Conductive Polymer Hydrogels

Damia Mawad, Antonio Lauto and Gordon G. Wallace

Abstract Combining electrical properties with synthetic scaffolds such as hydrogels is an attractive approach for the design of the ideal synthetic soft tissue, one that mimics the architecture of the native extracellular matrix and provides the electronic functionality needed for cell–cell communication. Conducting polymers (CPs) are carbon-based polymers that are electronically active and consequently are being investigated as the structural material for fabrication of electroactive hydrogels. CPs are attractive in that they could be processed in various forms, their chemistry could be modified to introduce different functionalities and most important is their capability to conduct electrons. In this chapter, electroconductive hydrogels (ECHs) fabricated from CP either as a single component or as an additive to conventional hydrogel networks are reviewed.

Keywords Conducting polymer · Hydrogel · Electroconductive · Single component · Hybrid

Abbreviations

3D	Three dimensional
AC	Alternating current
ADH	Adipoyl dihydrazide
APS	Ammonium persulfate

D. Mawad (✉)
Department of Materials, Imperial College London, London SW7 2AZ, UK
e-mail: damia.mawad@unsw.edu.au

D. Mawad
School of Materials Science and Engineering, UNSW, Sydney 2052, Australia

A. Lauto
Bioelectronics and Neuroscience (BENS) Research Group, University of Western Sydney, Sydney 2751, Australia

G.G. Wallace
Intelligent Polymer Research Institute, ARC Center of Excellence for Electromaterials Science, University of Wollongong, Wollongong 2500, Australia

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BF	Basic fuchsine
CCG	Chemically converted graphene
CNT	Carbon nanotube
CP	Conducting polymer
CTAB	Cetyl trimethyl ammonium bromide
DC	Direct current
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCI	1,1′-carbonyldiimidazole
ECH	Electroconductive hydrogel
Fmoc	*N*-fluorenylmethoxycarbonyl
FP	Phenylalanine
FTIR	Fourier transform infrared
Gd^{3+}	Gadolinium ion
GO	Graphene oxide
hMSC	Human mesenchymal stem cell
IC	Inhibitory concentration
LMWG	Low molecular weight gelator
MO	Sodium 4-[4′-(dimethylamino)phenyldiazo] phenylsulfonate
PANI	Poly(aniline)
PBS	Phosphate buffer solution
PCLF	Polycaprolactone fumarate
PEDOT	Poly(ethylenedioxythiophene)
PEG	Poly(ethylene glycol)
PMDIG	5,5′-(1,3,5,7-tetraoxopyrrolo[3,4-f]isoindole-2,6-diyl)diisophthalic acid
PPy	Polypyrrole
POWT	Poly(3-((*S*)-5-amino-5-carboxyl-3-oxapentyl)-2,5-thiophene) hydrochloride
PTAA	Poly(3-thiophene acetic acid)
PTh	Polythiophene
QCM	Quartz crystal microbalance
rGO	Reduced graphene oxide
ROS	Reactive oxygen species
SEM	Scanning electron microscopy
SWNT	Single wall nanotube

1 Introduction

The applicability of hydrogels across a range of biomedical applications such as biosensors, drug delivery and tissue engineering is driving researchers to develop 3D networks encompassing new tailored properties such as thermal, optical and electrical conductivities [1]. Electrically conductive hydrogels (ECHs) are attracting

much interest in the field of biomaterial science due to their unique properties, combining a hydrated 3D structure while imparting electronic functionality.

Conducting polymers (CPs) are synthetic polymers that are characterised by their ability to conduct electrons, while providing flexibility and processability. Additionally, their organic nature facilitates their chemical modification to introduce different functionalities meeting specific needs required in the biomedical field. Consequently, CPs gained popularity in more recent years as components of complex systems designed to electrically communicate with physiological tissues such as nerve, brain, muscle and cardiac tissues [2]. These systems could be in the form of electrodes or implantable scaffolds. The capacity to manipulate the processability of CPs into various forms led to the design and fabrication of flexible bioelectronics applicable for a wide range of therapeutics. Processing CPs into hydrated 3D hydrogel scaffolds is an attractive approach to achieving synthetic soft tissue, one that matches the mechanical properties of the native extracellular matrix and preserves the electronic functionality needed for cell–cell communication.

Conversely, achieving this goal is rather challenging due to the rigorous requirements for fabricating a hydrogel. A 3D hydrogel network consists of crosslinked hydrophilic polymers with high water content, exhibiting elastic behaviour and porous internal structures [3]. CPs are inherently rigid due to the conjugated system in the backbone, and thus exhibit high stiffness [4]. The backbone is somewhat hydrophobic in nature due to the aromatic rings in the backbone, which cause π–π stacking of the chains [5]. Also the stiffness is often attributed to unwanted cross links. As such, it is counter intuitive that these polymers might be suitable precursors for the synthesis of conductive hydrogels. However, with the advent of fabrication techniques, composite formulations and development of smart chemistries, researchers have succeeded to overcome many of these limitations. Two main fabrication routes are being investigated for the development of conductive hydrogels. One is to grow the conducting polymer in a prefabricated hydrogel; these are referred to as hybrid systems. The other is to use the CP as the sole polymeric component (continuous phase) in the hydrogel network: this could be achieved either by self-assembly or by introducing water soluble and cross-linkable moieties in the backbone. Subsequently, conductive hydrogels are being developed and tested for a plethora of biomedical applications.

This chapter presents an overview of the current state of conducting polymer hydrogels, with emphasis on 3D-network in which the conducting polymer is the continuous phase. We present an overview of conjugated polymers and their charge transport mechanism. We then briefly introduce the first approach taken to develop electroconductive hydrogels (ECHs) in which the conducting polymer is grown within a prefabricated conventional hydrogel made from insulators. Owing to the emergence of excellent reviews that discuss ECHs, we focus on single component conducting polymer hydrogels. These are 3D-networks formed only from CPs and free of any insulating matrix. We present selected research papers in this field; recent advances and challenges will be highlighted to gain a better insight of various strategies employed. This section will be followed by introducing the role

of other electrically active carbon-based materials such as graphene and carbon nanotubes (CNTs) in the fabrication of conductive hydrogels for biomedical applications. This is an emerging and rapidly growing field that warrants attention.

2 Conducting Polymers in 3D-Hydrogel Networks

2.1 *Conducting Polymers and the Origin of Their Conductivity*

The very first scientific paper reporting on organic CPs and their unique behaviour as semiconductors or metals was in 1977, published in the journal *Journal of the Chemical Society, Chemical Communications* and was co-authored by Shirakawa et al. [6]. The authors reported on the synthesis of polyacetylene and its doping by halogens to produce polymers with remarkable dc conductivity. Consequently, a new class of smart polymers has been introduced driving advances in material science, electronics and biomedical applications. This discovery was acknowledged by the awarding of the Chemistry Nobel Prize in 2000.

Halogenated polyacetylene was described to have electric conductivity due to mobile charge carriers introduced in the π complexes of the polymeric chain [6, 7]. CPs are also known as conjugated polymers because of the structure of their backbone that is formed from alternating single and double C–C bonds (C=C) (see Fig. 1a). Carbon has 3 sp^2 orbitals that lie in one plane and a *p*-orbital that is perpendicular to the plane (p_z) (see Fig. 1b).

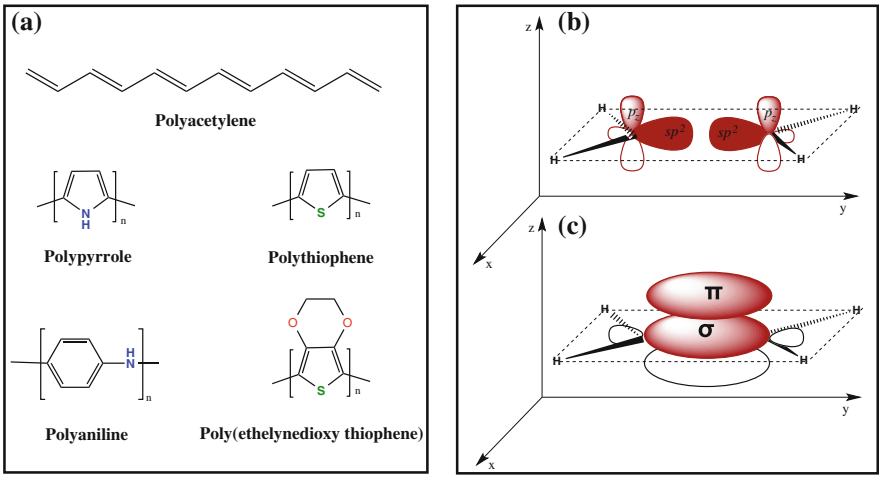

Fig. 1 **a** Chemical structures of conjugated polymers. **b** 2 sp^2 orbitals approach each other to form a σ bond and **c** the 2 p_z orbitals form a π bond which is in parallel to the σ bond plane

When two carbon atoms come close together, two of the sp^2 orbitals overlap forming a σ bond. This in turn brings two of the p_z orbitals in close proximity and they form π orbitals that are delocalized over the backbone chain (see Fig. 1c) [7]. The delocalised π orbitals can be either filled π-bonding orbital which forms the valence band or empty π*-anti-bonding orbital which is the conduction band [8]. These two states have degenerate energy levels [9] that upon excitation can allow charge mobility along the conjugated backbone and thus generating conductivity.

The term "doped" polymer refers to charge transfer to the backbone either by n-type (reduction) or p-type (oxidation). In case of n-type doping, an electron is introduced in the conduction band generating an "electron charge carrier," whereas for p-type doping an electron is abstracted from the valence band creating a "hole charge carrier." Therefore, doping is a mechanism by which an electron is either removed or added to the CP backbone creating unbound charge carriers. The mobility of these carriers is enhanced by the π orbital system of the conjugated backbone [10].

Thus conductivity in conjugated systems depends on the dopant, its type and efficiency to abstract or induce an electron within the backbone [8]. Additionally, conductivity is highly dependent on the mobility of these charge carriers that could occur intra or inter chain [10]. Hence any structural disorder in the conjugated polymer will cause deterioration in its value. Also, the packing of the polymeric chains highly affects the transport of the charges; too much disorder will hinder interchain hoping and dramatically lowers the conductivity.

This is particularly relevant and remains a challenge in the design and fabrication of conductive hydrogels. While electronic conductivity of a hydrogel in the dried state could be determined by standard techniques such as 2 or 4-probe measurements [11, 12], in their swollen state this task becomes more challenging. As the hydrogel swells, conducting polymer chains become further apart which might hinder electron transport [13]. Additionally, hydrogels for tissue engineering are swollen in a buffer at pH = 7.4. This introduces ions into the network, which contribute to ionic conductivity. As such, alternative techniques are sought such as AC impedance spectroscopy to discriminate between the components contributing to each of the electronic and ionic conductivity [14–16].

2.2 Electroconductive Hydrogels (ECHs)

ECH is the term used to describe a hybrid network fabricated from conventional insulating polymers combined with CPs. While the insulating polymer provides the 3D aqueous gel, the CP imparts electrical conductivity to the scaffold. Various synthetic approaches have been developed to fabricate hybrid networks. These include: (i) electro or chemical polymerization of a conducting monomer in a prefabricated hydrogel, and (ii) mixing the precursor monomers followed by simultaneous or step-wise polymerization to produce the ECH (Fig. 2). The end product is a hydrogel network in which the conducting polymer chains are physically entrapped within the conventional hydrogel matrix.

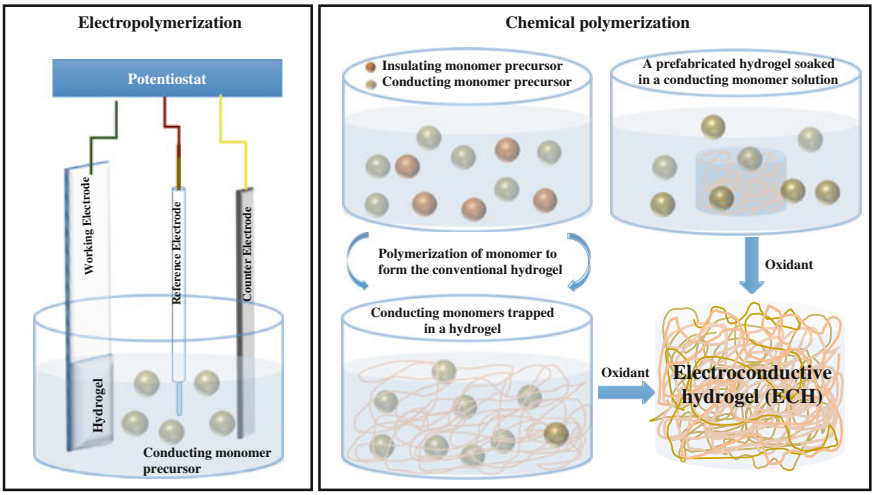

Fig. 2 Schematic representation of approaches developed to fabricate electroconductive hydrogels (ECHs). **Electropolymerization**: a prefabricated hydrogel around a working electrode such as ITO or gold is immersed in a monomer solution such as pyrrole or aniline. By applying either a voltage or a current, the conducting polymer grows in the pores of the hydrogel network. **Chemical polymerization**: this could be achieved in two ways; (i) the monomer precursors of both the insulator and the CP are mixed together, then polymerization occurs either simultaneously or step wise by the addition of the appropriate initiators/oxidants; (ii) a prefabricated hydrogel is soaked in a solution of the monomer precursor of the CP. The monomer diffuses into the pores of the hydrogel. Upon addition of an oxidant, the CP is chemically grown and gets physically entrapped within the network

The first reported ECH was by Gilmore et al. [17] describing the fabrication of a hybrid composite based on polypyrrole (PPy) directly electropolymerised on a preformed polyacrylamide hydrogel. Despite the introduction of the hydrophobic PPy polymer, the hybrid hydrogel retained its hydration/rehydration properties. Additionally, these gels were shown to be electroactive and conductive. This study has opened a new era in conducting polymer science. Owing to the many available hydrogels and a range of CPs, there have been a surge in the number of reports describing the fabrication of ECHs and their application in the biomedical field; these have been discussed in recent reviews [18–22]. Table 1 lists an up to date summary of ECHs reported in the past 10 years.

The ideal ECH network is one that combines both mechanical properties that are comparable to electroresponsive tissues (1–10 kPa) [48] and suitable conductivity for electrical stimulation. In a study by Ding et al. [34], biologically derived conductive hydrogel fabricated from methacrylate modified heparin and polyaniline (PANI) has been fabricated. In the first step, a heparin hydrogel network was formed by UV curing. The hydrogel was then soaked in an aniline solution to allow for the monomer to diffuse inside the porous structure. PANI was formed by oxidative polymerisation. By controlling the aniline monomer concentration, the electrical/ionic properties of the hydrogel could be tailored. Hydrogels formed from 1 and 0.1 M aniline solution

Table 1 Examples of ECHs: type of CP and insulator employed, fabrication technique and the application investigated

Conducting polymer	Insulating polymer	Fabrication route[a]	Application	Refs.
Polypyrrole	Agarose	Chemical	Self-healable electrodes	[23]
	Agarose	Electropolym	Patterned films	[24]
	Poly(hydroxyethylmethacrylate) (HEMA)	Electropolym	Implantable biosensors, bioelectronics	[25]
	Chitosan	Chemical		[26]
	Poly(HEMA)	Electropolym	Glucose responsive biotransducers	[27]
	Oligo(polyethylene glycol) fumarate (OPF)	Chemical	Tissue engineering	[28]
	Poly(HEMAco-PEGMA)	Electropolym	Coatings for implantable biosensors and neuronal prostheses	[29]
	Poly(acrylic acid)	Chemical	Drug delivery	[30]
	Poly(vinyl alcohol)	Electropolym	Drug delivery	[31]
Polyaniline	αCD-containing polyacrylamide (αCD-PAAm)	Chemical	Flexible supercapacitors	[32]
	iota-Carrageenan (ι-CGN)	Chemical	Tissue engineering Electrochemical capacitor	[33]
	Heparin	Chemical	Tissue engineering	[34]
	α-CD-based supramolecular hydrogel	Chemical	Biosensors	[35]
	Polyethyleneglycol diacrylate (PEGDA)	Chemical	Tissue engineering	[36]
	Poly(2-hydroxyethylmethacrylate-co-glycidylmethacrylate)	Chemical	Biosensors	[37]
	Chitosan	Chemical	Actuators	[38]

(continued)

Table 1 (continued)

Conducting polymer	Insulating polymer	Fabrication route[a]	Application	Refs.
PEDOT	Alginate	Chemical	Drug delivery	[39]
	Polyurethane (PU)	Electropolym	Tissue engineering	[40]
	Agarose	Electropolym	Autografts	[41]
	RGD-functionalized alginate	Electropolym	Drug delivery	[42]
	Poly(vinyl alcohol)/poly(acrylic acid)	Electropolym	Optogenetics	[43]
	Fibrin	Electropolym	Tissue engineering	[44]
	Agarose	Electropolym	Tissue engineering	[45]
	Alginate	Electropolym	Bioelectronic sensors	[46]
	Poly(ethylene glycol) methyl ether methacrylate (PPEGMA)/ poly(acrylic acid) (PAA)	Chemical	Soft strain sensors	[47]

[a]Fabrication route: the CP was either formed by chemical or electrochemical (Electropolym) polymerization

had an impedance of 900 and $2 \times 10^4\ \Omega$ at 0.01 Hz, respectively. The storage modulus was in the order of 900 Pa. Additionally, the heparin/PANI hydrogel supported the growth, proliferation and differentiation of C2C12 muscle cells. Runge et al. [28] reported the synthesis of a hydrogel scaffold based on polycaprolactone fumarate (PCLF) in which polypyrrole was chemically grown. The hydrogels exhibited a conductivity of $\sim 6 \times 10^{-3}$ S/cm in their dried state. In comparison to PCLF, neural cells seeded on the PCLF/PPy hydrogels showed better cell morphology denoted by elongated cell bodies, extended neurites and a higher cell number. This hybrid hydrogel presents potential for neural regeneration.

An injectable conductive hydrogel based on collagen and infused with poly (ethylenedioxy thiopehene) (PEDOT) or PPy fibres has been reported by Sirivisoot et al. [49]. Prefabricated PPy or PEDOT fibres were added to a cell-containing collagen solution, followed by its gelation at physiological pH and temperature. The conductive scaffolds supported the growth and differentiation of PC-12 and human mesenchymal stem cells (hSMCs) up to 7 days. Furthermore, compared to the collagen control, the conductive scaffolds induced an increased neurite growth of PC-12 cells. This study presents a simple but elegant fabrication technique for injectable cell seeded conductive scaffolds that could be potentially applied in vivo for nerve, muscle and cardiac applications.

While many of the reported ECHs demonstrated relevant properties for tissue engineering such as appropriate mechanical strength, remarkable hydration and biocompatibility, some limitations remain with the fabrication approach used to develop ECHs. Typically, growing the conducting polymer in a prefabricated hydrogel network, whether by electropolymerization or chemical oxidation, leads to physically entrapped CP chains. Upon hydration in physiological media, these polymeric chains diffuse out of the network causing a drop in conductivity as well as possible cytotoxic effects [50]. When the hybrid network is formed from a negatively charged insulator such as alginate, poly(acrylic acid) or polyacrylamide, ionic interactions occur between the positively charged conducting polymer and the insulator. However, the potential application of these hydrogels in tissue engineering requires incubation in pH = 7.4 which leads to neutralisation of the charges on the CP backbone and consequently dissociation from the network [51].

2.3 Single Component CP Hydrogel

"Single component" CP hydrogel is a term used to refer to conductive hydrogels made from the conjugated polymer as the main continuous phase. The advantage of this approach is to overcome the aforementioned limitations of ECHs. However, this is a rather challenging approach because conjugated polymers lack water solubility, functional side chains and flexibility. Up to date, there are scarce reports on the fabrication of single components hydrogels. Fabrication approaches used include self-assembly of the CP chains, crosslinking either chemically, using metal

ions, or by employing low molecular weight gelator (LMWG). We herein report the studies that investigated synthesis of single component conductive hydrogels and their characteristics.

2.3.1 Polythiophenes

The chemistry of the thiophene monomer is versatile; thiophene could be modified at α and β positions leading to a wide range of chemical structures. Consequently, a great diversity of thiophene-based materials has been prepared such as regioregular oligomers and polymers [52]. For biomedical applications in general and for the fabrication of a hydrogel network in particular, water solubility of the polymeric chains is a pre-requisite. As such, a range of water-soluble polythiophenes has been synthesised as described in a recent review by Das et al. [53]. Figure 3 highlights some of the chemical structures of water soluble polythiophenes used to fabricate conductive hydrogels.

The first reported polythiophene-based hydrogel was fabricated from poly (3-thiophene acetic acid) (PTAA) [54, 55]. The ionisable carboxylic groups on the side chains render PTAA water soluble. Additionally, by using appropriate crosslinkers, the functional carboxylic groups could be linked to form a 3D-network. Chen et al. [55] used adipoyl dihydrazide (ADH) as the crosslinker and *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a condensation agent to form the PTAA gel. The authors showed that conformational changes of PTAA backbone occur in response to the carboxylic groups ionisation under different pH, despite the chemical crosslinking of the polymeric chains. They also reported the electric conductivity ($4 \times 10^{-3} - 2.0 \times 10^{-2}$ S/cm) of the gels doped with 60 wt% $HClO_4$ solution.

Similarly taking advantage of the carboxylic groups on the PTAA backbone, Mawad et al. [56] reported the fabrication of a chemically crosslinked single component PTAA hydrogel (Fig. 4a) using a more amiable crosslinking agent, 1,1′-carbonyldiimidazole (DCI). In contrast to DCC used previously by Chen [55], CDI

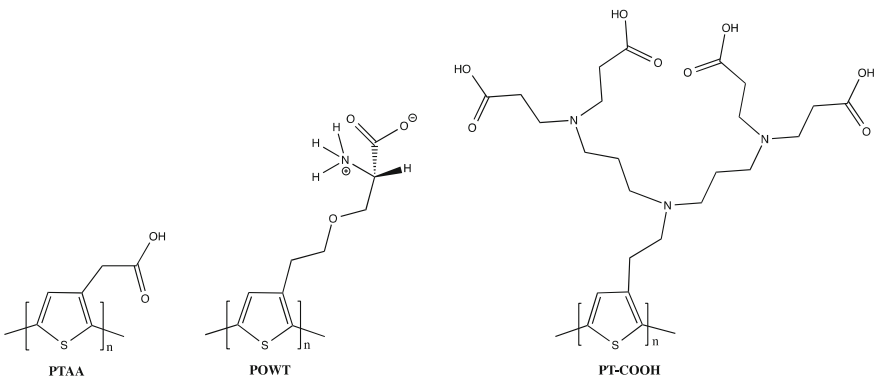

Fig. 3 Chemical structures of water-soluble polythiophenes. *PTAA* poly(3-thiophene acetic acid). *POWT* poly(3-((S)-5-amino-5-carboxyl-3-oxapentyl)-2,5-thiophene) hydrochloride

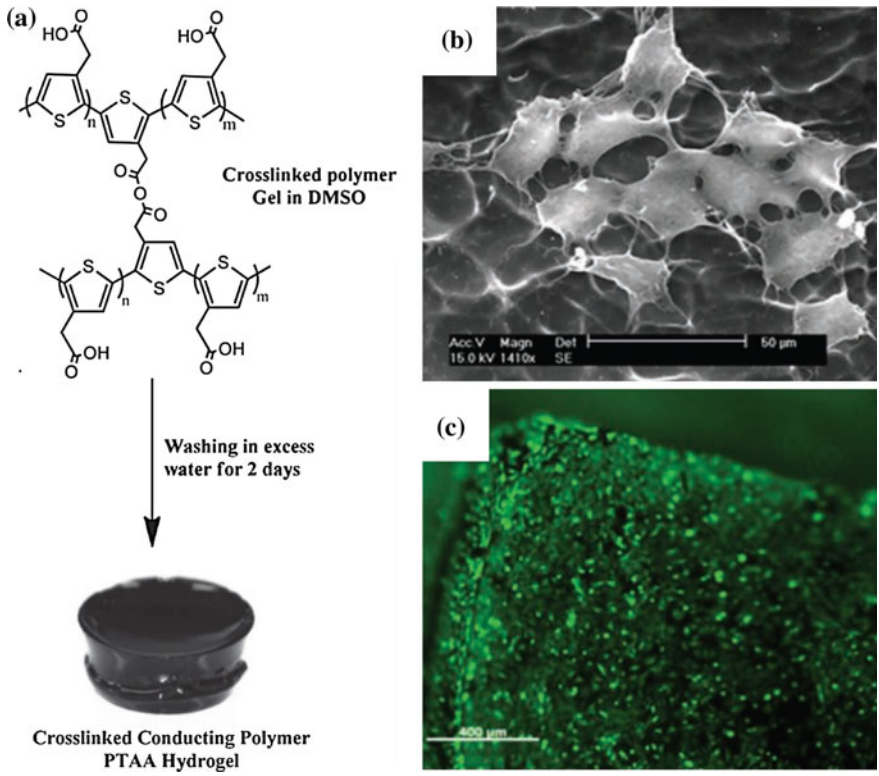

Fig. 4 **a** Schematic illustration of crosslinked PTAA polymeric chains. **b** Representative SEM images of myoblast cells adhered to the hydrogel substrates following 72 h incubation. *Scale bar* represents 50 μm. **c** Fluorescent images of myoblast cells on hydrogel substrates following 72 h incubation. Cells are stained with CalceinAM to visualise metabolically active cells. *Scale bar* represents 400 μm. Reprinted from [56]. Copyright 2012 with permission of John Wiley and Sons

and its decomposition products are water soluble and they could be easily washed from the network. The swelling ratio, internal porous structure and mechanical properties could be tuned by varying the ratio of the crosslinker (DCI) to the monomeric unit of PTAA. The hydrogels supported the adhesion and proliferation of C2C12 cells seeded on their surface (Fig. 4b, c). Of significance was the conductivity ($\sim 10^{-2}$ S/cm) and good electroactivity these hydrogels exhibited in physiological conditions. This is the only reported single component conductive hydrogel that has been tested as a scaffold for tissue engineering. In addition to having functional groups on its side chain, PTAA aqueous solution has been shown to have a half inhibitory concentration (IC_{50}) of 9.1 mg/mL [57], indicating a high degree of tolerance by the cells to this water-soluble polymer. These studies suggest that PTAA is a very promising CP candidate for biomedical applications.

A conductive hydrogel film based on water soluble zwitterionic polythiophene, poly(3-((S)-5-amino-5-carboxyl-3-oxapentyl)-2,5-thiophene) hydrochloride (POWT)

(Fig. 3), has been reported by Asberg et al. [58]. A thin film of POWT was deposited on a substrate from a 0.5 mg/mL POWT aqueous solution. While exposing the POWT film to buffer solutions of different pH, the hydration and stiffness of the film was monitored by quartz crystal microbalance (QCM). The authors reported that a hydrogel forms upon uptake of water and ions from the buffer. This hydrogel exhibited higher uptake of DNA in comparison to the compact POWT film. Since POWT is a conjugated polyelectrolyte, its polymeric chains change conformation after binding to the DNA strands. The authors suggested that by taking advantage of these conformational changes, POWT hydrogel could be applied as biochip for the specific binding and sensing of complementary DNA. Multifunctional hydrogels based on PT–COOH (Fig. 3) and DNA were fabricated by using gadolinium ions (Gd^{3+}) as a chelator. The hydrogel exhibited good swelling properties ($Q \sim 8$) and they were stable in phosphate buffer solution (PBS) for up to 60 h. Jurkat T cells were mixed with the DNA and PT–COOH solution followed by gelation using the Gd^{3+} ion. This is the first example of a conductive hydrogel that could form in situ allowing cell encapsulation prior to gelation. By irradiating the hydrogels with white light, the authors demonstrated that cells could be killed as a result of reactive oxygen species (ROS) produced by PT–COOH–Gd^{3+} complex in response to light.

2.3.2 Polyaniline

One approach to fabricate conducting polymer hydrogels is through the assembly of the polymeric chains with LMWG. LMWG are small organic molecules that can cause water or other solvents to form a network at very low concentrations [59]. PANI-based hydrogels have been prepared using LMWG such as 5,5′-(1,3,5,7-tetraoxopyrrolo[3,4-f]isoindole-2,6-diyl)diisophthalic acid (PMDIG) [60] and *N*-fluorenylmethoxycarbonyl (Fmoc) phenylalanine (FP) [61]. PMDIG-PANI hydrogels were fabricated by preparing a solution of anilinium chloride with the salt of PMDIG [60]. Upon addition of ammonium persulfate (APS), a stable hydrogel was formed after 24 h at 30 °C. FTIR spectra suggested that the supramolecular interactions between PANI and PMDIG are due to strong H-bonding between the two components as denoted by the shifts of both carbonyl and hydroxyl groups of the gelator in the hydrogel structure. The conductivity of the gel was 0.3×10^{-4} S/cm and the elasticity 14.59 kPa. In a similar fabrication approach, FP-PANI hydrogels were prepared and characterised [61]. Good electrical conductivity was achieved (1.2×10^{-2} S/cm) and the hydrogel exhibited a viscoelastic nature. Because of the Fmoc group on FP that can act as a weak acceptor while PANI acts as a donor, the photoconductivity of the FP-PANI hydrogel was investigated. The gel exhibited a reversible photoresponse under white light illumination. Such investigations open the way for the fabrication of responsive gels for applications such as optoelectronics and biosensors.

A conducting hydrogel fabricated from PANI chains crosslinked with phytic acid (Fig. 5a, b) has been prepared by Pan et al. [62]. The phytic acid was both the gelator and the dopant leading to a hydrogel with good electrical properties

(conductivity value of 0.11 S/cm) as well as high water content (~92.6 % wt/wt). Due to the porous structure and high surface area of the 3D network, the hydrogel exhibited high specific capacitance (480 F g^{-1}), and excellent cycling stability (~83 % capacitance after 10,000 cycles). Furthermore, the fabrication approach adopted in this study allowed micropatterning of the gel into various dimensions (Fig. 5c, d). This hydrogel can serve as a promising material for the fabrication of high energy storage electrodes. In a similar study by Zhai et al. [63], the PANI-phytic acid hydrogel was casted as a thin film on a platinum surface, followed by dipping it into a solution of chloroplatinic acid (H_2PtCl_6). Using formic acid, H_2PtCl_6 was reduced to Pt introducing Pt nanoparticles in the 3D network. The Pt/hydrogel electrode was tested as a glucose biosensor and it exhibited ultra-high sensitivity, low detection limit (0.7 µm), and fast response time (3 s).

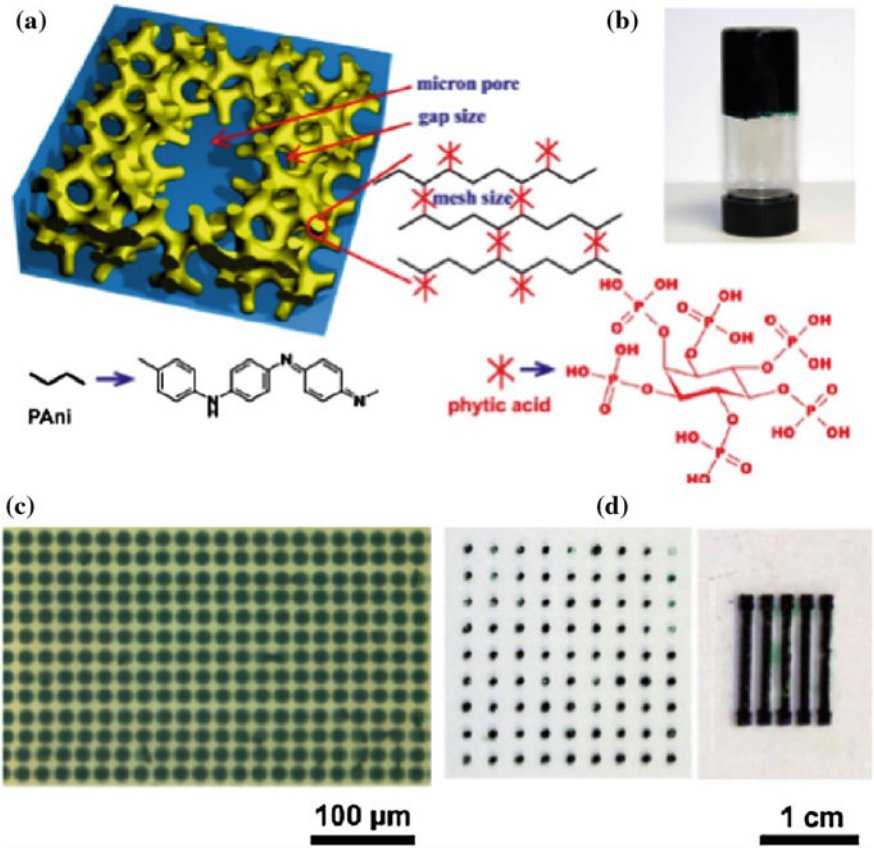

Fig. 5 Doped polyaniline hydrogels: **a** Schematic representation of the 3D network formed by crosslinking polyaniline with phytic acid. **b** Representative image showing the gel in a glass vial. **c** Ink jet printed hydrogel with dot dimension of 18 µm. **d** Patterned PANI hydrogels produced by mask-spray coating with either a dot diameter of 1 mm or line width of 2 mm. Reprinted from [62]. Copyright 2015, with permission of PNAS

2.3.3 Poly(Ethylenedioxythiophene) (PEDOT)

Amongst synthesised polythiophenes, PEDOT is of particular interest due to its high stability in aqueous solutions, high conductivity and versatility of side chains functionalization. To this effect, it has been explored for the fabrication of conductive hydrogels. Hydrogels based on alkoxysulfonate functionalised PEDOT have been fabricated in a one-step reaction by simply mixing the sulfonated EDOT (EDOT-S) monomer with an oxidant such as APS and $FeCl_3$ (Fig. 6a) [64]. Scanning electron microscopy (SEM) revealed that the internal 3D structure of the hydrogels could be controlled depending on the oxidant used (Fig. 6b) and its ratio. Additionally, the authors reported these gels to have conductivities in the range of 10^0–10^2 S/cm depending on the type of oxidant and monomer concentrations employed. The authors explained the formation mechanism of these hydrogels to be due to the ability of the amphiphilic EDOT-S monomers to form micelles in the aqueous solution, which upon addition of an oxidant fuse together and form lamellar sheets evolving into a 3D hydrogel network. In a follow up study [65], these hydrogels were tested for adsorption and desorption of dyes with different charges. Owing to the negatively charged sulfonic groups on the PEDOT side chains, the authors reported a high degree of adsorption (164 mg g^{-1}) of positively charged dyes such as basic fuchsine (BF). Similarly, desorption of the dye was demonstrated by the addition of the surfactant, cetyl trimethyl ammonium bromide (CTAB). By increasing the mass ratio of CTAB to the dried gel, desorption amounts up to 90 % of the adsorbed drug were obtained. These hydrogels exhibited favourable desorption efficiency in comparison to other reported systems [66].

2.3.4 Polypyrrole

The delocalised π-electron system along the backbone of conjugated polymers results in rigid polymeric chains; therefore, it remains a challenge to fabricate conducting hydrogels of high elastic nature. In a recent study by Lu et al. [67], a simple and scalable process has been reported for the synthesis of conductive and highly elastic PPy hydrogels with a conductivity value of 0.5×10^{-2} S/cm. Pyrrole monomer was dissolved in a mixed solvent of H_2O and ethanol (1:1) followed by the addition of equimolar amount of $Fe(NO_3)_3 \cdot 9H_2O$ (Fig. 7a). The gel was formed within several minutes and then left for 30 days at room temperature to undergo an ageing process. Compressive stress–strain measurements showed that aged PPy hydrogels were highly elastic (Fig. 7b); they could be compressed by ≥70 % with a full recovery to their original shape within 30 s. In contrast, PPy hydrogels that were not subject to the ageing process did not exhibit any elastic properties. The authors suggested that the origin of the elastic behaviour as a result of ageing is due to a secondary growth mechanism. Initially, polypyrrole forms immediately upon addition of the oxidant [68]. The insoluble polymers cluster together into spherical particles, then interconnect via π–π interactions leading to a 3D network. Over time, unreacted pyrrole monomers diffuse and oxidatively couple to the surface of these

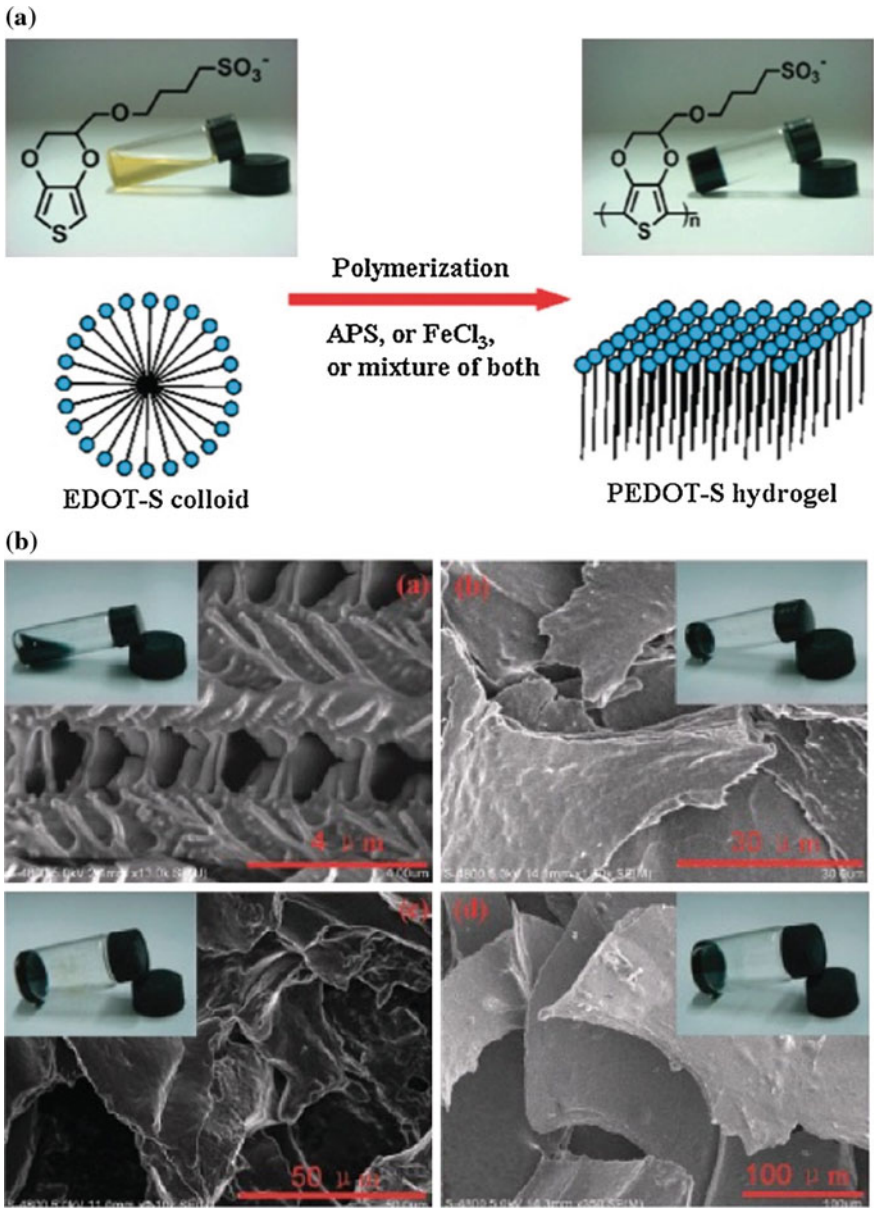

Fig. 6 **a** Schematic representation of the formation mechanism of PEDOT-S hydrogels. The amphiphilic monomers, EDOT-S, form micelles in solution, which upon addition of the oxidant convert into 3D hydrogel network. **b** SEM micrographs showing the internal structure of the gels synthesised by APS (a&b), $FeCl_3$ (**c**), and a mixture of APS and $FeCl_3$ (**d**). Reprinted from [64]. Copyright 2011, with permission of Royal Society of Chemistry

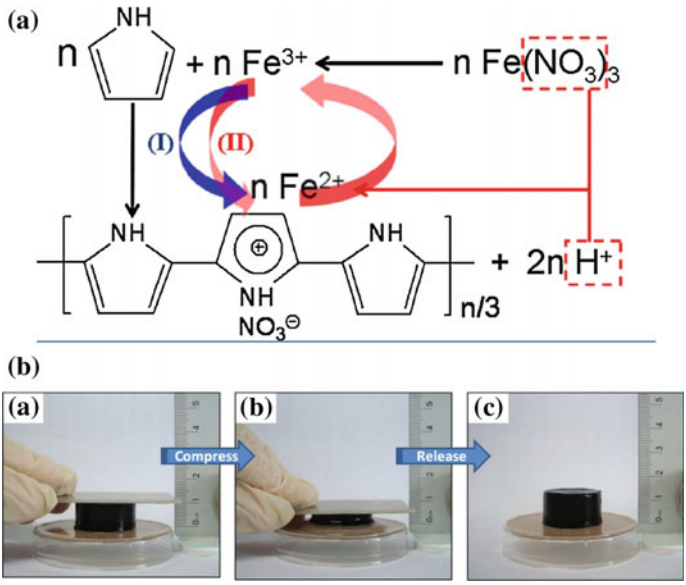

Fig. 7 **a** The polymerization process of polypyrrole by the addition of ferric nitrate. **b** Representative images showing the full recovery of the PPy hydrogels following compression by ≥70 %. Reprinted from [67]. Copyright 2014, with permission of Nature Publishing Group

particles forming protruded branches that eventually join together into building blocks. With ageing, a slow reaction process causes reinforcement of these joint branches, leading to a hydrogel that is less prone to fracturing and of high elasticity. The authors demonstrated the applicability of these elastic hydrogels for the efficient and fast removal of organic molecules from aqueous environments. Using methyl orange as a model dye, the hydrogel exhibited a high absorption efficiency of the dye (99.99 %) in just several seconds. Of significance is the ability to repeatedly reuse and refresh the hydrogel by simply treating it with 2 M NaOH at 80 °C. This highly elastic PPy hydrogel paves the way for the fabrication of elastic conducting hydrogels that have potential application in environmental engineering, biosensors and regenerative medicines.

Other PPy-based single component CP hydrogels have been fabricated by the self-assembly of PPy chains in the presence of sodium 4-[4′-(dimethylamino) phenyldiazo] phenylsulfonate (MO) [69, 70]. MO has a hydrophobic core with hydrophilic sulfonic groups at the side. The hydrophobic core stacks with neighbouring molecules causing MO to self-associate in aqueous media. Thus, MO forms cylindrical structure in water and can be used as a template for the polymerization of PPy microtubules [70]. Under static conditions, these microtubules can aggregate by van der Waals forces or chemical bonding resulting in a PPy conductive hydrogel [69]. The morphology and swelling/deswelling behaviour of these mesoscale networks have been studied in response to the type ($FeCl_3$, $Fe_2(SO_4)_3$, and $Fe(NO_3)_3$) and ratio of oxidant to the pyrrole monomer during synthesis. SEM

micrographs showed clearly that the morphology is highly dependent on the type of oxidant employed, with $Fe(NO_3)_3$ resulting in a more coarse and granulated network. This in turn had an effect on improving the swelling/deswelling properties of the hydrogel with repeated cycles. Additionally, the electrical conductivities were correlated to the hydrated state of the hydrogel prepared using $Fe(NO_3)_3$ as an oxidant. When the gel was shrunk, it exhibited a conductivity of 1.7×10^{-2} S/cm, in comparison to a value of 8.2×10^{-3} S/cm when swollen. The authors suggested that the higher conductivity in the shrunk state is due to the closer proximity between the polymeric chains facilitating electron transport. Also, they demonstrated that the conductivity of the hydrogels could be further tailored by controlling the pH of the media.

3 Carbon-Based Conductive Hydrogels

Other organic-based conductive materials are being explored in biomedical applications. These include materials such as graphene and CNTs that combine both excellent electrical properties with superior mechanical characteristics. For tissue engineering, these two materials are being incorporated in 3D hydrogel networks to fabricate conductive scaffolds for various applications [71, 72].

3.1 Graphene

Graphene and its derivatives, graphene oxide (GO) and reduced graphene oxide (rGO), are emerging materials that have attracted much attention in research due to their unique properties such as high thermal [73] and electrical conductivity [74], remarkable mechanical properties [75] and superior optical transmittance [76]. As such, graphene is being investigated for a range of applications including biological fuel cells, electrochemical biosensors and tissue engineering. A recent review by Wallace et al. [77] presents a comprehensive overview of graphene and its application across the biomedical field. For the fabrication of ECHs, graphene has attracted much attention as filler improving elasticity and the mechanical strength of the hydrogel, while imparting electric conductivity in the system. Similar to CPs, conductive hydrogels based on graphene or its derivatives are either a hybrid or a "single component".

Hybrid hydrogels have been fabricated from graphene or its derivatives and insulating polymers such as polypropylene oxide (PPO)—polyethylene oxide [78], hydroxyapatite [79], polyvinyl alcohol [80], and chitosan [81]. Primarily, graphene has been added to enhance the mechanical properties of these hydrogels. "Single component" graphene-based hydrogels are formed via self-assembly of graphene sheets producing a 3D network [82–84]. The first graphene-based hydrogel reported by Xu et al. [82] was fabricated via a one-step hydrothermal method (Fig. 8).

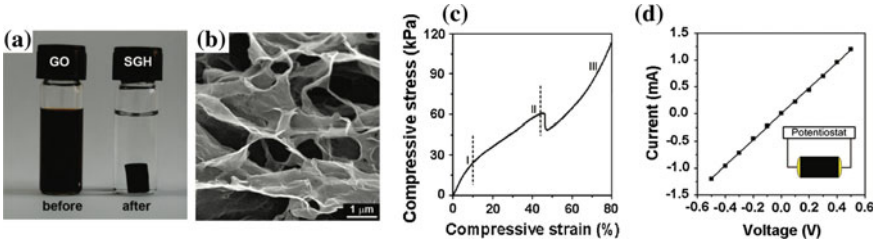

Fig. 8 **a** Fabrication of self-assembled graphene hydrogel (SGH) from a GO dispersion by photothermal reduction. **b** SEM micrograph of the porous internal structure of the SGH. **c** Compressive stress-strain curve of the SGH exhibiting 3 regions: (*I*) linear-elastic regime, (*II*) long plastic regime and (*III*) densification regime. **d** *I–V* curve of the SGH exhibiting an ohmic behaviour at room temperature, measured by the 2-probe technique (shown in the *Inset*). Reprinted from [82]. Copyright 2010, with permission of American chemical Society

A graphene oxide aqueous dispersion was heated up to 180 °C for a period of time causing the graphene sheets to self assemble into a mechanically robust 3D network hydrogel of high water content (97.4 % wt/wt) and elastic behaviour (Fig. 8c). By increasing the heating time from 1 to 12 h, the compressive modulus was varied from 29 ± 3 to 290 ± 20 kPa. Similarly, the conductivity (Fig. 8d) was increased from 0.23 ± 0.02 to 4.9 ± 0.2 mS/cm. In a similar mechanism, chemically converted graphene (CCG), prepared by chemical reduction of GO, has been shown to form a hydrogel film via a simple vacuum filtration process [83]. Gelation occurs during filtration as a result of the deposition of the CCG in a sheet-by-sheet fashion. The obtained product is a highly hydrated hydrogel film (92 % wt/wt) with remarkable conductivity of 0.87 S/cm in the swollen state. These graphene-based hydrogels combine critical properties such as mechanical strength, high electric conductivity and anisotropy due to sheets alignment.

3.2 Carbon Nanotubes (CNTs)

The rationale behind the incorporation of CNTs in hydrogel networks is to design engineered tissue constructs with properties closer to those of native electroresponsive tissue: mechanical integrity [85], nanofibrous architecture [86] and electric conductivity [87]. Subsequently, CNTs have been extensively investigated as additives into hydrogel networks; in particular, these hybrid hydrogels are being extensively investigated in cardiac tissue regeneration [88–90]. Gelatin hydrogels containing SWNTs [90] have been fabricated and tested both in vitro and in vivo as potential conductive hydrogels for the treatment of myocardium infarction (MI). SWNTs were mixed with gelatin solution and crosslinked with glutaraldehyde to produce the hydrogel. SEM revealed that the SWNTs were homogeneously distributed inside the porous structure. Despite the low conductivity of these hydrogels ($\sim 1 \times 10^{-6}$ S/cm), field stimulation revealed that neonatal cardiac cells seeded on

the SWNT/gelatin hydrogel became more compact and in closer proximity in comparison to the control gelatin scaffold. For the first time, carbon nanotube-based hydrogels were tested in vivo for cardiac regeneration. The hydrogels fused with the myocardium infarct causing its regeneration and remodelling. A CNT/gelatin hydrogel exhibiting anisotropic electric conductivity has been fabricated by Ahadian et al. [91]. This could be achieved by vertically aligning the CNTs within the hydrogel matrix through the application of dielectrophoresis (DEP). This anisotropy led to significant increase in the myogenic genes and proteins of electrically stimulated C2C12 cells cultured on the gels.

While CNTs are showing promising properties in tissue engineering, their biocompatibility remains under debate with reports in the literature showing either positive or negative effects [92]. Their toxicity is mainly explained by their small size, which causes increased reactivity and potential inflammation and toxicity. However, the mechanisms by which they induce toxic effects remain to be fully investigated and confirmed [93]. Additionally, it appears that the dosage of the CNTs introduced in vivo plays an important role in the triggered inflammatory reaction and the dosage threshold remains to be identified [94]. However, the attractive properties of CNTs have pushed researchers to investigate ways to enhance their biocompatibility. Functionalization of CNTs with carboxylic groups appears to alleviate this issue. Carboxylated CNTs have been shown to degrade by the enzyme, myeloperoxidase (MPO) into non-inflammatory degradation products [95].

4 Applications of Conducting Polymer Hydrogels

The possibility to develop a crosslinked network that combines porosity, mechanical integrity, high water content with good electroactive properties is driving the use of conducting polymer hydrogels in a wide range of applications including biosensors, drug delivery and tissue engineering.

Electrochemical biosensors are based on an enzymatic reaction triggered on the surface of an electrode that functions as the sensor substrate. Since enzymes are redox active, the reaction either results in electron transfer across the double layer of the electrode producing a current or alters the double layer potential generating a voltage [96]. CPs have been used as the interface between the electrode and the analyte due to their redox active nature. Their doping/dedoping mechanism leads to a change in surface resistance, current or electrochemical potential that could be monitored as a response in relation to analyte concentrations [97]. Additionally, CPs combine both electronic and ionic conductivities lowering the impedance between the electrode and the analyte interface. Subsequently, both ECHs [98, 99] and single component CP hydrogels [62, 63] have attracted particular attention as the interface in electrochemical biosensors since they combine the electro-response of the CP and the ability of the hydrogel to retain bioactive molecules of interest. The CP facilitates the electron transport across the interface [100], the porous

structure provides a large surface area and shorter diffusion length [101], and the high water content exhibited by the hydrogel component enhances the biocompatibility [1].

Conducting polymer hydrogels can serve as responsive drug delivery systems that undergo chemical or physical transitions under applied electric fields. By changing the redox state of the conducting polymer, the charge on the backbone can be varied as well as the volume of the CP scaffold. This in turn can be used to deliver drugs in a controlled manner. Anionic drugs could be easily loaded in the CP during synthesis. Following polymerization, CPs is in the oxidised form and the backbone is positively charged. These positive charges are balanced with anions to maintain electro-neutrality. Thus, negatively charged drugs can serve as the counterion and could be loaded during the polymerization process. Upon reduction, the CP backbone converts from a positively charged state to a neutral form; thus loosing the drug anion and causing its release [102]. Cationic drugs could also be loaded in CP networks. This could be achieved by electrostatic and hydrophobic interaction between the drug, the CP backbone and the anionic counter ion [103]. Alternatively, the cationic drug can be loaded post synthesis and following reduction of the CP network. Highest loading efficiencies could be achieved if the counterion has a large molecular weight. When the CP is reduced, it looses its positive charges allowing the cationic drugs to be attracted to the polymer backbone and to interact with the negatively charged counterion physically trapped inside the matrix [104, 105]. However, the application of conducting polymer hydrogels in delivery systems is limited by the low loading efficiency that could be achieved and the passive diffusion of the small counterions from the network.

One important application of conducting polymer hydrogel is tissue engineering. These systems are ideal candidates to serve as a 3D network for cell seeding and regeneration. The hydrogel component provides the hydrated environment needed, the porosity for exchange of nutrients, and the mechanical integrity to support the cells and promote their adhesion. On the other hand, the CP component provides the electronic communication required in electroresponsive tissues such as the heart, brain, muscle and nerve [20, 22]. Conductive hydrogels have shown promising results in regenerative medicine [106] and as highlighted throughout this chapter, many of the developed ECHs promote cell adhesion and proliferation; however, their long-term use remains limited by the degradation in their electronic properties after incubation in physiological conditions due to dopant loss.

5 Conclusion and Future Perspectives

In this chapter, the synthesis and use of conducting polymer hydrogels for biomedical applications have been reviewed. Two types of hydrogels were highlighted based on their fabrication routes. ECHs or hybrid networks are formed by incorporating the conducting material in insulating hydrophilic networks. Single component conducting hydrogels are formed by either self-assembly of the

conjugated polymeric chains or by modifying the CP with water soluble and chemically crosslinkable moieties.

Until now, the incorporation of CPs in a prefabricated hydrogel network has dominated the field of conductive hydrogels. Advances in fabrication techniques have enabled smart multifunctional conductive hydrogels with tailored architectures to promote cell alignment, release of biomolecules under demand, and growth and differentiation in response to electrical stimulation. The synthesis of single component conducting polymer hydrogels offers the possibility of tissue-engineered scaffolds with enhanced electrical properties. Designing a network free of an insulating matrix but made from conjugated chains improves the efficiency of electron transport in the system. Additionally, chemical binding or self-assembly of the CPs chains results in a more stable network that is resilient to environmental changes such as pH. With the advent of smart chemistries, the possibility to design single component conductive scaffolds with tailored properties more suited to tissue engineering should be more feasible. The field will greatly benefit from conjugated polymers that are water soluble, regioregular, have good electron transport and contain side functional groups that could be either decorated with relevant biomolecules, used as crosslinking sites, or modified with biodegradable linkers.

The search for the ideal tissue-engineered scaffold remains on-going. Concerning the introduction of electronic properties, CPs along with graphene and CNTs are the most promising candidates due to their flexibility, processability and functionalization. However, this field is still in its infancy and much work is required to develop a practical biomedical device with superior electronics and one that could be used in the clinic.

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