Chapter 6

Perspectives of Conductive Polymers Toward Smart Biomaterials for Tissue Engineering

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Additional information is available at the end of the chapter

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Abstract

Developing the stimuli-responsive biomaterials with tailor properties represents an important goal of the tissue-engineering community. Such biomaterial promises to become the conductive polymers (CPs), as a novel generation of organic materials that have both electrical and optical properties similar to those of metals and inorganic semiconductors but which also exhibit the attractive properties associated with conventional polymers, that is, easy synthesis and flexibility in processing. The fact that several tissues are responsive to electrical fields and stimuli has made conductive polymers attractive for various biological and medical applications. In this context, the chapter provides information on the basic properties of the conductive polymers and how these polymers can be optimized to generate specific properties for biomedical applications. The synthesis routes of novel materials and specific design techniques, as well as the mechanisms by which electrical conduction affects cells/tissues, are examined, and the significant impact of the conductive polymers in the biomedical field, that is, biosensors, tissue engineering, and neural probes, is demonstrated.

Keywords: conductive polymers, functionalization strategies, smart materials, biocompatibility, tissue engineering

1. Introduction

Electroactive biomaterials represent a part of a new generation of "smart biomaterials" that allow the direct delivery of electrical, electrochemical, and electromechanical stimulation to cells and/or tissues [1, 2]. The electroactive biomaterials' class includes conductive polymers

(CPs), electrets, and piezoelectric and photovoltaic materials [3]. Electrets and piezoelectric materials make possible the delivery of an electrical stimulus without being necessary an external power source, but the control over the stimulus is limited. On the other hand, the conductive polymers (CPs), allow excellent control of the electrical stimulus and possess both the electrical and optical properties, exhibiting a high conductivity/weight ratio, and also can be made biocompatible, biodegradable, and porous [1].

Produced for the first time few decades ago, the polypyrrole, PPy, dates since 1960 and only in 1977, the polyacetylene (PA) doped with iodine was recognized as the first inherent conductive polymer [4], and today there are several tens of conductive polymer systems (e.g., polyacetylene (PA), polythiophene (PT), poly(3,4-ethylenedioxythiophene) (PEDOT), and polyaniline (PANI)) [5]. Therefore, the conducting polymers, known as "synthetic metals," are polymers with a highly conjugated polymeric chain.

It can be presumed that typically organic polymers, considered to be insulators, become conductors, when they adopt different electronic structures. In conducting polymers delocalization of the electrons is generated by the carbon atoms engaged in π bonding, with sp^2p_z configuration, and by overlapping the orbitals of successive atoms, providing the mobility of polymer chains and implicitly the specific properties (e.g., the electrical conductivity, low ionization potential and energy optical transitions, and also high electron affinity). Therefore, the specific properties abovementioned make these polymers considerable for a wide range of applications, from the electronic to medical field [6]. Additionally, the conducting polymers can be designed for the transport of the small electronic signals in the body, acting as artificial nerves) [5].

Consequently, the conductive polymers represent dynamic structures with complex properties which have gained a great interest in various scientific fields because of their vast versatility. On the other hand, they possess very good electrical and optical properties and allow an excellent control of the electrical stimulus, and furthermore, a great advantage of conductive polymers is that the physicochemical properties can be tailored to the specific needs required by different applications, by incorporating antibodies, enzymes, and other biological moieties. Additionally, their properties can be altered and controlled through stimulation (e.g., electricity, light, pH) even after synthesis.

These complex properties can be controlled only if the nature of the processes that regulate them during the synthesis of the conducting polymers and the extent to which these properties are changed by the application of an electrical stimulus are known and understood.

Considering the vast possibilities to use the new electroactive materials in biomedicine, this chapter gathers all of the available information concerning the most commonly conductive polymers and their mechanism of conduction. The implications of the classical and modern synthesis methods in designing the new electroactive systems are analyzed in accordance with the phenomena underlying their conductivity and the ways to tailor their biocompatibility, biomolecule doping, and drug release for tissue-engineering applications.

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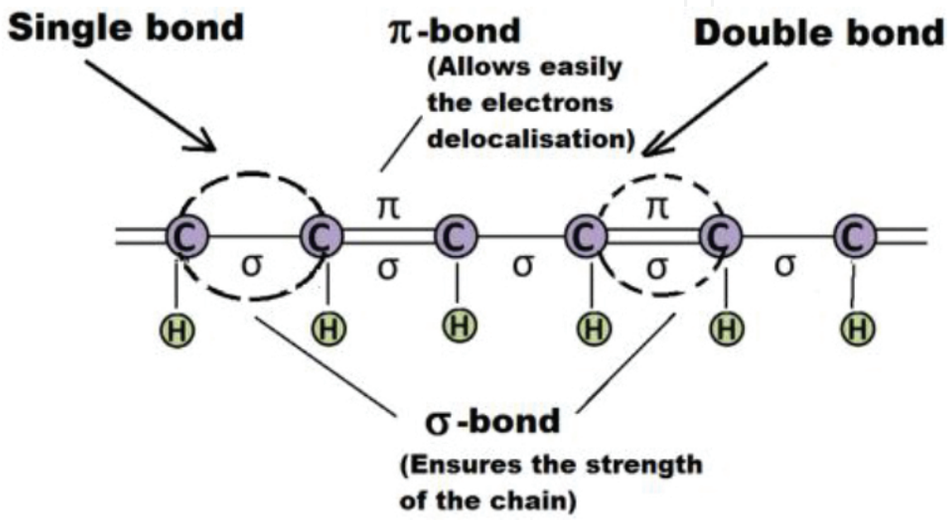
2. Conductivity source and doping of the conductive polymers

Conductive polymers can conduct charges as a result of ease with which electrons jump within and between the polymer chains [2]. These polymers are considered unique, because they possess a conjugated backbone, meaning that it is formed by a series of alternating double and single bonds with sp^2-hybridized atoms [4]. Both types of linkages are chemically strong, single ones containing localized σ-bond, while those double a less strongly localized π-bond [7] (see **Scheme 1**).



Scheme 1. Schematic representation of a conjugated chain, containing alternating single and double bonds.

Such an alternating double bond system exhibits a delocalization over the entire chain, as result of the electronic wave functions, allowing charge mobility along the polymer backbone and between the adjacent chains, mobility which is limited by both disorder and Coulombic interactions between the electrons and holes [8]. Consequently, the conductivity is a measure of electrical conduction and thus represents the capacity of a material to conduct current. Generally, the materials with conductivities less than 10^{-8} S/cm are considered insulators, materials with conductivities between 10^{-8} and 10^{3} S/cm are considered semiconductors, and materials with conductivities greater than 10^{3} S/cm are considered conductors [8]. Therefore, dopants exhibit a main role in improving of the polymers' conductivity [2, 7, 9]. Thus, the polymers in their pure (undoped) state are described as electronic insulators; when these polymers are doped, the conductivity changes from insulators to metals.

Doping is the process of oxidation (p-doping) or reduction (n-doping) of a neutral polymer, delivering a counter anion or cation (i.e., dopant), respectively. Thereby, the dopant introduces a charge carrier into the system by removing or adding electrons from/to the polymer chain, relocalizing them as polarons (i.e., radical ions) or bipolarons (i.e., dications or dianions) into the polymer (**Figure 1**) [2, 7, 9, 10].

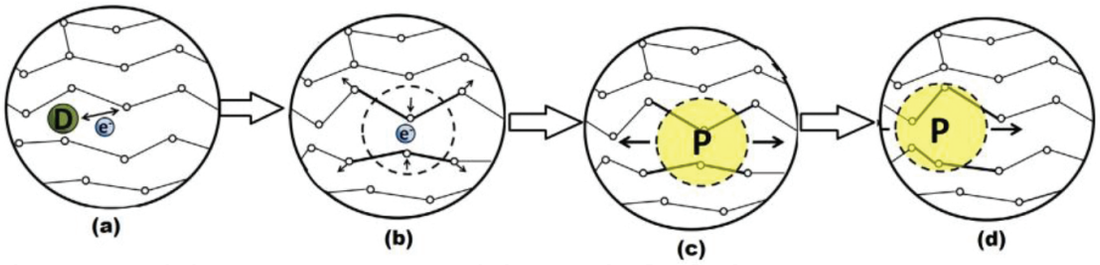


Figure 1. Illustration of the charge transport mechanism in conductive polymers: (a) the dopant removes or adds an electron from/to the polymer chain, generating a charge delocalized; (b) the chain is energetically favorable to localize this charge and surround it with a local distortion of the crystal lattice; (c) the charge surrounded by a distortion appears as a radical ion associated with a lattice distortion (known as a polaron); and (d) the polaron can move along the polymer chain, allowing it to conduct electricity.

Therefore, by doping, new electronic states are introduced within the band gap of material, which strongly interact between them at high concentrations. As a result of these interactions, an overlapping of the electronic wave functions occurs and generates a band of electronic state within the band gap, in the place of the discrete levels.

Upon doping, a conducting polymer system is produced as a result of close association of the counterions with the charged CP backbone. The attraction of the electrons from one repeat unit to the nuclei neighboring units determines charge mobility along the chains or between the chains, process known as "electron hopping." The ordered movement of these charge carriers along the conjugated CP backbone produces electrical conductivity. A conducting polymer can be considered more conductive, when the band gap energy is smaller (i.e., distance between conducting band and valence band).

As abovementioned, the doping process produces a number of charged carriers in polymer, and these carriers must be mobile in order to contribute to conductivity. This parameter, σ, is proportional with the carrier concentration, n, and mobility, μ.

The transport mechanism of the carriers in a conducting polymer is manifested more likely as a "hopping transport," similarly with that of amorphous semiconductors and less similar with that of crystalline semiconductors—band transport. Therefore, can be concluded that the doping creates the active sites—polarons—which allow carriers (electronic and holes) to move from one site to another, by hopping mechanism.

There are many factors that influence the charge transport mechanisms and implicitly conductivity, namely, the dopant, oxidation level/doping percentage, synthesis method, and temperature. These will affect not only electroactivity but also the surface and bulk structural properties of the polymer, for example, the color, porosity, and volume [2, 8, 11]. Doping can be performed chemically, electrochemically, or via photodoping [8, 11, 12]. Therefore, small (e.g., Cl^-) and large (e.g., sodium polystyrenesulfonate, PSS) dopants can modulate both the electrical conductivities and surface structural properties. On the other hand, larger dopants, such as hyaluronic acid (HA), can affect the material properties more dramatically (surface topography and physical handling properties [13]) and can increase the polymer density. Large dopants are better integrated into the polymer and will not be leached out with time or by the

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application of an electrical stimulus, thereby giving the polymer a greater electrochemical stability [9, 14, 15].

Surface properties, as the roughness, morphology, wettability, and stiffness, are known to affect the adhesion and proliferation of multiple cell types [16]. It is important to note that the nature of the dopants has a strongly influence on the bulk and surface properties of conductive polymers [17]. Indeed, by use of different dopants, different modifications of these properties have been observed. For example, hyaluronic acid (HA)-doped PPy is rougher and more brittle than PSS-doped PPy [16]. Chloride anions are frequently used to dope CPs, due to their biological compatibility, for example, PPyCl.

To incorporate molecules that are not capable of redox chemistry, such as biological dopants, it is necessary to synthesize/dope CPs electrochemically. In literature [18], the relevant biological effects of dopants—dextran sulfate (DS), poly(2-methoxyaniline-5-sulfonic acid) (PMAS), para-toluenesulfonic (pTS) acid, HA, and chitosan (CS)—were compared, and it was found that the PMAS- and CS-doped films possessed a much lower surface roughness and Young's modulus than the films prepared with the other dopants. In the same study, it was also evidenced that the PMAS- and CS-doped films have sustained the adhesion and differentiation of skeletal myoblasts much better than their counterparts. These observations show the importance of relationship between dopant—material property—cellular behavior and highlight the preservation of this correlation when choosing the doping molecule.

It can be concluded that dopants with large molecule are physically trapped and implicitly more stable in the CP, without being easily excluded and/or exchanged by the application of an electrical potential. Instead, small dopants can be easily diffused from CP and/or exchanged with other ions within the surrounding environment. Therefore, properties of conductive polymers can be adjusted by the doping process.

3. Synthesis routes and processing

Currently, the conductive polymers can be synthesized by two main methods, chemically or electrochemically, each having advantages and disadvantages [19]. The chemical synthesis provides not only many routes to synthesize a wide variety of CPs but also permits to obtain a scale-up of such materials, which, currently, by electrochemical synthesis is not possible. Thus, the chemical synthesis methods include either condensation polymerization, that is, step-growth polymerization, or addition polymerization, that is, chain-growth polymerization.

During the chemical synthesis the monomer solution is mixed with an oxidizing agent (e.g., ferric chloride, ammonium persulfate), obtaining polymers in the various forms, which makes the method to be selected for commercial applications [20]. The conductivity of the created polymer is highly susceptible to the choice and purity of the solvent, oxidant, relative concentration of the reagents, reaction time, temperature, stirring rate, etc. Unfortunately, the conductivity of the polymers synthesized by the chemical method is always lower than that of their electrochemically synthesized counterparts [20].

The electrochemical synthesis is a common alternative method for CPs obtaining, because this synthetic procedure is relatively straightforward [19]. This technique dates from 1968 when "pyrrole black" was obtained as a precipitate, using a platinum electrode, by exposing an aqueous solution of pyrrole and sulfuric acid to an oxidative potential [8, 21]. Nowadays, the electrochemical polymerization is performed using a three-electrode system (working, counter, and reference electrodes) placed into a solution containing the monomer of the polymer, appropriate solvent, and electrolyte (dopant) (**Figure 2**) [8, 22].

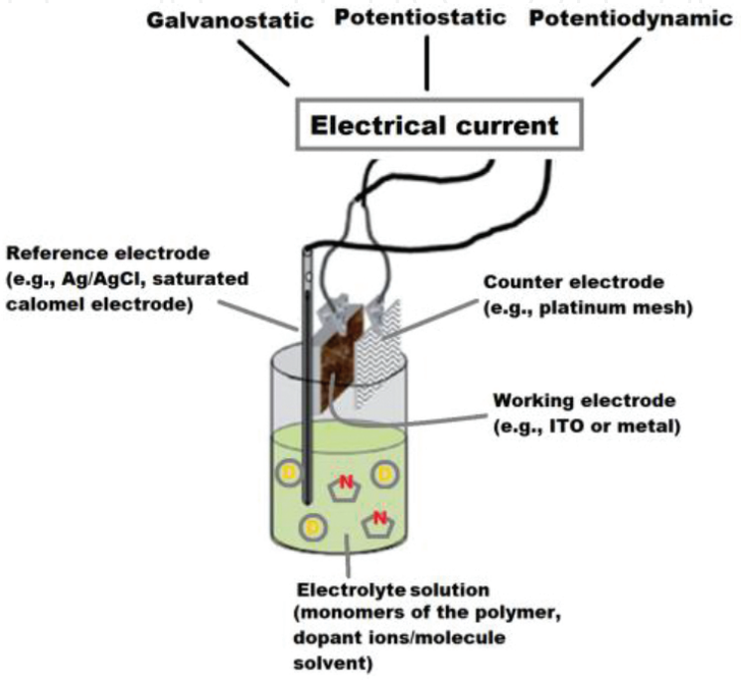

Figure 2. Schematic representation of the equipment for electrochemical synthesis.

This method allows the deposition of a thin film of the polymer with a well-controlled thickness and morphology. The electrical current is passed through the solution and the electrodeposition occurs at the positively charged working electrode or anode, forming insoluble polymer chains on the electrode surface.

Generally, the electrochemical polymerization can be achieved using three techniques: potentiostatic (to obtain thin films), galvanostatic (to obtain thick films), and potentiodynamic [23, 24]. In the potentiostatic polymerization, the potential of the electrodes is controlled, while the current varies [23]. This protects the integrity of the component to be coated, making this method ideal for the manufacture of biosensors. The electrical current can vary depending on a number of factors (e.g., the electrode material, the plating conditions), thus a coulometer being necessary to control the amount of polymer that is deposited. Instead, in galvanostatic polymerization, the electrical current is controlled; this means that the rate at which the polymer is deposited remains constant and can be controlled accurately [23]. In the course of the potentiodynamic deposition, the polymerizing potential is swept between a low and high potential limit in cycles. This determines the deposition of polymer in layers, each layer

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becoming electrically active before the next to be synthesized [25]. Important variables, including the deposition time and temperature, solvent system, electrolyte, electrode system, and deposition charge, must be considered, because each of these parameters exhibits an effect on film morphology (thickness and topography), conductivity, and mechanical properties, these having a direct impact on the utility of the material for biomedical applications. Consequently, the electrochemical polymerization represents a new way to achieve a range of composite materials with the special properties. Therefore, the doping and processing take place simultaneously in the electrochemical polymerization.

One way to compensate the shortcomings of a conductive polymer is to use it together with another polymer, combining the positive qualities of both materials. For example, functionalized polysulfone with quaternary ammonium groups (PSFQ) was combined with polyvinyl alcohol (PVA) and/or cellulose acetate phthalate (CAP) into its matrix, yielding flexible, biocompatible, and biodegradable composites with improved conductivity compared to the PSFQ [26]. Interactions between blood and a polymer surface depend on blood composition, blood flow, and physicochemical properties of the polymer surface, such as hydrophobicity/hydrophilicity, roughness, and flexibility, or on the toxicological and electrical properties [27, 28]. Consequently, it is assumed that the quaternization effect and choosing of an appropriate additive (PVA and/or CAP) significantly improve the ionic conductivity and also could optimize electric properties required by ionic exchange membrane [29]. Additionally, PSFQ/CAP and PSFQ/PVA composites were able to maintain its electroactivity and established compatibility with some blood compound (e.g., red blood cells (RBC) and platelets) and also with plasma protein (e.g., albumin, immunoglobulin G (IgG), and fibrinogen) [26, 27, 30]. These results seem to be applicable for evaluating bacterial cell adhesion on polymer surfaces and could be employed for studying possible induced infections or for obtaining biomembranes.

Electrospinning is a versatile process that allows to process some conductive polymers into nano- and microfibers [31]. In this context, solutions processable of cationic ionomers (PSFQ) have received widespread attention for their promising roles as exchange membranes and antibacterial coatings. Therefore, the solutions of the polysulfone ionomers were processed by electrospinning to create new fibrous materials that can modulate biomembrane properties. In particular, their biological activity (investigated against Gram-positive *Staphylococcus aureus* and the Gram-negative *Escherichia coli* bacteria) depends on their structure and physicochemical properties which affects the interaction with the cytoplasmic membrane of bacteria and influences their cell metabolism [32]. Consequently, the electrospinning proved to extend the possible applications of quaternized polysulfones by preparing continuous fine fibers with characteristics which recommend them for applications as biomaterials and membranes in various fields.

Additionally, the conductive polymers have also been successfully polymerized inside of the hydrogel networks [33]. This allows the creation of electroactive hydrogels, which combine the redox switching capabilities of conductive polymers with the fast ion mobility and biocompatibility of the hydrogels. These electroactive hydrogels can be of various sizes, binding the bioactive molecules and nanotemplated in order to mimic the extracellular matrix

[34]. These properties make them ideal for implantable biosensors, drug release devices, and deep-brain stimulators.

4. General functionalization strategies of conductive polymers for specific applications

As already mentioned, CPs have electrical and optical properties similar to those of metals and inorganic semiconductors and also are ease of synthesized and processed, which makes them suitable for a wide range of applications in the microelectronics industry [35] and, more recently, in the biological field. Good cellular response to the biomaterial is essential for many biomedical applications [36]. Therefore, many types of conductive polymers (e.g., PPy, PANI, and polyethyleneimine (PEI)) have been shown to support the growth of a large variety of cell [1, 2]. Additionally, the improvement of the conductive polymer biocompatibility can be easily accomplished by bonding the biocompatible molecules, segments, and side chains on the polymer [37]. However, there are few studies of the reduced biocompatibility [5, 38]. It was found that this variation in biocompatibility is due to the dopants and different preparation protocols used in the experiments; for example, it was shown that rinsing, extraction, and aging have a significant effect on the biocompatibility [39], generating changes of the polymer surface topography, which can have as a result an altered cell behavior [5].

Studies of the conductive polymers for applications in biomedical field were expanded greatly; since 1980s these materials were compatible with many biological molecules such as those used in biosensors. Most of CPs present significant characteristics for biomedical applications, namely, the biocompatibility, ability to entrap and/or release the biological molecules (i.e., reversible doping), or ability to transfer the charge by biochemical reaction. Additionally, they have the capacity to easily modify the electrical, chemical, and physical properties for a better match to specific applications [36, 40].

Although a wide range of CPs has been explored for a number of applications, as described in more detail below, considerable research remains to be performed, contributing thus to extending possible applications of these "smart" materials.

4.1. Overview on the conductive polymers functionalization

There is always the desire to optimize the material properties when it targeted a specific application. Thus, the optimization of the roughness, porosity, hydrophobicity, conductivity, degradability properties of the conductive polymers, and binding of the biological molecules (capable to make them promising candidates for biomedical applications) can be achieved through different techniques (see **Figure 3**) [8].

(1) Physical adsorption represents the simplest method. The resulted product is sensitive to pH, and adsorbed molecule dissociates and thus compromises the conductivity of the polymer, making the material to become "inactive." In this method, a solution containing functionalizing agent is placed in contact with the polymer, after it was synthesized. The

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biomolecules are physically absorbed due the static interactions between the polymer matrix and charge of the molecule [8, 41, 42].

(2) Another non-covalent method is entrapment [43]. This occurs by mixing the desired molecule with the monomer of the polymer, dopant, and solvent, prior to the synthesis. After the electrochemical polymerization, the molecules of the functionalizing agent from the proximity of the electrode are incorporated into the growing polymer. This technique was firstly applied to link large molecules (e.g., enzymes, DNA), which once entrapped are unable to leave the polymer due to their size [44].

(3) The process of doping CPs, necessary to induce conductivity, can also be exploited to modify CPs non-covalently and to introduce new properties for a desired application. This allows the bonding of a wide range of biomolecules (dopants), as long as they are charged [45, 46]. For example, by doping the collagen, heparin, chitosan, and ATP have been successfully bound in conductive polymers as growth factors [2, 12].

(4) Introducing of the bioactive molecules through doping exhibits a higher negative effect on the polymer's conductivity than the covalent bonding [2, 11, 45]. Thus, alternatively, covalent methods can be used to permanently functionalize CPs. By this method, the biological molecules will be strongly bound and will not be released, thereby enhancing the long-term stability of the polymer [45].

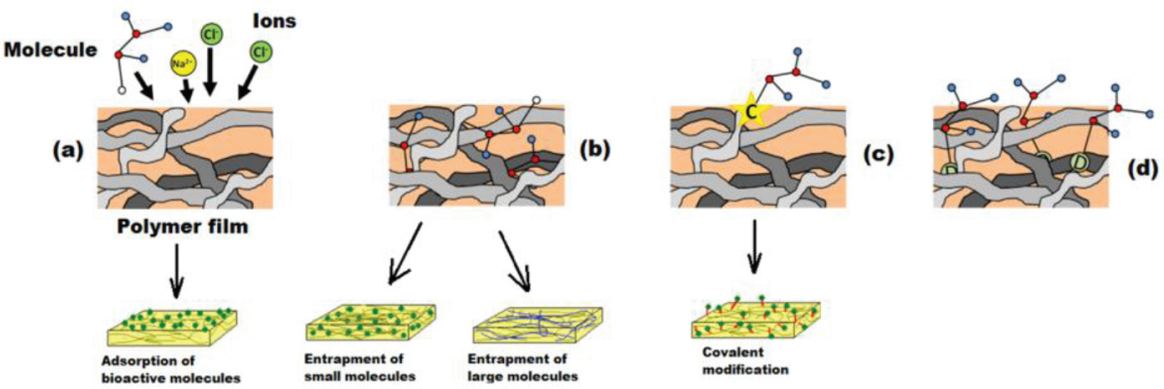

Figure 3. Modification strategies applied to conductive polymers: (a) physical adsorption, (b) entrapping, (c) covalent bonding, and (d) exploiting the doping.

It is important to note that the steric effects of any incorporated functional group may disrupt the planarity of the conjugated system and implicitly decrease the conductivity. Functionalization of CPs with different biomolecules has allowed medical engineers to modify CPs with sensible biological elements. Thus, through different ways, CPs with enhanced adhesion and proliferation of a cell variety with improved biocompatibility have been developed.

4.2. Specific applications: from concept to biomedical perspectives

Conducting polymers have attracted great interest as suitable matrices for biomolecules, because they improve the stability, speed, and sensitivity [47, 48] and, therefore, can be widely

used in medical diagnostics [49, 50]. The conductive and semiconductive properties of these polymers make them an important materials' class used in a wide range of applications, from the electronic and biotechnological ones (such as rechargeable batteries, electronic displays, solar cells, ion-exchange membrane in fuel cells, chemical sensors, and biosensors) to drug release systems and tissue applications (used to transport small electronic signals in the body acting as an artificial nerves or used as films in a neurotransmitter as a drug release system into the brain).

4.2.1. Biosensor applications

Biosensors are of great interest, because these interesting bio-devices have been shown to have applications in clinical diagnostics, environmental monitoring, food freshness, and bioprocess monitoring [47, 51–53]. The first biosensor device was created by integrating an enzyme into an electrode [54], but subsequently, for clinical purposes a great progress in monitoring and diagnosing metabolites (e.g., glucose, hormones, antibodies, antigens) has been made. A biosensor is a chemical sensing device in which a biologically entity is coupled to a transducer to allow the quantitative development of some complex biochemical parameter [55]. The interaction of the detection element with the interest analyte produces a chemical signal that is transmitted to the transducer, which ultimately transforms the input into an electrical signal (**Figure 4**). The major challenge when using CPs in the design of the biosensor with electrochemical transducer is to understand the mechanism of the electrons transfer. Depending on the way in which the chemical signal is transmitted, the biosensors can be divided in several categories: amperometric, potentiometric, conductometric, optical, calorimetric, and piezoelectric [56].

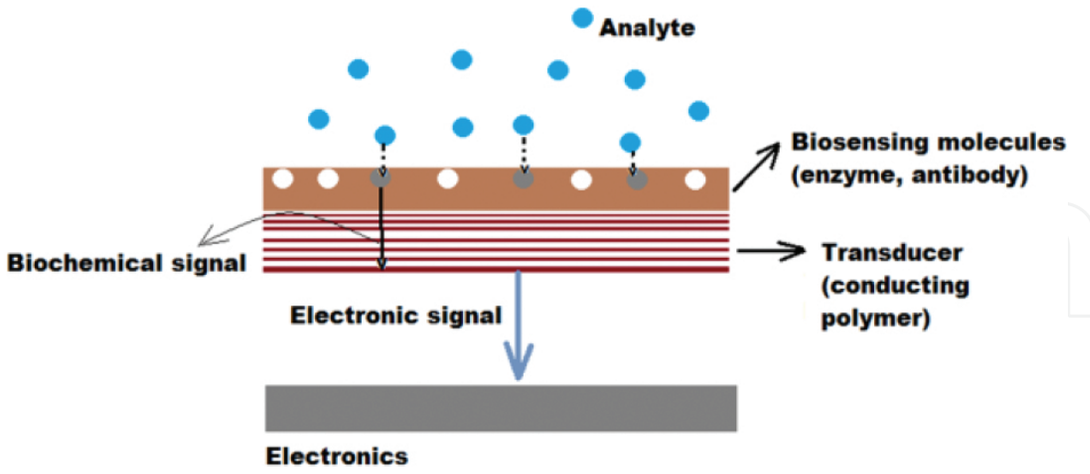

Figure 4. Scheme of a conductive polymer-based biosensor.

There are three so-called generations of biosensors:

(1) First generation of biosensors where the normal product of the reaction diffuses to the transducer and causes the electrical response.

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(2) Second generation of biosensors involves the specific "mediators" between the reaction and the transducer, generating an improved response in two steps. Firstly, a redox reaction between the enzyme and substrate, reoxidized by the mediator, occurs, and secondly, the mediator is oxidized by the electrode.

(3) Third generation of biosensors is autonomous and arises from the nature of the sensor; the reaction itself causes the response and no product or mediator is not directly involved. The third generation of sensors is accompanied by co-immobilization of the enzyme and mediator at the electrode surface, that is, the direct electrical contact of enzyme to electrode occurs.

An important aspect in the biosensor applications is represented by the integration of conductive polymer in biological recognition components (such as glucose, cholesterol, urea, triglycerides, creatinines, and pesticides) [8]. Rahman et al. [41, 57], using the covalent immobilization method of pyruvate oxidase on the nanoparticle-comprised poly-(terthiophene carboxylic acid), poly-TTCA, have obtained a biosensor for amperometric detection of the phosphate ions. For example, literature reported that for the fabrication of the DNA sensors, copolymers of PPy and oligonucleotides bearing a pyrrole group were used [8]. Additionally, literature has been shown as example the immunosensors for detecting *Listeria monocytogenes*, created by covalent binding of the *Listeria* monoclonal antibody to a copolymer of carboxylic acid-functionalized PPy and regular PPy [8]. Trojanowicz and Miernik [58] have developed avidin–biotin (N-(biotinoyl)-1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine, triethylammonium salt) interactions for the immobilization of the glucose oxidase on bilayer lipid membrane formed on polypyrrole and poly-o-phenylylenediamine electrodeposited onto platinum wire, respectively. These types of membrane-based glucose biosensors cause a significant reduction from the electroactive species (e.g., ascorbic acid, cholesterol, and uric acid), giving a stable response [59].

The recent progress in the molecular biology/recombinant DNA technologies has opened enormous possibilities for the microorganisms' adjustment to improve the activity of an existing enzyme or to emit a foreign enzyme/protein in a host cell to be used for enhancing the specific activity. There have been various strategies to modify the microbes for application to microbial biosensors. For example, Lei et al. [59, 60] have reported a cell biosensor using PNP-degrader *Pseudomonas putida* JS444 for the estimation of organophosphorus nerve agent with p-nitrophenyl constituent. This biosensor was found to be stable for only 5 days.

Recent advances in carbon nanotubes (CNTs) include their incorporation in CP-based biosensors. For example, preliminary studies have been performed on the exploration of the properties of both PPy/CNT and PANI/CNT devices as pH sensors [61]. Moreover, for label-free detection of DNA, DNA-doped PPy in conjunction with CNTs was used. Similarly, DNA sensors have been created from a composite of PPy and CNTs functionalized with carboxylic groups by covalently immobilization of DNA on CNTs [62]. In general, the presence of CNTs generates an increase of the biosensors overall sensitivity and selectivity.

4.2.2. Tissue-engineering applications

The development of biosensors has created a basis for using the conductive polymers in many biological environments; in fact it was the first step to explore CPs as biomaterials for different cells. Literature has shown that the cells (e.g., fibroblasts, neurons, and osteoblasts) responded to the electrical fields created by electrets [63] or between electrodes, *in vitro* and *in vivo* studies [64, 65]. The general properties of CPs, desired for the tissue-engineering applications, include the conductivity, reversible oxidation, redox stability, biocompatibility, hydrophobicity (contact angle with water is 40–70°, promoting cell adhesion), three-dimensional geometry, and surface topography.

Literature states that PPy was one of the first CPs studied for its effect on the mammalian cells [66]. Moreover the adhesion and growth of various cells (endothelial cells [66, 67], rat pheochromocytoma cells (PC12) [68], neurons, and support cells), associated with dorsal root ganglia (DRG) [69], primary neurons [70], keratinocytes [71], and mesenchymal stem cells [72], were reported. Because the advantage of using CPs in tissue-engineering applications consists in ability to subject the cells to an electrical field, studies concerning the cell compatibility, when a current or voltage is applied to PPy, have been made. In addition to the biocompatibility of PPy, several studies have shown that the electrical stimulation using PPy doped with p-toluene sulfonate (PPyTS) can modulate the cellular response. Most of these studies were based on the passive adsorption of the biomolecules from serum or on the coating of purified protein solutions at PPy surface. In one of the first studies [66] performed to assess the suitability of CPs to support the cell growth and control the cell function, aortic endothelial cells were cultured on fibronectin (FN)-coated PPy films and exposed to the oxidizing potentials (see **Figure 5**). Oxidized PPy leads to the cell spreading, because the reduction of PPy to its neutral state causes the cell rounding and a concomitant drop in DNA synthesis (≈98%). Despite the changes in cellular morphology, the cell viability and adhesion were very good on both oxidized and neutral PPy.

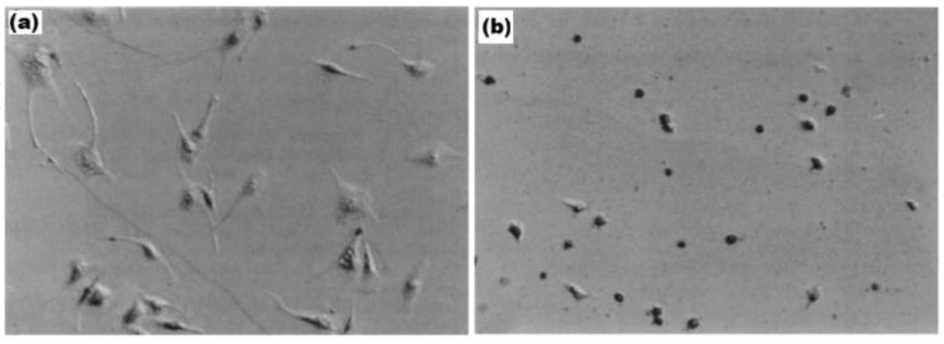

Figure 5. Photomicrograph of endothelial cells cultured on fibronectin-coated PPyTS: (a) PPy in native oxidized state and (b) PPyTs reduced by the application of −0.5 V for 4 h.

Also, in literature many studies on the entrapped biomolecules, for example, adenosine 50-triphosphate (ATP) [73] and nerve growth factor (NGF) [68] in PPy, as well as other CPs for both drug delivery and tissue-engineering applications, exist. The dopant confers to the

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material new properties; thus, function of dopant nature, some specific properties of PPy, needed in tissue applications (e.g., the growth of different cell or specific aspects of wound healing), can be optimized. For example, PPy doped with HA has been synthesized and investigated for tissue-engineering applications, because of HA's inherent role in the wound healing and angiogenesis [8, 13]. According to **Figure 6**, *in vivo* studies realized for PPyPSS films and PPyHA bilayer films showed that the PPyHA bilayer films were biocompatible and promoted vascularization as a result of the HA presence. Both films were implanted in subcutaneous pouches at rats. Tissues surrounding the material were harvested after 2 weeks, fixed, imbedded, and stained with hematoxylin and eosin.

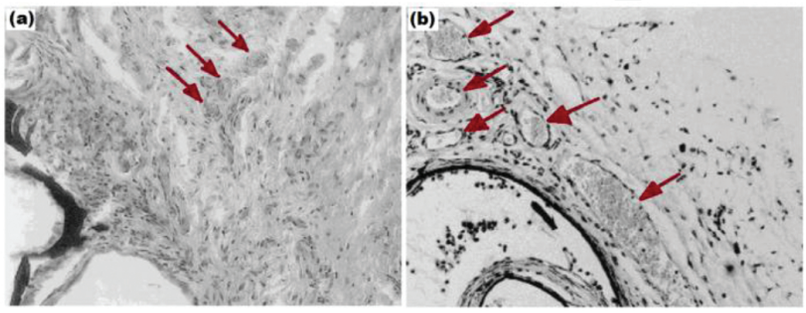

Figure 6. *In vivo* tissue response to PPyPSS films (a) and PPyHA bilayer films (b). The black lines in the images represent the films and the blood vessels are denoted by arrows.

It is important to note that both the surface topography and conductivity are significantly altered when the biomolecules are exclusively used as dopants (see examples in **Figure 7**) [13, 71].

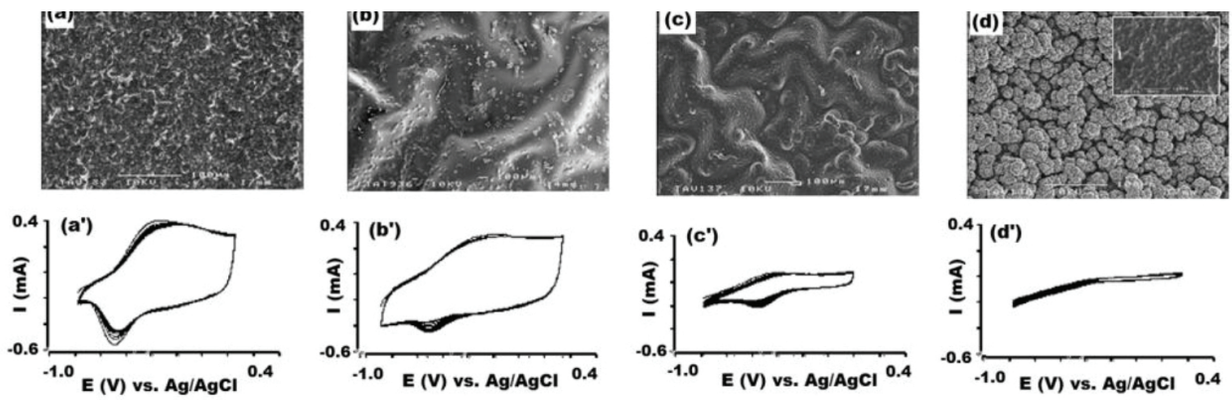

Figure 7. Topography using scanning electron microscopy (SEM) (a–d) and corresponding cyclic voltammograms (CVs indicating electrical activity of the materials) (a′–d′) for thick films of PPyCl (a,a′), PPy doped with poly(vinyl sulfate) (b,b′), PPy doped with dermatan sulfate (c,c′), and PPy doped with collagen (d,d′) (inset is for thin film of collagen-doped PPy). A narrow CV spectrum correlates to decreased electroactivity.

Researchers have shown that the exploration of PANI for tissue-engineering applications has progressed more slowly than the development of PPy for similar applications. However,

recently, there were more evidences concerning the ability and variants of PANI to support the cell growth and PANI's biocompatibility *in vivo* arousing interest to be used in tissue-engineering applications. For this reason, other methods have been sought to modify PANI to render it biocompatible while maintaining the desirable electrical properties of the material. For example, wettability properties of PANI have been modified by the entrapment of a triblock copolymer, [poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO)] (see **Figure 8**) [8, 74].

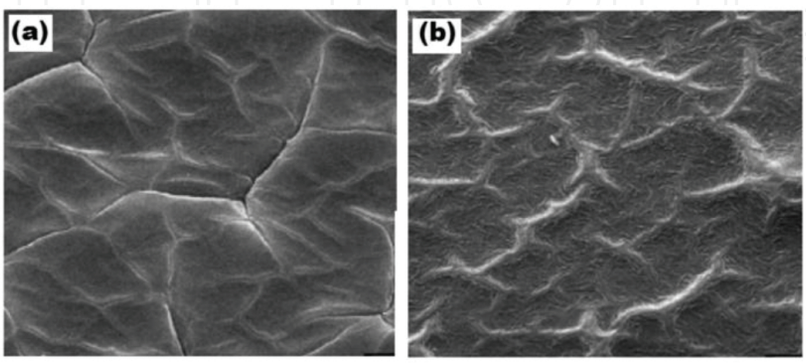

Figure 8. SEM image of PANI films immersed in N-methylpyrrolidinone (NMP) for 300 s followed by dipping in water (a) and immersed in 0.03 g/mL pluronic polymer/NMP solution followed by dipping in water (b) for 20 μm scan area and magnification of 1000x.

Moreover, literature presents that the cross-linked composites of PANI–gelatin exhibit good biocompatibility *in vivo* [8]. Due to the optimal mechanical properties, the gelatins allow it to be electrically spun into fibers, generating three-dimensional scaffolds as a function of PANI:gelatin ratio (**Figure 9**) [75].

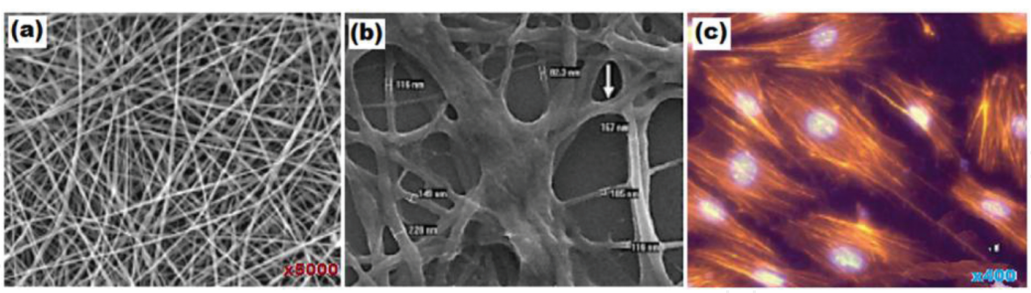

Figure 9. SEM images of PANI–gelatin blend fibers at 45:55 (w/w) ratio (a) and of myoblast cells cultured on 45:55 PANI–gelatin blend fibers (b) and (c) morphology of myoblast cells at 20 h after post-seeding on 45:55 PANI–gelatin blend fibers (staining is for nuclei-bisbenzimide and actin cytoskeleton phalloidin—fibers autofluoresce).

4.2.3. Neural probe applications

Many of the advances made in tissue-engineering applications, especially regarding the neurons, are relevant for the optimized neural electrodes' development. Significant in this research area is the necessity of an interface between the electrodes and neural tissue and

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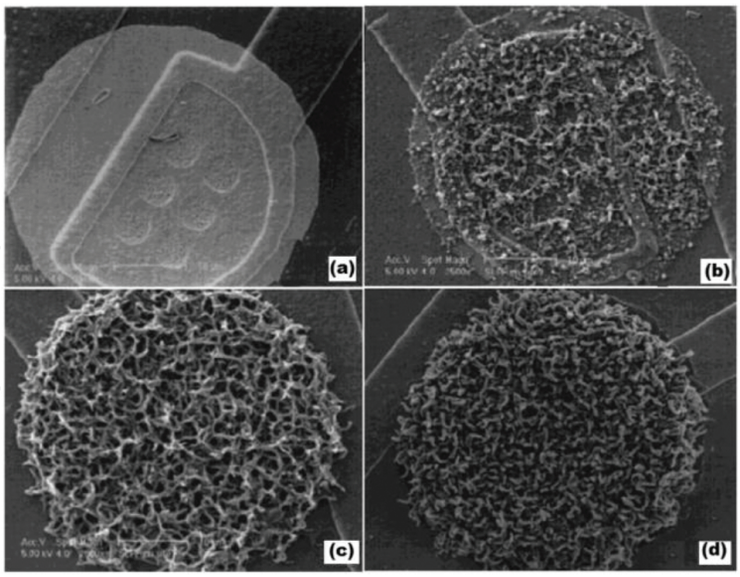

Figure 10. SEM images (a–d) of PPySLPF-coated electrode sites function of the deposition time which increased, corresponding to a total charge of 0 mC (a), 1 mC (b), 4 mC (c), and 10 mC (d). The area of the uncoated electrode is 1250 μm^2 (scan area for all images is 10 μm).

efficient transmission of the signal between the cells and electrode, thus integrating the device seamlessly with the native neuronal signaling network [8]. Therefore, conductive polymers (e.g., PPy commonly explored, PEDOT recently studied) can be considered as potential candidates for neuronal probe applications, due to their special properties, namely, the high surface area and ability to promote an effective ion exchange between the recording sites and surrounding tissue. In this context, George et al. [76] have designed a neural probe, which could also be used as a neural scaffold, starting from PPy doped with PSS or sodium dodecylbenzenesulfonate (NaDBS). The aim of this study was to investigate the effectiveness of an implant specially manufactured by the electrochemical deposition (the dopant and temperature were varied) of PPy on a patterned gold template. It was found that PPy doped with NaDBS is more conductive than PPyPSS, which could increase the signal transportation from the cells to electrode. Moreover, PPy augmented with biological moieties may offer advantages for the neural probe applications. The careful selection of the bioactive molecule is essential to enhance the neuron adhesion, which will increase the signal received from neurons and in the same time, to minimize the astrocyte adhesion, which would interfere with the neuronal signal. For example, a silicon-based 4-pronged neural probe was micropatterned with a layer of gold. Thus, PPy doped with either SLPF (the silk-like polymer having fibronectin fragments) or laminin-derived nonapeptide p31 (CDPGYIGSR) was deposited on the gold sites [77]. The entrapment of these peptide sequences has enhanced the cell attachment, growth, and migration, but at a particular deposition time, the surface area and the conductivity of PPy were maximized. The integration of the probe into the neural tissue and increasing the conductivity lead to an increase in surface area (see **Figure 10**), improving the signal transportation. Finally, it was demonstrated that glial cells preferentially attached to PPySLPF and neuroblastoma cells adhered significantly better to PPyCDPGYIGSR compared to

$PPyCH_3COO^-$, further suggesting the enhancement of electrode–neuron interactions in the presence of PPy doped with bioactive peptides.

In addition to CP modification with peptides, the deposition of the CP within a hydrogel network represents another attractive strategy to better integration of CP with target cells [78]. Hydrogels are attractive, because they are biocompatible and porous and can be tailored to possess the mechanical properties of the surrounding tissue (e.g., brain tissue), thus creating a better electrode–cell interface.

As previously mentioned, PEDOT has recently explored as an alternative to PPy, because it is more stable to oxidation and more conductive. In literature comparative studies concerning the electrochemical deposition of PEDOT and PEDOT–MeOH for the neural probes were presented [79]. Both materials lead to an improvement of the electrochemical stability and surface area increasing, compared to the controls' sample, and implicitly to a decrease of the impedance. The two forms of PEDOT were successfully doped with the laminin-derived DCDPGYIGSR peptide and the rat glial cells preferentially grown on PEDOT–DCDPGYIGSR. PEDOT–MeOH has not been tested *in vivo*, but the advantage of using this CP over PEDOT is that its monomer is more soluble in water, which would permit the polymer synthesis in the aqueous systems that are necessary for the incorporation of many biomolecules. Additionally, future studies will be focused on the depositing agents in order to minimize the immune response, to reduce the encapsulation, and to induce the nerve growth toward the electrode [80].

4.2.4. Drug delivery

Besides biosensors, tissue engineering, and neural probes, there are other important investigations of CPs for biological applications. These include the using of CPs as drug-delivery mediators, actuators, and antioxidants. Many disciplines of science, including the medical, pharmaceutical, and agricultural fields, require the controlled delivery of the chemical compounds [33]. This has been a great challenge, but in present, the use of the conductive polymers as a substrate material for controllable drug-delivery devices promises to overcome this [33]. The molecules linked in such polymers through doping can be expelled through the application of an electrical potential. The fact that they can be porous and show delocalized charge carriers helps to the diffusion of the linked molecules [33]. This represents another reason for conductive polymers to be considered suitable for drug release applications.

In experiments, concerning drug-delivery applications, many therapeutic drugs including 2-ethylhexyl phosphate [81], dopamine [82], naproxen [83], heparin [84], and dexamethasone have already been bound and successfully released from these polymers. By electrical stimulation [84], the release of the heparin from PVA hydrogels covalently immobilized on PPy films has been triggered. There are a few factors that limit the application of the conductive polymers for drug release, namely, the molecules loaded in polymer tend to leach out through diffusion being replaced by other molecules from the polymer's environment [85]. This passive loss of charge becomes worse when a relatively small amount of drug is bounded in polymer. Additionally, both charge and molecular weight restrict the molecules which can be bound and released. This can be easily overcome through the use of biotin–streptavidin coupling; the

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biotin acts as the dopant, while the bioactive molecule is covalently bound to the biotin and then released by electrical stimulation. Another advantage is that the biotin provides more uniform release kinetics. A problem that persists is the tiredness of the conductive polymer with repeated cycles of electrical stimulation: repeated cycles can cause irreversible oxidation in the polymer, which coincide with the dedoping and the reduced conductivity, which ultimately limits its useful lifetime [33].

5. Conclusions

Unlike many other materials, CPs have uses in a diverse array of applications ranging from photovoltaic devices to nerve regeneration. The unique property that ties all these applications is their conductivity and, in addition, ease of preparation and functionalization. This fact is especially true in biomedicine, whether for biosensors or for control over cell proliferation and differentiation. Tissue engineering is a new concept in which cells are seeded on material scaffolds and then implanted in defected part of body. The ability of conductive scaffolds to accept and modulate the growth of a few different cells, including endothelial, nerve, and chromaffin cells, has shown a bright future of this "smart" material in the field of tissue engineering and regenerative medicine.

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