SUMMARY OF THE DISSERTATION DONE

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Conductive Polymers: Opportunities & Challenges in Biomedical Applications

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1. INTRODUCTION

Conductive polymers (CPs) are recognized as a class of organic materials with unique electrical and optical properties similar to those of inorganic semiconductors and metals. CPs can be synthesized using simple, versatile, and cost-effective approaches. They can be readily assembled into supramolecular structures with multifunctional capabilities by using simple electropolymerization processes.1 A diverse array of methodologies have been developed to modify and tune the CPs to integrate and interface them into biomedical applications, including biomaterials and biosensors. Such novel innovations are coveted in various fields of biomedicine such as bioengineering, regenerative medicine, and biosensors, as they could potentially lay the foundation for future breakthroughs. CPs have demonstrated promising capabilities to induce various cellular mechanisms, which broaden their unique applications in the biomedical field. Moreover, they are attractive for various biomedical applications due to their intelligent response to electrical fields from different types of tissues, including muscle, connective tissue, epithelium, and nervous tissue. CPs have been used to enhance the electrical sensitivity, speed, and stability of various biomedical devices and their interfaces with biological tissues. There are various types of CPs known to interact with biological samples, while retaining their biocompatibility; thus, one can expect that CPs could be qualified as viable candidates for use in numerous biological and medical applications. There are a large numbers of CPs, and their classifications are based on their types of electric charge, such as delocalized π electrons, conductive nanomaterials, and ions. In this paper, different types of conjugated π CPs and their unique properties and their synthesis routes will be discussed in depth.

2. CONJUGATED π CONDUCTIVE POLYMERS

Conjugated π polymers are a class of materials with electrons held in their backbones.8 Delocalized π-electrons move freely within the unsaturated backbone to construct an electrical pathway for mobile charge carriers.9,10 Polyacetylene (PA), polythiophene (PT), poly[3,4-(ethylenedioxy)thiophene] (PEDOT), polypyrrole (PPy), polyphenylene, and polyaniline (PANi) are some of the most widely used CPs in 3D tissue engineering scaffold construction for the development of human organs, and their chemical structures are depicted in Figure 1. 11 Table 1 provides a summary of conjugated π conductive polymers, including their formulas, electrical conductivities, and applications.

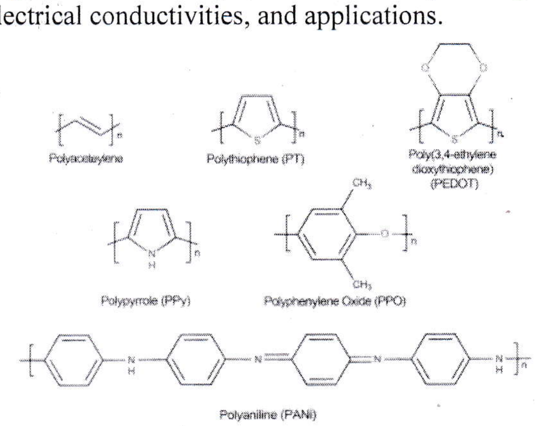


Figure 1. Chemical structures of π-conjugated polymers.

2.1) Polyacetylene

2.1.1. Properties and Structure: PA is, for all intents and purposes, considered to be a Nobel Prize-winning macro molecule.12 PA is a conjugated polymer whose functional derivatives demonstrate multifaceted properties that have been extensively reviewed in the literature. Some of its useful features include electrical conductivity, photoconductivity, gas permeability, supramolecular assemblies, chiral recognition, helical graphitic nanofiber formation, and liquid crystal. The primitive discovery of electrical conductivity in the doped form has generated much interest in CPs, which engendered an exciting field of research on synthetic metals. The chemical structure of PA is a linear polyene chain [−(HC□CH)n−]. Its backbone provides an important opportunity for decoration with pendants due to the presence of repeated units of two hydrogen atoms. Each repeated unit of hydrogen could thus be replaced by one or two substitutes to yield monosubstituted or disubstituted PAs, respectively.

2.1.2. Polyacetylene Synthesis: Acetylene only or other monomers could be used in a number of methods to develop and synthesize polyacetylene. One of the methods is named Ziegler−Natta catalysis and involves the use of titanium and aluminum in the presence of gaseous acetylene. By changing the temperature and amount of catalyst, this method could be a beneficial way to develop polyacetylene while monitoring the structure and watching for the final polymer products. Note that there is a possibility that metal existing in the monomer's triple bonds could occur. Studies show that the polyacetylene could be synthesized by substituting the catalyst with CoNO3/

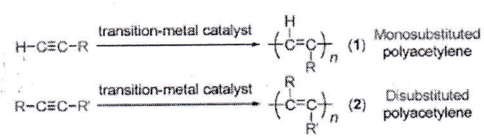
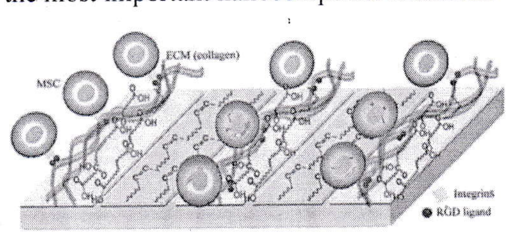


Figure 2. Polyacetylene development. Reprinted from ref 12. Copyright 2005 American Chemical Society.

2.1.3. Compound and Composites: This section explains the use of different materials for hybridization with polyacetylene to improve the conductivity, such as dihexadecyl hydrogen phosphate,21 quaternized cellulose NPs,22 and Au NPs.23 Polyacetylenes are also called acetylene black (AB) or polyacetylene black depending on the preparation method. It is possible that AB derives other substitutions, which does not influence the physical properties such as conductivity and color.

3. Polyaniline

3.1. Properties and Structure: One of the most promising conjugated CPs is PANi, due to it preparation simplicity, high electrical conductivity, and great environmental stability.158 These properties make PANi suitable to be employed on different sensor applications, such as pH switching electrical conducting biomaterials,159 electrically active redox biopolymers, and matrixes for nanocomposite CP preparation.160,161 Thus, tremendous development in PANi-based nanocomposite biopolymer preparation has been done. PANi is the only CP which by protonation or charge transfer doping can regulate the electrical properties. Due to control of the electrical,162 magnetic,163 mechanical,164 and thermal165,166 properties of the organic−inorganic nano composites compared to the organic polymers, they are considered among the most important nanocomposite materials.



3.2. Polyaniline Synthesis: Polyaniline can be obtained from a three-component-state physical mixture of leucoemer aldine [(C6H4NH)n], emeraldine [([C6H4NH]2[C6H4N]2)n], and per-nigraniline [(C6H4N)n]. Emeraldine [([C6H4NH]2- [C6H4N]2)n] is doped with acid and is in the most stable and conductive of the three states of the physical mixture used to obtain polyaniline.

Developing and synthesizing the polyaniline is easy, but on the contray, the mechanism is not as easy. In the process, the oxidant ammonium persulfate is required. Each component is dissolved in acid and slowly mixed. An exothermic reaction results.

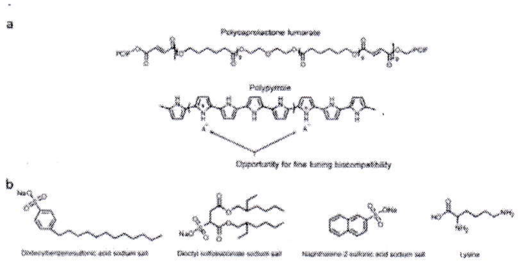
4. CONDUCTIVE COMPOSITE BIOPOLYMERS

Due to their biological behavior in critical substitution and restoration, polymeric tissue engineering scaffold materials have been broadly investigated in TE.184−186 Among the TE scaffold materials that have been employed in recent decades due to their excellent biodegradability and biocompatibility, there are a considerable number of synthetic and natural biopolymers, including polyurethane,187 poly(ε-caprolactone) (PCL),188 chitosan (CS),189,190 collagen,191 polylactide (PLA),192−194 alongside their composites.195−198 New bio materials displaying particular target functions subject to external control or adjustment by surrounding stimulation, such as light,199 electrical signal,200 magnetic power,201 and pH changes,202,203 have recently been investigated.

4.1) Modified Biopolymers with Conjugated π Conductive Polymers:

CPs are an innovative series of materials that have the same mechanical and processing qualities of organic polymers while also displaying the electrical and optical features of metal and semiconductors.204,205 Among these polymers, the ones that have so far attracted the greatest attention for both their scientific and their commercial potential are chemically stable polythiophene, polypyrrole, and PANi, alongside their corresponding derivatives.

4.1.1. Polythiophene: By oxidative polymerization of the parent monomers aniline and EDOT in p-toluenesulfonic acid (p-TSA) aqueous solutions, bilayer nanostructured PANi and PEDOT CP composites have been successfully produced.210 Initially, PANi nanofibers were produced in the p-TSA solution using ammonium persulfate (APS) as the oxidant. Then the PANi nanofibers were coated by PEDOT through EDOT oxidative polymerization, eventually forming the PEDOT/ PANi bilayer nanofibers. The PEDOT/PANi nanocomposite electrical conductivity at room temperature was 2 orders of magnitude greater than that of the PANi nanofibers. In addition, on a glassy carbon electrode, PEDOT/PANi nanocomposites indicated stronger electrocatalytic activity for the ascorbic acid oxidation in comparison with PANi nanofibers.



Structure were not affected by polymerization. In comparison to uncoated PPY, PPy-coated silk fabrics were much more thermally stable, because of the PPy layer protection against thermal degradation. Coated PPy with silk fabrics displayed interesting electrical characteristics. In addition, its resistance decreased exponentially with the increase in PPy concentration or reaction time.

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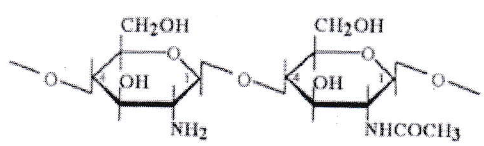
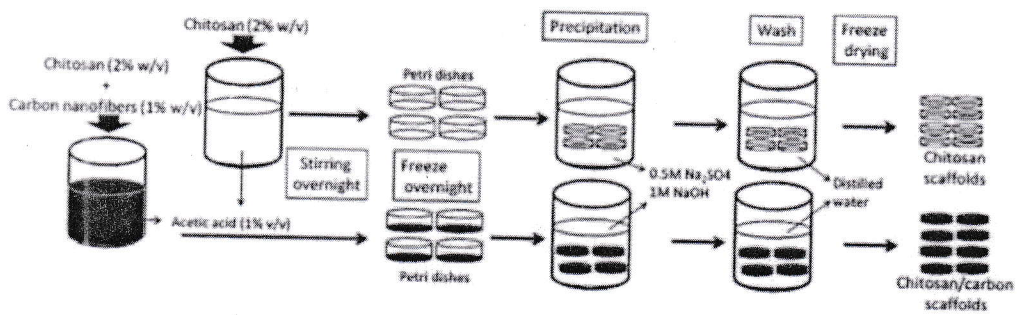
5. MODIFIED NATURAL POLYMERS FOR CONDUCTIVITY

A large number of natural polymers have been modified mainly with conductive filler in the development of conductive natural nanocomposites. The following are examples of the key polymer.

5.1. Chitosan: As potent inducers of chondrogenesis, glycosaminoglycans and GAG analogues can be employed as components in scaffolds for cartilaginous tissues.379 Chitosan, for instance, is a natural polysaccharide that can be purified from the exoskeleton of crustaceans. It is a linear, partially deacetylated chitin derivative consisting of D-glucosamine residues linked by $\beta(1\rightarrow 4)$ glycosidic bonds, randomly interspersed with N-acetylglucos amine residues. It therefore somewhat resembles components of articular cartilage such as hyaluronic acid and certain GAGs, as illustrated in Figure 62. 380 The average molecular weight of chitosan ranges from 50000 to 1000000, depending on source isolation and the preparation methods. The degree of deacetylation varies from 50% to 90% and determines its crystalline properties. Chitin with 0% deacetylation and chitosan with 100% deacetylation give maximal crystallinity, while intermediate degrees of deacetylation give minimum crystallinity. The stable crystal structure means that chitosan is insoluble in alkaline solution. However, chitosan is soluble in acidic solutions below pH 5 as the amino group then becomes protonated. The pH-dependent solubility is a useful characteristic that permits processing under mild conditions; viscous solutions can be gelled either in alkaline solutions or in baths of nonsolvents such as methanol. The strong gel fibers can then be extracted and dried.





5.2. Other Polymers with 3D Network Structure: An example of a 3D network structure polymer is hydrogels. They have 3D networks consisting of cross-linked hydrophilic polymer molecules. Hydrogels are soft, water-filled polymer networks; their mechanical properties could be fine-tuned to different tissues, and they are materials with FDA approval. Hydrogels have been used extensively in clinical medicine, including in plastic surgery as fillers, and are considered a multimillion dollar market. They have huge potential in the field of tissue engineering for a variety of reasons; they have a rubberlike consistency akin to soft tissue, are extremely biocompatible, and allow for convenient regulation of the concentrations of oxygen, nutrients, and other biological substances.401−404 Hydrogels also have been used in a 3D scaffold for repair and replacement of organs405 as well as stem cells406 and drug delivery. The conductive hydrogels represent a class of functional materials which combine the soft-wet feature of hydrogels with the electrical properties of CPs. Applications of conductive hydrogels in biomedicine are growing; these currently include chemical sensors/biosensors and medical devices such as conduits for nerve regeneration, cardiac patches, and deep brain stimulation devices. CP hydrogels have received intense interest in terms of research and development, due to their modifiable three dimensional (3D) matrix. They are promising candidates for bioelectronics and nanodevices for energy applications, due to their hybrid nature, harboring both a conductive nature and also structural integrity.

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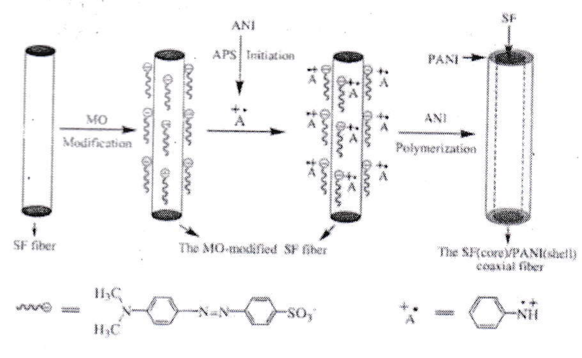
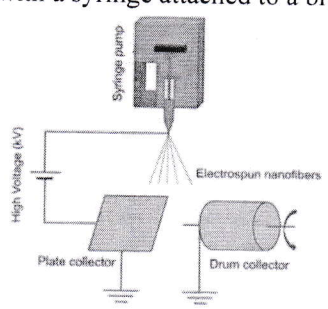


6. FABRICATION OF THE 3D SCAFFOLD USING THE CONDUCTIVE POLYMER

To date, scaffolds with bioactivity were constructed using various methods, including solvent casting and particulate leaching, gas foaming, freeze-drying, electrospinning, phase separation, and deposition.11 The development of scaffolds displaying conductivity is usually undertaken based on electrospinning and deposition.

5.1. Electrospinning: Employed in tissue-associated scaffolds, electrospinning is an economical, fast, and simple approach for construction of fibrous scaffolds.432 Cells are helped to proliferate, migrate, and differentiate by electrospun nanofibers which are able to replicate the natural ECM architecture and are characterized by interlinked pores, high surface area-to-volume ratios, and nanoscaled fiber diameters. Due to the above reasons, the nanofibrous scaffolds produced by electrospinning have been vastly employed in tissue engineering. The three main components of the electrospinning unit are a high electric potential (5−30 kV), a syringe pump with a syringe attached to a blunt needle, and a collector.



7. BIOMEDICAL APPLICATIONS OF CONDUCTIVE POLYMERS

CPs have been used in different biomedical applications, including actuators,446 biosensors,447 neural prostheses,448,449 wound healing, and controlled release systems.450 Further more, CPs have been employed to regulate cell functions via applying ES for electrically excitable cells, including muscle and neuronal cells.89,451 Numerous investigations have shown that ES via a CP significantly improves cell spreading and neurite outgrowth.115,451,452 The design of electrically conducting devices for biomedical and biotechnological applications has become a topic of growing interest.453 Fundamentally, these devices use electromagnetic fields that regulate biological processes to interact with tissues. CPs are being widely studied as suitable candidates for these biomedical devices because of both their electrical behavior and their biocompatibility. Among other applications, CPs have been used as biosensors,85 neural electrodes,454 bioactuators,455 drug delivery systems,456 or tissue scaffolds.457,458 For TE purposes, conducting scaffolds are intended to display similar features (chemical, mechanical, and topological) to the ECM in native tissues, thus behaving as an adequate substrate onto which cells are able to attach and communicate. Furthermore, their electrical properties can regulate cellular functions, including differentiation, adhesion, proliferation, and migration, via ES.459 However, CPs exhibit

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brittleness and poor mechanical properties when used individually. Therefore, the blending of CP with another polymer, generally insulating, results in flexible conducting polymer-based scaffolds. Generally, the polymeric matrix embeds CP moieties, thus improving the mechanical stability and processability of the final product. To obtain flexible CP based scaffolds that recapitulate the structure and function of the ECM, several approaches have been followed by using different polymeric materials as the matrix (elastomers460 and hydrogels)415,461 and microfabrication technology for tailoring topographical and mechanical properties462 and functional nanomaterials, which include nanofibers,463 nanotubes,456 or nanomembranes.464 Interestingly, research pertaining to robust ultrathin membranes made of two macroscopic dimensions and one nanodimension has recently gained attention.465 Although in the past decade several authors have reported selfsupported nanomembranes made of inorganic materials (e.g., silicon, metal, NPs, carbon nanotubes, and grapheme),466,467,427,468,469 the number of studies based on soft materials is still relatively scarce. Recently, a spin-coating method was used to fabricate robust and flexible nano membranes made of a variety of cross-linked synthetic materials (e.g., inorganic−soft material hybrids, thermosetting resins, and photopolymers).470−474 Nevertheless, the bio compatibility and elasticity of these nanomembranes were not comparable to those of basement membranes, which are amorphous sheetlike structures of fibers that underlie the epithelium and play a critical role in cell proliferation, differentiation, and migration. Furthermore, free-standing nanomembranes have also been prepared using biopolymers (e.g., polysaccharides, silk, and biodegradable poly(lactic acid)).

7.1. Tissue Engineering and Regenerative Medicine:

With an aging population, the burdens of fatal diseases such as cancer and organ failure are set to increase. The application of tissue-engineered organs and regenerative medicine such as stem cell and gene delivery to damaged organs are of huge interest to multidisciplinary researchers. The key to success is the development of a functional 3D scaffold, thereby highlighting the potential role of CPs due to their conductivity and surface energies.

7.1.1. Neural System: The capability to govern and manipulate engineered self-assembled substrates at the nano or microscale confers macroscopic physicochemical character istics otherwise not seen in the bulk material. The outcome of this is a degree of functional integration between the physiological systems and manipulated engineered substrates, which was previously not achievable. The field of central nervous system (CNS) neuroprotection and regeneration will significantly benefit from progress in nanotechnology, in parallel with advances in neurophysiology, neuropathology, and cell biology. The goal is to enhance the technologies, via multidisciplinary research, to help achieve the neuroprotection tissue integration and active signaling leading to axon growth. In some scenarios, there are requirements to introduce the substrates to the patients by a neurosurgeon. To lead bionanotechnology toward treatment of neurological disorders to its complete potential, it is critical for neurologists, neurosurgeons, and neuroscientists to engage and devote to the scientific procedure in addition to engineering scientists.478 Debilitating conditions associated with peripheral nervous system (PNS) and CNS damage have fueled a major effort to regenerate injured nerves. The use of autografts is the gold standard therapy for segmental nerve loss, but it has major constraints, such as (1) the challenge of obtaining sufficient sizes and lengths of the necessary donor nerve and 2) the complex anatomical misalignment between the grafted and host nerves.

8. CONCLUSION AND FUTURE PERSPECTIVE

A comprehensive overview of various CPs and their advantages and associated challenges, from synthesis to applications, were fully discussed. To bring CPs into clinical practice, there are some major limitations, which should be properly addressed, including their processability, cytotoxicity, considerable

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gap between in vitro and in vivo outcomes, and suboptimal mechanical and magnetic properties. Thanks to new technologies (e.g., nanotechnology and the 3D printing technique), some of the predetermined limitations (e.g., magnetic and mechanical properties) are being resolved. However, the major obstacle, which is the huge gap between in vitro and in vivo results, needs to be addressed in the future. There is a lack of knowledge with regard to the interactions of CPs with proteins (the protein corona decoration on CPs); such knowledge can help researchers in the field not only to better predict the biological fate of CPs, but also to diminish the gap between in vitro and in vivo outcomes. Taking advantage of the unique properties of CPs, one may expect to direct the corona decoration in vivo, thus facilitating new exciting biomedical applications for these polymers. Fine-tuning the mechanical properties and biocompatibility of CPs is a major challenge in surgical implant applications such as coating electrodes for deep brain stimulation or medical devices for insertion inside biological tissues and organs. This problem has been partially solved with nontoxic chemical functionalization of conductive nanoparticles to enhance their integration into biological tissues. There are some nonbiodegradable CPs functionalized with graphene oxide which seem promising. However, when it comes to bioabsorbable CPs, different limitations are seen due to the inherent inability of CPs to degrade naturally. Attempts have been made to circumvent these problems by blending degradable materials such as polycaprolactone, polylactide, and polyglycolide and their copolymers or ester link ages.504,641,642 Seifalian et al. proposed an alternative to create a CP using a conductive nanoparticle nanostructure holding the scaffold while the backbone of the bulk CP was degraded,504,643 allowing a controllable degradation rate. Nevertheless, more in-depth in vivo studies on the degradation kinetics of bioabsorbable CPs and their nanotoxicology status must be robustly evaluated before embarking on more ambitious undertakings such as clinical trials in humans. Evidently, the application of CPs for use in human biological tissue is still in its nascent stages, although the rate and volume of publications pertaining to their use in biomedicine appear promising.

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