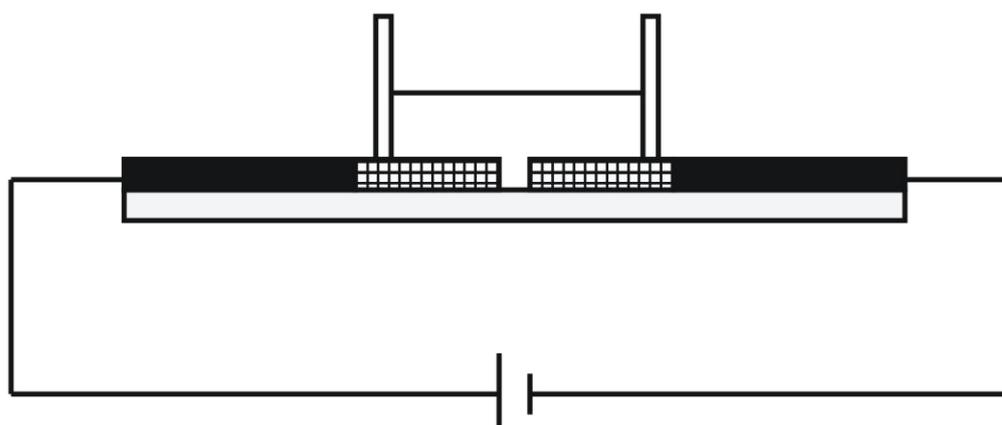
a



b



c



*Fig. 1 (a) Chemical structures of the monomer ethylenedioxythiophene (EDOT) and iron(III)tosylate. (b) A sketch of the set-up for both switching and cell stimulation: two vapour phase polymerized PEDOT coated fiber surfaces (dashed), a container comprising the electrolyte or cell culture medium, and silver tape (black) mounted on a glass substrate. (c) Photograph of electrochromic switch at 3.0V with blue gel electrolyte.*

Cells were cultured on VPP-coated fiber, glass slides (Adcell, Thermo scientific) and cell culture dishes (Corning) for 24-48 h. Cells were loaded with FURA-2 AM (1.7 $\mu$ M, Sigma) for 1 h. L-type VOCC blocker Nifedepin from Tocris (UK) was used at final concentration 50  $\mu$ M. Samples were mounted on a Nikon upright Eclipse 80i microscope with a CFI Fluor DLL 40x dip down objective for ratiometric Ca<sup>2+</sup> imaging. Excitation at 340 and 380 nm was achieved with a DeltaRAM illuminator and a DeltaRAM-V monochromator with a computer controlled SC-500 shutter controller. Emission (510 nm) was collected with a Photometrics Coolsnap CCD camera. Data was analyzed using Image J (U. S. National Institutes of Health).

Cells were stimulated by applying a voltage to the VPP-coated samples using a Hewlett Packard E3632A DC power supply. Ca<sup>2+</sup> signalling was recorded for cells growing on the cathode.

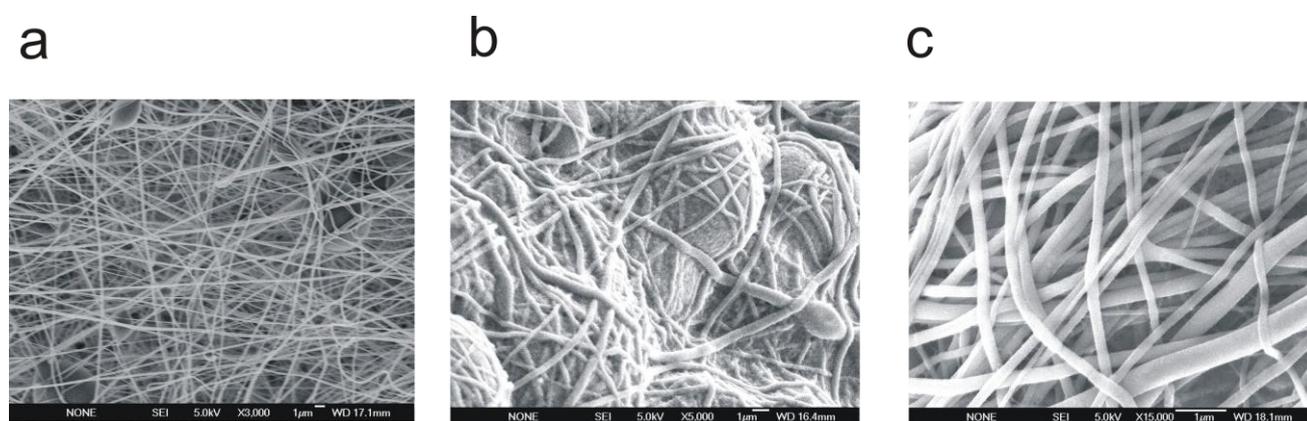
After Ca<sup>2+</sup> recordings, cells were fixed in 2% glutaraldehyde complemented with 0.1 M sodium cacodylate buffer, 0.1 M sucrose and 3 mM CaCl<sub>2</sub>, pH 7.4, then rinsed in distilled water and sequentially placed in 70% ethanol (10 min), 95% ethanol (10 min), absolute ethanol (15 min) all at +8 °C, and into acetone. Specimens were dried using a critical point dryer (Balzer, CPD 010) using carbon dioxide, then mounted on an aluminum stub and coated with 3 nm platinum (Bal-Tec SCD 005) and analyzed in an Ultra 55 field emission scanning electron microscope (Zeiss) at 5 kV.

Additionally cells cultured on VPP-coated fibers and cell culture treated glass were fixed in 4% PFA and stained with Tritc-phalloidin (Sigma) to detect F-actin. Samples were visualized in a LSM 510 (Zeiss) confocal laser scanning microscope. Image stacks were analyzed with LSM Image browser (Zeiss).

### 3. RESULTS

#### 3.1 PEDOT COATED NANO-FIBERS

The electrospun PET nano-fibers formed an evenly distributed nano-fibrous mat. The fibers had a diameter of 200-400 nm and were arranged in a randomly woven 3D structure with pore sizes of 5-10  $\mu\text{m}$  (Fig. 2a). This fiber structure and porosity were substantially obscured when PEDOT was formed via spin coating (Fig. 2b). These PEDOT coatings covered both the fibers but also the pores resulting in a comprehensive polymer layer leaving only the surface topography visible. The VPP-PEDOT process, instead, resulted in uniform and selective coatings of about 100 nm PEDOT on the fibers, preserving the 3D porous structure of the substrate itself (Fig. 2c). The VPP-PEDOT samples were relatively paler as compared to the spin coated films corresponding to a thinner film. Both processes resulted in a film with good adhesion to the substrate. In some of the uncoated and coated PET nano-fiber mats a few spheres were randomly present. This is an experimental artefact of polymer microdrops falling on the collector as long electrospun times were needed.



*Fig. 2 Scanning electron microscope images of the PET fibers, (a) uncoated electrospun PET fibers, (b) with spin coated chemical polymerized PEDOT, and (c) with vapour phase polymerized PEDOT.*

#### 3.2 ELECTRICAL AND ELECTROCHEMICAL CHARACTERIZATION

In order to determine the electrical properties, the sheet resistance of VPP-coated fiber mats was measured. The resistance ranged from 1000 to 20,000  $\Omega/\text{square}$  and was inversely

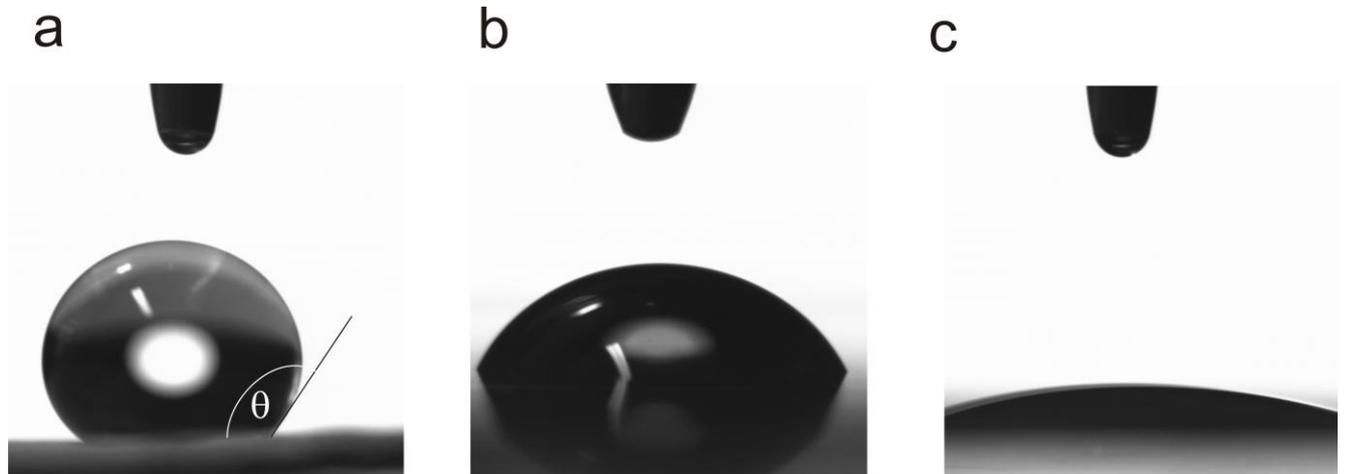
proportional to the deposition time (1 - 6 h). This is a slight increase (6h deposition) compared to the sheet resistance of a planar bar coated PEDOT surface that was 227  $\Omega$ /square. In the further experiments, described below the VPP-coated fiber mats that were polymerized for 6 h were chosen. This resistivity (1000  $\Omega$ /square) proved to be adequate to deliver a potential fast enough for both electrochemical switching and cell stimulation.

Two VPP-PEDOT electrode films coated on planar foils of PET exhibit a full electrochemical switch when they are biased at a potential difference of 1.0 V. For VPP-PEDOT fiber electrodes the switch is typically very slow and incomplete at a voltage  $\leq$  1.0 V. A full switch can be achieved at a voltage difference from 1.5 - 3.0 V. At above 3.0 V there is a risk for over-oxidation of the VPP-PEDOT coatings [21]. In the 1.5-3.0 V range the VPP-PEDOT coated PET nano-fibers could be reversibly switched for at least 20 full switch cycles resulting in neither any degradation of the electrochemical switching behaviour nor delamination of the VPP-PEDOT film. The switching resulted in a clear electrochromic effect where the reduced electrode became dark blue while the oxidized electrode turned paler (Fig. 1c). No notable differences of the electrochemical switching behaviour could be observed using different electrolytes, such as aqueous salt gels or solutions, or cell culture media.

### 3.3 CONTACT ANGLE MEASUREMENTS

Water droplets added onto planar PET surfaces typically exhibit a contact angle ( $\theta$ ) ranging from 80° to 90° [22]. The uncoated PET nano-fibers were found to be strongly hydrophobic with a contact angle of around 147° (Fig. 3a). Planar VPP-PEDOT surfaces are hydrophilic (Fig. 3b,  $\theta$ ~62°). Coating the PET nano-fibers with VPP-PEDOT makes them super-hydrophilic, actually making static contact angle measurements impossible. Therefore, rapid snap shots were taken and due to the fast absorption only the initial contact angles could be qualitatively measured (Fig. 3c,  $\theta$  ~14°). In less than 0.046 seconds the entire droplet was absorbed into the mat. The characteristics of the apparent contact angle of water droplets

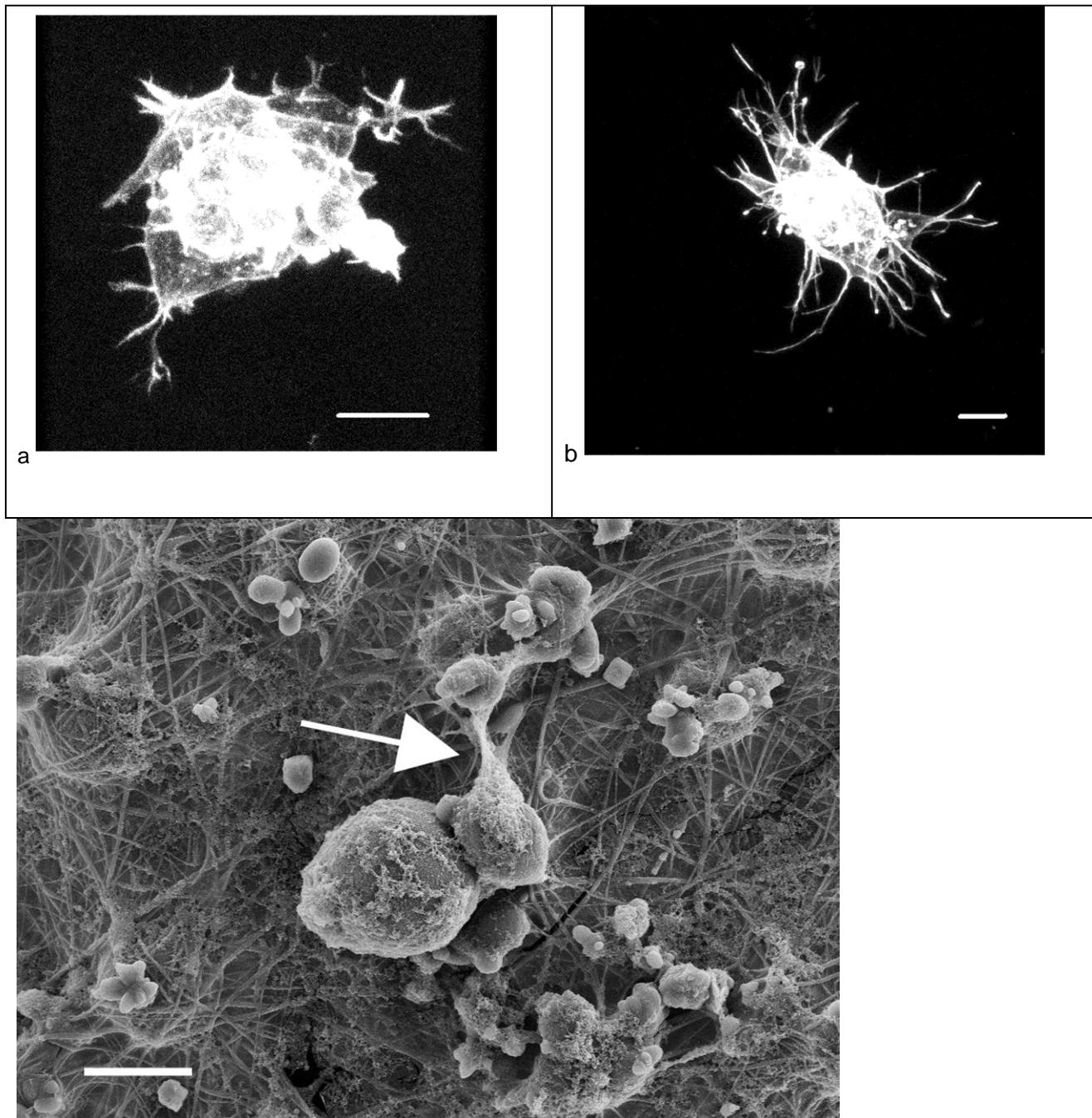
added onto structured surfaces can be treated using the theories of Cassie-Baxter and Wenzel. Those theories predict the contact angle of a water droplet that either fills the grooves or stands on top of a structured surface, respectively [23].



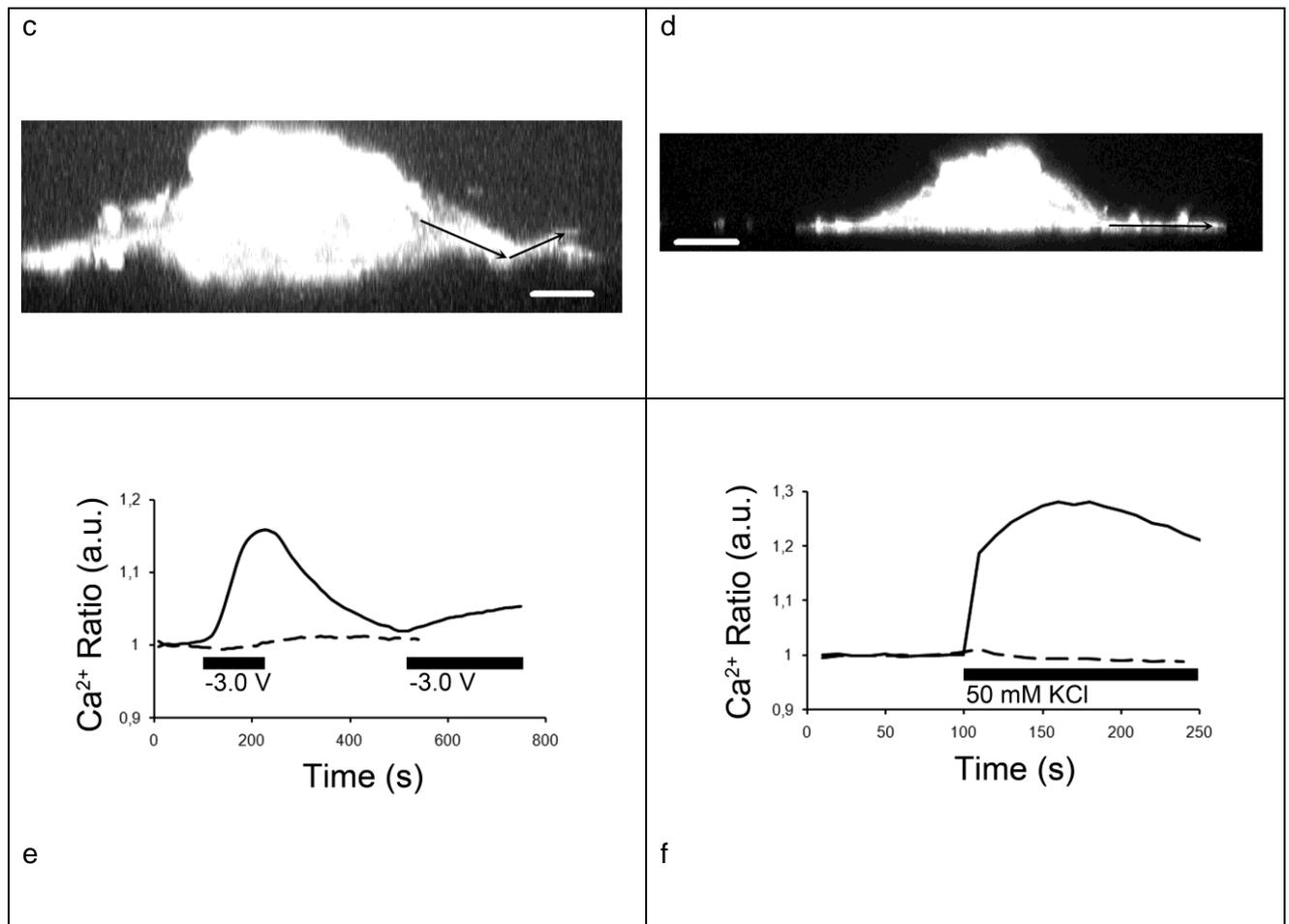
*Fig. 3 Photographs of static contact angles of the droplets on (a) uncoated electrospun PET fibers, (b) bar coated chemical polymerized PEDOT on planar PET foil, and (c) vapour phase polymerized PEDOT coated nano-fibers.*

#### 3.4 STIMULATION OF NEUROBLASTOMA CELLS

The SH-SY5Y cells cultured on the 3D surfaces formed neurites (Fig. 4, 5) a typical indicator of neural cell viability and adhesion [24, 25].



*Fig. 4 Scanning electron microscopy image of SH-SY5Y cells growing on fibers. Neurite indicated by arrow. Scale bar = 10  $\mu$ m.*



*Fig. 5 Confocal micrograph top view Y-axis projection of Tritc-phalloidin stained cluster of SH-SY5Y cells growing on (a) VPP-PEDOT coated nano-fiber surface (b) cell culture treated glass. Scale bar = 20 μm. Confocal micrograph side view Z-projection of Tritc-phalloidin stained cluster of SH-SY5Y cells growing on (c) VPP-PEDOT coated nano-fiber surface (scale bar = 10 μm) and (d) cell culture treated glass. Scale bar = 20 μm. Arrows indicate the direction of neurites. (e) Solid line shows intracellular Ca<sup>2+</sup> flux in FURA-2-AM loaded SH-SY5Y cells cultured on nano-fiber surface. A potential of -3.0 V is applied at 100 s. The potential is turned off at 250 s and turned on again at 500 s. Dashed line shows cell treated with 50 μM nifedipine in order to block the VOCCs and stimulated with -3.0 V at 100 s until 380 s. (f) Solid line shows intracellular Ca<sup>2+</sup> flux in FURA-2-AM loaded SH-SY5Y cells cultured in cell culture dish 50 mM KCl was added at 100 s. Dashed line shows cell treated with 50 μM nifedipine in order to block the VOCCs and stimulated in the same way.*

Actin is a structural protein that makes up the cytoskeleton and is important for neurite outgrowth [26]. We stained cellular actin with TRITC-phalloidin and imaged with confocal microscopy. Staining of F-actin in cells cultivated on fibers (Fig. 5a) showed well-developed actin cytoskeleton similar to cells cultured on glass (Fig. 5b). Also, the actin containing neurite extensions aligned to the topography of the different substrates, i.e. on 3D nano-fibers neurites extend in all three dimensions whereas on the flat glass surface they only extend horizontally.

SH-SY5Y cells can respond to depolarization with  $\text{Ca}^{2+}$  influx through voltage operated calcium channels (VOCCs) [27, 28]. The conducting properties of the coated fibers were used to activate the VOCCs by membrane depolarization [15]. A potential of -3.0 V applied via the nano-fibers elicited a cellular  $\text{Ca}^{2+}$  response. When the potential was turned off the intracellular  $\text{Ca}^{2+}$  decreased to baseline. Thereafter a second stimulation of -3.0 V was applied, to which the cells responded, although with a considerably slower  $\text{Ca}^{2+}$  response, possibly due to desensitization of VOCC [29]. As a control the membrane was depolarized by adding 50 mM KCl (aq), resulting in a similar response (Fig. 5f). The L-type VOCC blocker nifedipine inhibited  $\text{Ca}^{2+}$  response, both with electrical stimulation using the nano-fibers and when KCl was used to depolarize the cells, suggesting that the  $\text{Ca}^{2+}$  response is mediated via VOCCs. The  $\text{Ca}^{2+}$  increase induced by the nano-fibers was less steep than the one induced by KCl this could be due to the conducting electrochemical properties of PEDOT. This suggests that PEDOT nano-fibers are well suited as electrodes for electrical stimulation of cells in culture.

#### 4. DISCUSSION AND CONCLUSION

Electrospun PET nano-fibers were coated with PEDOT:tosylate. By using vapour phase polymerization an uniform coating was supplied while maintaining the 3D structure and morphology of the scaffold substrate. The VPP-PEDOT nano-fiber electrodes were found to be stable in aqueous and cell culture media and showed good electrochemical reversibility. In contrast, chemical polymerisation of PEDOT:tosylate, manufactured via spin coating, basically buried the nano-fiber structure within the layer of PEDOT:tosylate.

Electrical device characteristics such as sheet resistance and electrochromic redox switching were maintained.

The PEDOT coating was especially interesting with respect to wettability. The hydrophobic PET fibers turned super-hydrophilic upon coating. The wettability changed from a Cassie-Baxter state into a Wenzel state [23].

The nano-fibers were well suited to provide cells with a substrate for adhesion and proliferation, and in the same time offer a 3D environment for cells. Cells adhered well and showed healthy morphology. These conducting scaffolds were used to electrically stimulate  $\text{Ca}^{2+}$  signalling in SH-SY5Y neuroblastoma cells. The response time of the  $\text{Ca}^{2+}$  increase could be connected to the reaction time of the electrochemical switch, which is voltage dependent. At the start of the stimulation VOCCs in the direct vicinity of the fibers will be activated first and as the potential increases the depolarization is propagated to VOCCs located further away from the fibers, resulting in the smooth appearance of the response. This may allow for fine tuning of the  $\text{Ca}^{2+}$  response according to a specific application.

Based on the experimental results, the PEDOT coated nano-fibrous PET scaffold could be used as 3D electrode in various cell signalling applications. This artificial structure features a morphological similarity to the extracellular matrix of biological tissue, which is characterized by a wide range of pore diameters and high porosity. In addition, it offers more substrate surface for cell attachment compared with planar structures and guarantees a high-permeability of the substrate to allow for nutrient exchange. The electroactive polymer provides added functionality to stimulate cells or record cell signalling. Conducting polymers and PET fibers are soft, flexible, and easy to manufacture, thus allowing for low cost and non-rigid electrical interfaces for biological systems.

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## BIOGRAPHIES

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