Smart design for flexible, functionalized and electroresponsive hybrid platform based on poly(3,4-ethylenedioxythiophene) derivatives to improve cell viability [◇]

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ABSTRACT

Development of smart functionalized materials for tissue engineering has attracted significant attention in recent years. In this work we have functionalized a free-standing film isotactic polypropylene (i-PP), a synthetic polymer that is typically used for biomedical applications (*e.g.* fabrication of implants), for engineering a 3D all-polymer flexible interface that enhances cell proliferation by a factor of *ca.* three. A hierarchical construction process consisting of three steps was engineered as follows: 1) functionalization of i-PP by applying a plasma treatment, resulting in i-PP_f; 2) i-PP_f surface coating with a layer of polyhydroxymethy-3,4-ethylenedioxythiophene nanoparticles (PHMeEDOT NPs) by *in situ* chemical oxidative polymerization of HMeEDOT; and 3) deposition on the previously activated and PHMeEDOT NPs coated i-PP film (i-PP_f/NPs) of a graft conjugated copolymer, having poly(3,4-ethylenedioxythiophene) (PEDOT) backbone, and randomly distributed short poly(ϵ -caprolactone) (PCL) side chains (PEDOT-*g*-PCL), as a coating layer of ~ 9 μm in thickness. The properties of the resulting bioplateform, which can be defined as a robust macroscopic composite coated with a "molecular composite", were investigated in detail, and both adhesion and proliferation of two human cell lines have been evaluated, as well. Results demonstrate that the incorporation of the PEDOT-*g*-PCL layer significantly improves cell attachment and cell growth not only when compared to i-PP but also with respect to the same platform coated with only PEDOT, constructed in a similar manner, as control.

INTRODUCTION

Conducting polymers (CPs) as polymeric bio-interfaces have gained significant attention due their biocompatibility combined with their unique electrochemical and electrical properties.¹⁻⁶ Thus, their ability to accommodate and transport electronic and ionic charge have made CPs attractive candidates as biomaterials in applications that require communication across interfaces by exchanging charge, as for example bioactive interfaces. Thus, CPs interchange charge at the interface with cell membranes, stimulating cell adhesion and proliferation.⁷⁻¹² Furthermore, CPs are responsive to electrical, electrochemical and mechanical stimuli, influencing the behavior of cells or tissue cultured onto them.⁹⁻¹² Functionalization with biomolecules has been used to optimize their cell binding ability. For example, conjugates involving CPs functionalized with the Arg-Gly-Asp (RGD) peptide have shown improvements in cell attachment, further colonization and cell survival.^{13,14}

In the last decade, graft copolymers with a CP backbone have become a promising family of materials for diverse biomedical applications. These materials take advantage of the unique electrochemical and electrical properties of CPs and the chemical and/or physical properties of the grafted side chains. For example, conducting grafted copolymers have been used to fabricate electrochemical sensors for bioanalytics (*e.g* quantitative detection of NADH, serotonin, dopamine, cocaine and non-Hodgkin lymphoma gene);¹⁵⁻¹⁹ to construct surfaces with antimicrobial¹⁶ or imaging activity;²⁰ to prevent the non-specific adhesion of cells and proteins;^{21,22} to prepare nanocarrier systems that enable size-selective encapsulation of drug molecules and their sustained release;²³ and to promote cell activity for tissue engineering.²⁴⁻²⁶

Graft copolymers with CP backbones and flexible, stimuli-sensitive side chains are interesting polymeric architectures that, in former reports, were also named "molecular

composites" based on their macroscopic properties.^{27,28} This type of polymers can be prepared using three different approaches:²⁹ 1) "*grafting to*" in which end-functionalized side chains (already polymerized) are connected to reactive sites of the CP backbone; 2) "*grafting from*" that consists on the growing of the side chains from the initiation sites of the CP; and 3) "*grafting through*", which involves the synthesis of electroactive macromonomers that can be homopolymerized²² or copolymerized with an appropriate low-molecular weight compound^{16,17,20} or with another macromonomer.¹⁵ The "*grafting through*" strategy allows for the tuning of side chains grafting density and branching points distance adjustment, giving the possibility to modulate the materials properties for a targeted application.^{30,31}

In recent years we have used such an approach to prepare graft copolymers having polythiophene backbone and polyethylene glycol (PTh-g-PEG) as side chains.^{15,22,25,26} Also, we obtained a conducting graft copolymer by electrochemical copolymerization of hydroxymethy-3,4-ethylenedioxythiophene (HMeEDOT) and a thiophene-ended poly(ϵ -caprolactone) (PCL) macromonomer (PTh-g-PCL).¹⁷ In spite of the promising biomedical applications of PTh-g-PEG and PTh-g-PCL, the applicability of those materials is severely limited because of the electrodes (*i.e.* typically steel or indium tin oxide (ITO)) used in the electro(co)polymerization processes. Therefore, achievement of self-standing and flexible graft-copolymers based on CPs is highly desirable to provide applicability.

In order to overcome the above mentioned drawbacks, in this work we engineered a new 3D all-polymers flexible system, which was constructed in a hierarchical manner, combining using different polymerization techniques and based on a combination of a macroscopic composite with a "*molecular composite*" as an outer layer. This top layer is represented by a graft CP, having poly(3,4-ethylenedioxythiophene) (PEDOT)

backbone and randomly distributed short PCL side chains (PEDOT-*g*-PCL). This material has been obtained using, in the last step, the *grafting through* approach. More specifically, a new synthesized EDOT-containing macromonomer has been electrocopolymerized with 3,4-ethylenedioxythiophene (EDOT) as coating layer on isotactic polypropylene (i-PP) used for biomedical implants, which has been previously functionalized and electroactivated by applying a plasma treatment and depositing poly(hydroxymethyl-3,4-ethylenedioxythiophene) nanoparticles (PHMeEDOT NPs), respectively. After chemical, electrochemical, thermal and morphological characterization of resulting bioactive platform, which is flexible and free-standing, the adhesion and proliferation of two human cell lines were examined. Results demonstrate the promising potential of the bioplateform layered with PEDOT-*g*-PCL for tissue engineering applications, improving by a factor of *ca.* three the capacity to proliferate cells with respect to the biomedical i-PP used as support.

RESULTS AND DISCUSSION

Synthesis of the macromonomer

The EDOT-PCL macromonomer (Scheme S1), one of the few reported to date,³²⁻³⁶ was obtained by ring-opening polymerization of ϵ -caprolactone (ϵ -CL) using HMeEDOT as initiator and stannous octanoate, Sn(Oct)₂, as catalyst. Details about in bulk ϵ -CL polymerization are provided in the Supplementary Information.

¹H and ¹³C NMR spectra of the macromonomer in CDCl₃ are shown in Figures S1 and S2, respectively, while the FTIR spectrum is displayed in Figure S3. The molecular weight of the EDOT-PCL macromonomer, as estimated from ¹H-NMR data (*M_n* H-NMR), is 2055 Da, indicating that the polymerization degree (PD) is 16.5. The results of GPC measurement (Figure S4) and an explanatory discussion on the structural

characterization of EDOT-PCL macromonomer and of its properties in bulk can be found in the Supporting Information.

^1H NMR (CDCl_3 , δ in ppm): 6.37 (**a,b**); 4.42-4.36 (**c**); 4.33-4.23 (**d,e**), 4.10-4.05 (**j**), 3.69-3.66 (**k**); 2.42-2.29 (**f**); 1.73-1.58 (**i,g**); 1.44-1.36 (**h**); (Figure S1)

^{13}C NMR (CDCl_3 , δ in ppm): (173.46, 172.9 (**h**); 141 (**c,d**); 99.9(**a,b**); 71.9, 71.48 (**e**); 65.56 (**f**); 64.08(**g,o**); 62.6, 62.36 (**r**); 34, 33.76 (**i**), 32.2 (**p**); 28.28 (**m**); 25.47 (**j**), 24.53 (**k**); (Figure S2).

IR (KBr), cm^{-1} : 3539.32; 3439.55;(PCL); 3114.58; (thiophene ring -Th- of EDOT); 2946.39 - 2866.58; (- CH_2 , -CH aliphatic in EDOT and PCL); 1725.13; (PCL); 1487.3; (Th); 1471.63; (PCL); 1420.36 (Th); 1399; (PCL) 1369.09; (EDOT); 1295.04; 1245.19; (PCL); 1192.5; (PCL and EDOT); 1107.05; 1045.81; (EDOT); 962; (PCL); 933.3; 860.67; 840.73; (Th); (Figure S3 and detailed discussion in Supporting Information).

Preparation of bioactive platform

The bioactive platform was prepared using a three-step process (Figure 1a). Firstly, the surface of i-PP films ($10 \times 10 \text{ cm}^2$) commonly used for biomedical applications (*e.g.* surgical sutures and meshes), which were kindly supplied by Braun Surgical S.A. (Rubí, Barcelona, Spain), was functionalized with oxygen plasma (0.30 mbar) during 180 seconds and using a power discharge of 250 W. Secondly, the functionalized i-PP (i-PP_f) films were cut in $0.5 \times 1.5 \text{ cm}^2$ samples, which were coated with PHMeEDOT NPs by immersing each one in 5 mL of 0.2 M HCl with 50 mM MHeEDOT monomer during 30 min and under agitation (250 rpm). The oxidative chemical polymerization of the monomer was conducted by slowly dropping 1 mL of 0.2 M HCl solution containing 60 mM of ammonium persulfate (APS). The reaction was kept at 37 °C and 80 rpm for 24 h. After this period, the functionalized and electroactivated material,

hereafter named i-PP_f/NPs, was washed with a 0.2 M NaOH solution to balance the charge, and then dried.

These two construction steps provided the unique opportunity to engineer the bioplatfroms surface at the molecular level. Thus, the first formed PHMeEDOT polymer chains, due to the free hydroxyl functional groups, could be oriented and strongly anchored to i-PP_f surface via the hydrogen bonding with existing polar groups ((*e.g.* C=O and C–O) formed during the plasma discharge. This orientation of the first polymer chains will drive the organization of all other grown polymer chains inside of NPs governed also by other types of physical intermolecular interactions (hydrophobic, π - π stacking).

In the last step, the EDOT-PCL macromonomer and the EDOT monomer were electrocopolymerized on i-PP_f/NPs films. For this purpose, each i-PP_f/NPs film was introduced in a three-electrode cell filled with 20 mL of an acetonitrile solution containing 0.1 M LiClO₄ as supporting electrolyte and both EDOT and EDOT-PCL in a millimolar ratio of 7/3. Electrocopolymerization was conducted at a constant potential of 1.40 V and adjusting the polymerization charge to 1.0 C. It should be noted that, in this process PHMeEDOT NPs acted as polymerization nuclei for the growing of PEDOT-*g*-PCL chains. For the sake of comparison, bioplatfroms without PCL side groups were also prepared using only EDOT monomer (10 mM) in the electropolymerization step, which was conducted using identical experimental conditions. It is worth noting that the used electro(co)polymerization technique enables a precise control of the coating thickness (see below) through the polymerization charge, as was proved in early kinetic studies on PEDOT and other ICPs.³⁷

Though electrochemically silent (*vide infra*), the PHMeEDOT NPs layer seems that did not block the charge transport through the interface. This layer, offering surface-

confined electrochemically reaction sites in the form of radical cations, allow for covalent connection of the new growing copolymeric/polymeric chains to the support surface.^{38,39} Thus, subsequent PEDOT-*g*-PCL copolymer or PEDOT homopolymer formation continue due to nucleation from existing PHMeEDOT,⁴⁰ in the form of surface tethered chains. However, the existence of the physically adsorbed PEDOT-*g*-PCL copolymer or PEDOT chains, as non-covalent coating on the PHMeEDOT NPs film surface, especially formed in the latest phase of the electropolymerization, can't be excluded. These chains could form strong π - π stacks with the NPs surface in a similar manner as the previously reported PCL-decorated poly-*p*-phenylene formed with the carbon nanotubes surface.⁴¹ Hereafter, flexible and free-standing bioplatfroms formed by i-PP_f/NPs and coated with a PEDOT-*g*-PCL or PEDOT (control) layer are denoted i-PP_f/PEDOT-*g*-PCL or i-PP_f/PEDOT, respectively.

Figure 1b shows photographs of i-PP, i-PP_f/NPs, i-PP_f/PEDOT and i-PP_f/PEDOT-*g*-PCL. The translucent i-PP film becomes opaque and blueish after the incorporation of PHMeEDOT NPs, which in turn converts in dark blue when PEDOT and PEDOT-*g*-PCL layers are deposited by electro(co)polymerization. These visual transformations suggest that both the oxidative polymerization and the electro(co)polymerization occurred successfully.

Chemical characterization and wettability

The FTIR and Raman spectra of i-PP_f/PEDOT and i-PP_f/PEDOT-*g*-PCL are compared in Figure 2a-b. On the other hand, the spectra of biomedical i-PP and i-PP_f were reported in recent work^{42,43} and have not been repeated here, while Figures S5 and S6 show the FTIR and Raman spectra, respectively, of i-PP_f/NPs with the corresponding discussion.

The FTIR spectra of both bioplatforms are dominated by the absorption bands of i-PP substrate and PEDOT backbone. The characteristic absorption peaks of i-PP correspond to the deformation vibration of the CH₂ group at 1461 cm⁻¹, the methyl group vibrations at 1385 cm⁻¹, and the characteristic vibrations of CH₂ groups at absorption peaks at 998 and 1164 cm⁻¹.⁴²⁻⁴⁴ Besides, the intense broad signals appearing at around 1600 cm⁻¹ are attributed to the C=O stretching of the functional groups created by the oxygen plasma treatment.^{42,43} The PEDOT bands revealed in the spectra are the C–S and C–S–C vibrations in the thiophene ring at around 869, 757 and 628 cm⁻¹. Unfortunately, the distinctive peak of PCL side chains, which corresponds to the C=O stretching at ~1723 cm⁻¹,⁴⁵ overlaps with the broad peak of i-PP_f. Although the detection by FTIR spectroscopy of PCL side chains is almost hindered by their short length and low grafting density, as compared to PEDOT chains, as well as by the interferences with i-PP_f signals, their identification have achieved by high resolution Raman spectroscopy.

Although the characteristics peaks of PEDOT backbone predominate in the 785 nm laser Raman spectra recorded for two coated bioplatforms (Figure 2b), some clear differences allowed us to identify the presence of PCL side chains in i-PP_f/PEDOT-*g*-PCL. More specifically, the following peaks were collected in the spectra of the two systems: the vibration mode of the thiophene C–S bond at 988 cm⁻¹; the stretching of the ethylendioxy group at 1085 cm⁻¹; the C–C inter-ring stretching at 1258 cm⁻¹; the C–C stretching at 1365 cm⁻¹; and the C=C stretching at 1420 cm⁻¹. The C=O and C–C stretching peaks (1575 and 1137 cm⁻¹, respectively), which can be attributed to both i-PP_f and PCL, are consistently more intense for i-PP_f/PEDOT-*g*-PCL than for i-PP_f/PEDOT.

Evidence of the successful EDOT-PCL macromolecular incorporation in the i-PP_f/PEDOT-*g*-PCL bioplatfrom is also provided by the surface wettability. The contact

angle (CA) for milli-Q water was $CA = 102^\circ \pm 3^\circ$, $78^\circ \pm 5^\circ$, $82^\circ \pm 3^\circ$, $< 20^\circ$ and $84 \pm 5^\circ$ for i-PP, i-PP_f, i-PP_f/NPs, i-PP_f/PEDOT and i-PP_f/PEDOT-g-PCL films (Figure 3), respectively. After plasma treatment, hydrophobic i-PP transforms into slightly hydrophilic i-PP_f due not only to the apparition of polar groups (*e.g.* C=O and C–O, as proved by FTIR^{42,43}) but also by the creation of a superficial nano-patterning, as observed by SEM (see below). However, the functionalization in the next step with PHMeEDOT NPs, surprisingly, does not increase the wettability. This phenomenon has been attributed to the combined action of two different factors (discussed in the next sub-sections): 1) PHMeEDOT NPs do completely cover the i-PP_f surface; and 2) the topographic changes experienced by i-PP_f/NPs occurred at the submicrometric length-scale-rather than at the nanometric one.

On the other hand, the hydrophilicity of PEDOT should be attributed to the large amount of dopant counterions.⁴⁶ This could be the explanation for which, after the coating with a homogenous PEDOT layer, in the third step of the control bioplaform construction, the resulting surface becomes very hydrophilic. Instead, i-PP_f/PEDOT-g-PCL is poorly hydrophilic due to effect of the PCL side chains. However, the copolymerization of EDOT-PCL with EDOT monomers prevents i-PP_f/PEDOT-g-CPL from behaving as a pure hydrophobic system (*i.e.* PCL typically exhibits water CA of $\sim 120^\circ$ ⁴⁷), which is expected to be beneficial for tissue engineering applications.

Flexibility, electrochemical and thermal characterization

Figure 4 illustrates the robustness and flexibility of the i-PP_f/PEDOT-g-CPL platform. As is shown, the PEDOT-g-CPL remains intact after significant bending deformation, no sign of damage being detected at the surface. This reflects the excellent adhesion between the i-PP_f substrate and the copolymer layer. Moreover, Figure S7

supports the strength of the interlayer forces upon stress-strain since the only damage was in the position in which the clamps held the platforms when applying the tension.

Electrochemical characterization was performed using cyclic voltammetry. Figure 2c compares the cyclic voltammograms recorded for i-PP_f/NPs and i-PP_f/PEDOT in 0.1 M phosphate buffer saline (PBS) solution. As is shown, the electrochemical activity of i-PP_f is practically inexistent, even after the functionalization with PHMeEDOT NPs. This reflects that the latter only nucleates the growing of PEDOT or PEDOT-*g*-PCL chains during the electrochemical polymerization and, therefore, no other active role can be attributed to PHMeEDOT NPs. Instead, the electrochemical activity increases considerably after polymerization of the PEDOT layer, as is evidenced by the area of the voltammogram. After 50 consecutive oxidation-reduction cycles, the area of the voltammograms recorded for i-PP_f/PEDOT samples decreases very slightly (Figure 2c), indicating that this is an electrochemical stable bioplatfrom. More specifically, the loss of electroactivity (LEA) after 50 cycles was of only $6\% \pm 1$.

The electroactivity of i-PP_f/PEDOT-*g*-PCL is significantly higher than that of i-PP_f/PEDOT, as deduced from the comparison of the areas of the voltammograms (Figure 2d). Considering the fact that the thickness of the two electroactive layers are very similar (9.0 ± 2.5 and 8.2 ± 2.4 μm for the PEDOT-*g*-PCL and PEDOT, respectively, as determined by profilometry), that observation suggests that PEDOT-*g*-PCL morphological and structural features could be responsible for this behaviour. Thus, a more porous morphology evidenced by SEM observations (see next subsection), will allow access and escape of dopant ions during the oxidation and reduction process, respectively, much easier for the graft copolymer than for the homopolymer. On the other hand, the presence of PCL polar steric side chains in PEDOT-*g*-PCL,⁴⁸ due to their high ionic conductivity,⁴⁹ to their high ion-solvating capability,⁵⁰ and to the

presence of hydroxyl end groups⁵¹ can facilitate and enhance the ionic transport in the bulk of mixed electronic-ionic PEDOT conjugated main chain during the redox process in an aqueous electrolyte.

However, the loss of electrochemical activity is much faster for i-PP_f/PEDOT-*g*-PCL, which experiences a LEA of 29% $\pm$ 5% after 50 redox cycles (Figure 2d), than for i-PP_f/PEDOT. This behavior has been attributed to the electrochemical degradation of PCL side chains, which are probably damaged by the successive potential scanning processes, being known the fact that the ester groups in PCL are redox active close to the lithium stripping and plating potential, forming degradation products.⁵¹ The progressive degradation affects the molecular structure of the grafted copolymer, reflected in the film reduced porosity and thus making more difficult the access and release of dopant ions when oxidation and reduction potentials are applied, respectively.

Thermal characterization and stability of the resulting bioactive platforms were analyzed by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), respectively. Prior to the evaluation of i-PP_f/PEDOT and i-PP_f/PEDOT-*g*-PCL, the thermal properties of the EDOT-PCL macromonomer, i-PP, i-PP_f and i-PP_f/NPs were examined. A three step protocol consisting in heating-cooling-heating (described in the Supporting Information) was applied to all samples. The calorimetric parameters corresponding to the heating and cooling runs are summarized in Table S1.

DSC traces of both heating runs for EDOT-PCL macromonomer (Figure 5a), revealed a double-melting. In addition to the main endothermic peak, a second shoulder is also present. Such a phenomenon was reported previously in the case of PCL blends⁵³ or for hyperbranched structures.⁵⁴ This behavior of EDOT-PCL macromonomer can be associated to a morphological effect which implies the presence of two populations of crystals, which differ in size and thickness. Being noticed for the first time in the case of

a PCL-containing electroactive macromonomer, this phenomenon could also be explained by the peculiar geometry and character of bicyclic EDOT moiety, which seems to interfere with PCL crystallization both from solution and melt state in a particular fashion. Detailed explanations are given in Supporting Information. The experimental values of melting and crystallization peaks for the EDOT-PCL macromonomer were found around 50 °C and 27 °C, respectively (Figure 5a), indicating that a crystalline phase was developed. These values are in full agreement with those reported for PCL.⁵⁵ The degree of crystallinity, measured in the first and second heating runs, was high, close to 78% and 58%, respectively. On the other hand, thermogravimetric experiments of the EDOT-PCL macromonomer (Figure 5b) showed a continuous mass loss from 250 to 350 °C characterized by a single DTGA peak (*i.e.* the highest thermal degradation temperature) at 332 °C with 3.4% of char yield.

This behavior is expectable, as long as it was shown that the thermal stability of PCL is dependent on its molecular weight. Thus, the initial degradation temperature (IDT) of a PCL oligomer containing 16 repeat units ($M_n = 1800$) was determined as 230 °C.⁵⁶ Moreover, in previous studies related to other electroactive PCL-containing macromonomers, was experimentally found that PCL thermal stability depends on and it is increased by the aromatic moiety attached to it.^{57,58} This trend is also confirmed in the present case of EDOT-PCL, for which polymerization degree of PCL is 16.5 as determined from ¹H-NMR results. The EDOT moiety placed at one of the PCL chain ends increased its thermal stability by increasing the IDT with 20 °C (from the reported value of 230 °C⁵⁶ to 250 °C).

No significant differences were detected in DCS test among i-PP, i-PP_f and i-PP_f/NPs formulations, as shown in Figure S8. In all cases, a melting point around 158 °C and a crystallization peak at 114 °C were observed in the first and second runs, respectively.

These data are consistent with those found in the literature since i-PP grades melt in the range of 100 – 180 °C, depending on their molecular structure.⁵⁹ The melting point observed in the i-PP grade used in this work seems to be related with the β -form of i-PP, since this form is less stable and shows a melting temperature (~155 °C) lower than α -form (~170 °C).⁶⁰ Heats of fusion were used to evaluate the crystallinity of polymers (see Eq. S2), taking into account the heat of fusion for 100% crystalline i-PP (209 J/g). Crystallinities measured for solution-crystallized samples were slightly lower than those measured for melt-crystallized samples (around 37% vs. 43%). The influence of PHMeEDOT NPs on the crystallization of i-PP was not significant, no appreciable variations being observed neither in the crystallization temperature nor in crystallinity for i-PP_f/NPs.

Thermogravimetric analyses demonstrated that thermal stability increased as the functionalization of i-PP increases (Figure S9). Decomposition took place according to a single step, with a DTGA maximum degradation peak increasing from 416 °C for i-PP to 453 °C for i-PP_f/NPs. The onset degradation temperature (taken in the TGA curve as the temperature at which the weight loss is 5%) was high for all samples and also increased as i-PP was functionalized (338 °C, 361 °C and 413 °C for i-PP, i-PP_f and i-PP_f/NPs, respectively), reflecting that functionalization with plasma and posterior electroactivation with PHMeEDOT NPs enhanced the thermal stability of the polymer.

DSC thermograms of i-PP_f/PEDOT-g-PCL and i-PP_f/PEDOT are presented in Figure 5c-d, while the evaluated values are listed in Table S1. A similar thermal behavior, in relation to the melting and crystallization, was observed. However, it should be noted that polymerization with EDOT or EDOT-PCL had significant effects on the i-PP crystal structure. More specifically, a decrease in the crystallinity is observed (40% and

35% measured in the second heating for i-PP_f/PEDOT and i-PP_f/PEDOT-g-PCL, respectively).

On the other hand, in all the traces of i-PP_f/PEDOT-g-PCL in Figure 5c, the characteristic peaks for melting or crystallization of PCL side chains are missing. This phenomenon was noticed before for both linear⁶¹ and ramified conjugated rod-coil systems.⁶² It was explained either based on the value of PCL polymerization degree (in the case of the linear structure) or based on the value of the molar fraction of the incorporated PCL-macromonomer in the final copolymer (in case of graft copolymer). In the case of i-PP_f/PEDOT-g-PCL, based on our experience,³¹ we assume that, due to well-recognized PCL lower crystallization rate⁶³ and due to PEDOT-g-PCL copolymer architecture which drive the inter-chains interactions that could take place in the molten state (high π - π stacking between conjugated main chains and/or main chains and side chains interactions) delays, hinder and prevent the crystallization of PCL side chains.

The thermal stability of the two bioactive platforms (Figure 5e) is higher than those showed for i-PP and i-PP_f though slightly lower than i-PP_f/NPs (Figure S8). Both platforms showed a similar TGA and DTGA curves (Figure 5e) with the same T_{max}, 450 °C, which is the same value observed for i-PP_f/NPs. Also, both platforms reached the final degradation at the same temperature, 475 °C, and left a char of 3% and 5% for i-PP_f/PEDOT and i-PP_f/PEDOT-g-PCL, respectively, which is related with the proportion of EDOT and EDOT-PCL in the final samples. However there is a slight difference in the onset temperature. i-PP_f/PEDOT-g-PCL started to degrade 23 °C later than i-PP_f/PEDOT, supporting the improvement in performance of the bioactive platform when PCL side groups are grafted.

Morphological and topographical characterization

Figure S10 displays representative scanning electron microscopy (SEM) micrographs and both 2D height and phase contrast atomic force microscopy (AFM) images of biomedical i-PP. The surface of this substrate is homogeneous, smooth and relatively flat, exhibiting a root-mean-square roughness (R_q) of 30 ± 6 nm only. The effects of the functionalization and electroactivation on the morphology and topography of i-PP_f and i-PP_f/NPs are shown in Figure 6. The surface becomes more complex after functionalization. Thus, the plasma treatment causes the apparition of a superficial and homogeneous nano-patterning on the whole surface (Figure 6a). This morphological change affects significantly the topography, showing a slight increase of the surface roughness ($R_q = 38 \pm 6$ nm) due to the apparition of small and sharp peaks abundantly and homogeneously distributed. Abundant PHMeEDOT NPs with capricious morphology are clearly detected in the surface of i-PP_f/NPs (Figure 6b), which experiences a drastic increment of the roughness ($R_q = 312 \pm 12$ nm) in comparison to i-PP_f. Those NPs, which organize in a porous layer of 1.1 ± 0.1 μ m in thickness, were randomly distributed on the i-PP_f surface, forming a random contact network structure. However, the contact between such NPs was not large enough to ensure percolation and to form conduction paths, which explains the inexistent electrochemical activity of i-PP_f/NPs films (Figure 2c).

Figure 7 shows significant morphological differences between i-PP_f/PEDOT and i-PP_f/PEDOT-*g*-PCL. In the former, the PEDOT homopolymer completely covers the PHMeEDOT NPs, integrating them into a single conducting layer with continuous and well-defined conduction paths. This layer exhibits the typical heterogeneous morphology of electropolymerized PEDOT films,^{64,65} which consists on the aggregation of dense clusters of packed molecules. Thus, the linear growing of PEDOT chains, which are exclusively formed by α - α linkages (*i.e.* the β -positions of the thiophene ring

are occupied by the dioxane ring), favors the formation of compact spheroidal clusters that aggregate leaving a large number of submicrometric pores among them. This unique structure favours the access and escape of dopant ions during redox processes, explaining the excellent electrochemical behavior reported for PEDOT.⁶⁴⁻⁶⁷ Moreover, this morphological organization results in a rough surface with $R_q = 611 \pm 57$ nm, as is shown in the AFM images included in Figure 7a.

The microscopic texture of i-PP_f/PEDOT-g-PCL is smoother than in i-PP_f/PEDOT, which has been attributed to the superficial location of the PCL side chains. This assumption is confirmed by the contrast in the AFM phase image included in Figure 7b, which allows distinguishing between two phases in i-PP_f/PEDOT-g-PCL. Phase imaging is a powerful tool that is sensitive to surface stiffness/softness and adhesion between the tip and surface. The image recorded for i-PP_f/PEDOT-g-PCL shows bright and dark domains, which correspond to chemical-dependent phase shifts of up to 174°. The bright areas, which correspond to large phase angles, are associated with the PEDOT phase, whereas the dark areas represent the PCL phase. It is worth noting that the PCL phase occupies the main part of the surface, whereas the PEDOT phase only appears in regions largely dominated by the incorporation of EDOT monomers with respect to EDOT-PCL macromonomer. These results can be explained if the experimental details are taken into account. For electropolymerization, it was used the acetonitrile as reaction medium, which is a marginal solvent for PCL. During the solvent evaporation and film forming, the PCL side chains of PEDOT-g-PCL naturally migrate toward the surface, most probable exposing the richest aliphatic part of them. On the other hand, the roughness of i-PP_f/PEDOT-g-PCL ($R_q = 448 \pm 34$ nm) is significantly lower than that of i-PP_f/PEDOT, even though the thickness of the PEDOT-g-PCL and PEDOT layers are very similar (9.0 ± 2.5 and 8.2 ± 2.4 μm, respectively).

Another important difference between i-PP_f/PEDOT-*g*-PCL and i-PP_f/PEDOT refers to the structure of the pores. Although both bioplatfroms display a porous surface with a large number of submicrometric pores, i-PP_f/PEDOT-*g*-PCL shows a unique distribution of nanometric pores with sizes comprised within ~50 and ~100 nm. These additional nanopores, which have been attributed to the self-organization of the PCL side chains, are consistent with both the high electrochemical activity and the low electrochemical stability of i-PP_f/PEDOT-*g*-PCL in comparison to i-PP_f/PEDOT. When cycled in the range from -0.3 V to 0.9 V, PCL side chains are expected to be very sensitive to the electrochemical degradation, especially due to their low molecular weight. Thus, nanometric pores probably collapsed after a few consecutive redox cycles, reducing drastically the electrochemical activity of the system when the number of redox cycles increases.

Monitoring the influence of PEDOT-*g*-PCL in cellular adhesion and proliferation

The effect of a graft copolymer layer in cell adhesion and proliferation was evaluated by considering two cell lines, HeLa and IMR-90, both extensively used in scientific research because of their fast growth. HeLa is a human immortal carcinogenic cell line with epithelial morphology, while IMR-90 primary cells are human Caucasian fetal lung fibroblasts (no-carcinogenic). Quantitative results for cell adhesion and proliferation assays (24 h and 7 days of cell culture, respectively) on tissue culture polystyrene (TCPS, control), i-PP, i-PP_f, i-PP_f/NPs, i-PP_f/PEDOT and i-PP_f/PEDOT-*g*-PCL are displayed in Figure 8. Results, which correspond to the average of three independent replicas for each system, are expressed in terms of cell viability (cv) relative to the TCPS control material.

The amount of cells adhered to the surface of biomedical i-PP is similar (HeLa) or slightly higher (IMR-90) than that of TCPS control, which is a well-known biocompatible material used for metal implants. This behavior is approximately maintained after plasma treatment of i-PP_f, indicating that the functionalization does not have a major impact on the interaction and attachment of the cells to the surface. This has been attributed to the fact that, although the plasma treatment causes the apparition of a homogeneous nano-patterning (Figure 6a), the increment in the surface roughness (from $R_q = 30 \pm 6$ nm for i-PP to $R_q = 38 \pm 6$ nm for i-PP_f) is not large enough to affect the adhesion of the cells. Thus, the roughness of both i-PP and i-PP_f surfaces is significantly lower than the diameter of filopodia filaments in cells (*ca.* 100-200 nm⁶⁸), which are thin, actin-rich structures protruding from the lamellipodial actin network that play a crucial role in cell adhesion.^{69,70}

The incorporation of the first CP layer introduces important changes that, in addition, depend on the cell line. More specifically, PHMeEDOT NPs promotes IMR-90 cells adhesion by around 80% with respect to the control, while reduces the attachment of HeLa cells by approximately 50%. Considering the sub-micrometric roughness of i-PP_f/NPs, this variation is consistent with the filopodia recognition capacity of submicrometric topographies, which was found to be dependent on the cell shape and texture.⁶⁹ IMR-90 presents the typical fusiform-shape with normal texture while HeLa are soft irregularly-shaped cells, as shown in confocal micrographs displayed in Figure 9, which makes difficult the recognition of the textures. However, the addition of the second CP layer results in a significant increment of cell adhesion with respect to i-PP_f/NPs, this effect being especially remarkable for IMR-90 cells. Thus, the attachment of fibroblast cells is higher for i-PP_f/PEDOT and i-PP_f/PEDOT-*g*-PCL than for i-PP by

~70% and ~90%, respectively, while for HeLa cells the adhesion increment is negligible for i-PP_f/PEDOT and of ~60% for i-PP_f/PEDOT-g-PCL.

The different response of HeLa and IMR-90 cells towards CPs can be interpreted on the basis of their contrasted fibronectin content. More specifically, PEDOT and, in general CPs, have a great affinity towards fibronectin, its adsorption being an essential step for promoting cell-adhesion.^{71,72} In cell lines derived from non-carcinogenic tissues fibronectin was found to be predominantly in the extracellular matrix, whereas carcinogenic cell lines display very little or no fibronectin.⁷³ The absence of extracellular fibronectin was specifically demonstrated for tumor HeLa cells that, instead, contain such a protein in the cell nucleus.⁷⁴ This feature explains the significantly lower adhesion of HeLa cells to i-PP_f/PEDOT-g-PCL and, especially to i-PP_f/PEDOT, with respect to that found for IMPR-90 cells.

Covalent grafting of biocompatible side chains to CPs is a smart strategy to improve the biocompatibility of structures based on such class of polymers, the chemical and physical properties of which mimics the features of a natural extracellular matrix (*e.g.* CP structures enable ion diffusion and ion exchange at the interface).⁷⁵ Analysis of cell viability through simple proliferation assays is a useful tool for assessing the impact of scaffolds in cell metabolism and, therefore, determine its potential use for tissue engineering applications. Results from cell proliferation for the examined materials (and the TCPS control) are shown in Figure 8b, while representative confocal images are displayed in Figure 9 (micrographs for control TCPS are shown in Figure S12).

Not unexpectedly, results depend on the cell line. Proliferation of HeLa cells on i-PP and i-PP_f ($cv = 116\% \pm 2\%$ and $129\% \pm 19\%$, respectively) was slightly better than for the control TCPS, whereas that of i-PP_f/NPs was clearly worse ($cv = 60\% \pm 24\%$). Instead, i-PP_f/PEDOT ($cv = 144\% \pm 19\%$) shows a significant increase in cell number

due to cell division (cytokinesis) with respect to both pristine and plasma-functionalized i-PP substrates. These results indicate that the doping level of chemically polymerized PHMeEDOT NPs is not high enough to facilitate the exchange of ions with adhered HeLa cells, which in turn is affected by the low cell adhesion due to the lack of fibronectin in the extracellular matrix (as discussed above). In contrast, PEDOT prepared using the experimental conditions described in this work is known to achieve a very high doping level.³⁷ It generally occurs for CPs synthesized by electropolymerization with respect to chemical oxidative polymerization,⁷⁶ and therefore, a very high concentration of counterions is contained inside the polymeric matrix. These unique electronic and chemical structures facilitate the exchange of ions at the PEDOT...cell interface, promoting cell division. Indeed, this behavior is so favorable that it overcomes the limitations associated to the lack of extracellular fibronectin in HeLa cells, improving the response of electrochemically inert surfaces (*i.e.* steel, i-PP, i-PP_f and i-PP_f/NPs). It is worth noting that these results, which are supported by confocal micrographs displayed in Figure 9, are fully consistent with the cyclic voltammograms displayed in Figure 2c.

i-PP_f/PEDOT-*g*-PCL exhibits an extraordinary, unprecedented high capacity for promoting HeLa cells growth with $cv = 268\% \pm 15\%$ (Figure 9d). The superior features of this bioplatfrom has been attributed to the synergy among the electrochemical activity of the PEDOT, the high biocompatibility of PCL, which is frequently used for biomedical applications, and the ionic conductivity due to the dopant anions of PEDOT that, in turn, is enhanced by ion solvating polymer property of PCL chains.^{49,50} The addition of the graft copolymer layer to biomedical i-PP improves the cell viability by a factor of 2.3.

Results are more impressive for IMR-90 cells. In this case the viability for i-PP and i-PP_f surfaces ($cv = 68\% \pm 9\%$ and $72\% \pm 4\%$, respectively) is lower than for the control, which has been attributed to the poor wettability of these substrates (*i.e.* growth of fibrin-containing cells is promoted on hydrophilic surfaces in comparison to hydrophobic ones). This situation is reversed for i-PP_f/NPs ($cv = 98\% \pm 9\%$), even though its water contact angle is similar to that of i-PP_f. Again, this behavior has been associated to the ability of CPs to exchange ions with cells, as is supported by the results obtained when a relatively thick layer of PEDOT is deposited on PHMeEDOT NPs. Thus, the cv of i-PP_f/PEDOT ($cv = 137\% \pm 11\%$) increased by twice when compared to that of the i-PP substrate for biomedical applications.

For i-PP_f/PEDOT-g-PCL ($cv = 196\% \pm 22\%$), the improvement represents an increase of almost a factor of 3 and 1.5 with respect to i-PP and i-PP_f/PEDOT, evidencing the benefits of the PCL grafting. These results prove the synergy between PEDOT and PCL effects at the bioplateform interface. Thus, the grafted copolymer approach presented in this study represents a smart strategy to functionalize currently used biomedical plastics, as i-PP, for matching of flexibility and charge transport between the biointerface material and living tissues, promoting considerably cell adhesion and growing.

CONCLUSIONS

Improvement of well-established polymeric materials for biomedical applications is a current challenge. In this study, a conjugated graft copolymer is used as a molecular composite to coat previously functionalized and electroactivated i-PP intended for biomedical applications. Our idea was to optimize the properties of a new material used at abiotic/biotic interface and, by addressing the chemical design toward side chain

functionalization of a CP with PCL polar side chains (biocompatible, with high ionic conductivity, ion-solvating capability and broad electrochemical stability window), we succeeded to significantly improve the ion transport and ion-to electron transduction with an ion-rich, living, water-laden, dynamic biological environment.

The surface of i-PP functionalized with oxygen plasma treatment has been coated with PHMeEDOT NPs prepared by chemical oxidative polymerization, which functioned as polymerization nuclei for *in situ* electrocopolymerization of EDOT-PCL macromonomer and EDOT monomer. The resulting bioplatfrom is a flexible substrate coated with a graft copolymer that presents, synergistically, the advantages of PEDOT backbone and those of PCL side chains. This study shows that i-PEDOT/PEDOT-g-PCL has many favorable properties with respect to i-PP and i-PP/PEDOT for tissue engineering applications. This has been confirmed by cell adhesion and proliferation assays using two human cell lines with very different characteristics (HeLa and IMR-90), i-PEDOT/PEDOT-g-PCL improving cell viability of i-PP by a factor of almost three. Overall, this study has wide implications in polymeric medical devices currently used as implants, which can be upgraded enhancing their tissue integration performance. Future investigations will be oriented towards this field, studying the impact of PEDOT-g-PCL in cell differentiation and the integration of i-PEDOT/PEDOT-g-PCL.

CONFLICTS OF INTEREST

There are no conflicts to declare.

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CAPTIONS TO FIGURES

Figure 1. (a) Sketch representing the three steps used to prepare i-PP_f/PEDOT-g-PCL bioplatforms. (b) Photographs of pristine i-PP, i-PP_f/NP, i-PP_f/PEDOT and i-PP_f/PEDOT-g-PCL films.

Figure 2. (a) FTIR and (b) Raman spectra recorded for i-PP_f/PEDOT and i-PP_f/PEDOT-g-PCL bioplatforms. (c) Comparison of the cyclic voltammograms recorded in PBS 0.1 M for i-PP_f/NPs and i-PP_f/PEDOT. (d) Comparison of the cyclic voltammograms recorded in PBS 0.1 M for i-PP_f/PEDOT and i-PP_f/PEDOT-g-PCL. Voltammograms recorded for i-PP_f/PEDOT and i-PP_f/PEDOT-g-PCL after 50 consecutive redox cycles (dotted lines) are included in (c) and (d), respectively. CV assays were conducted using the following parameters: scan rate, 50 mV/s; initial and final potential, -0.20 V; reversal potential, +0.80 V.

Figure 3. Contact angle for examined materials. Photos of the contact angles are also provided.

Figure 4. i-PP_f/PEDOT-g-PCL ($0.5 \times 1.5 \text{ cm}^2$) (a) before, (b-c) during, and (d) after a deformation.

Figure 5. For (a, b) EDOT-PCL macromonomer and (c, e) i-PP_f/PEDOT-g-PCL and (d, e) i-PP_f/PEDOT bioplatforms: (a, c, d) DSC thermograms and (b, e) both TGA and DTGA curves.

Figure 6. For (a) i-PP_f and (b) i-PP_f/NPs: Representative SEM micrographs and 2D AFM height and phase contrast images.

Figure 7. For (a) i-PP_f/PEDOT and (b) i-PP_f/PCL-g-PCL: High and low magnification SEM micrographs and 2D AFM height and phase contrast images.

Figure 8. (a) Cellular adhesion and (b) cellular proliferation on the surface of i-PP, i-PP_f, i-PP_f/NPs, i-PP_f/PEDOT and i-PP_f/PEDOT-g-PCL. TCPS was used as a control

substrate. Human HeLa and IMR-90 cells were cultured during (a) 24 h and (b) 7 days. Asterisk marks (*) represent a significant difference with the control when the Student's T-test was applied ($p < 0.05$).

Figure 9. Confocal microscopy micrographs (10 $\times$) displaying the morphology of HeLa (left) and IMR-90 (right) cells after incubation for 7 days on (a) i-PP, (b) i-PP_f (c) i-PP_f/NPs (d) i-PP_f/PEDOT and (e) i-PP_f/PEDOT-*g*-PCL.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8

Figure 9

Graphical abstract