Poly(3,4-ethylenedioxythiophene):poly(styrene sulfonate) in antibacterial, tissue engineering and biosensors applications: Progress, challenges and perspectives

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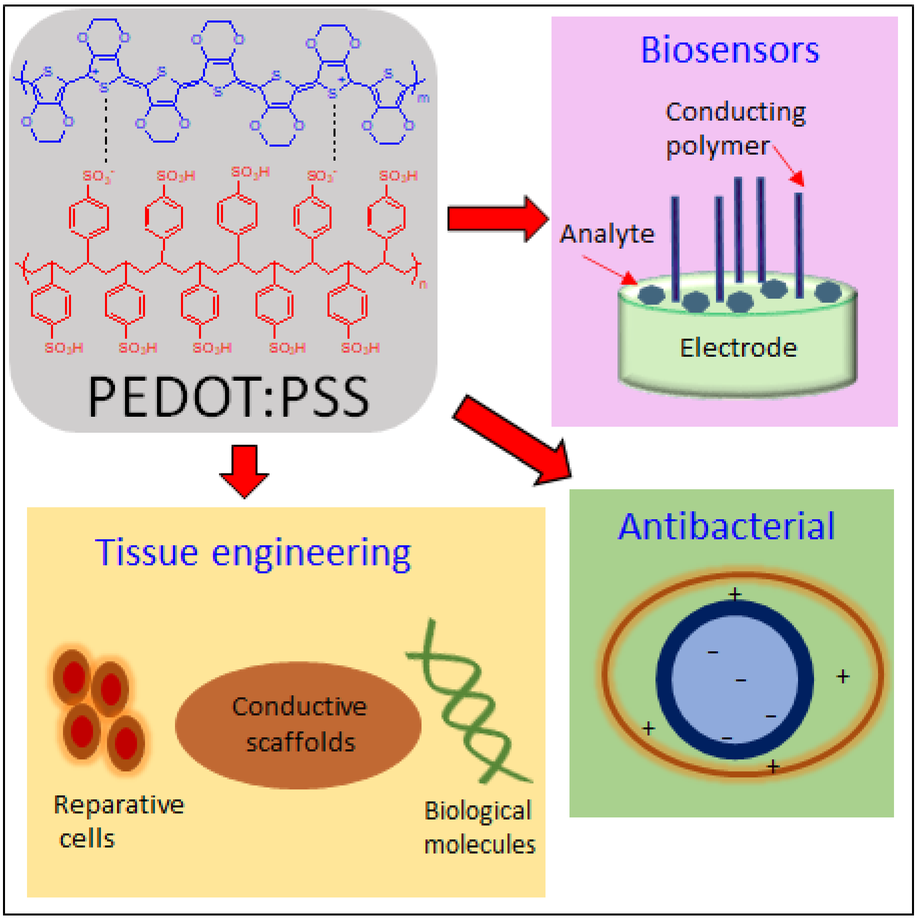
Abstract

With the advancement of applications in biomedicines and bioelectronics, conducting polymers have attained huge significant attention. For such applications, poly(3,4-ethylenedioxythiophene):poly(styrene sulfonate) (PEDOT:PSS) is considered a potential conducting polymer because of its low cost, considerable stability, high conductivity and mechanical strength. Most importantly, its easy aqueous solution processability makes it more attractive. Over the last few years, PEDOT:PSS has been predominantly explored and investigated for different optoelectronic flexible devices, and recently it has been studied for biomedical applications.PEDOT:PSS based materials have made progress in biomedicines due to their properties such as biocompatibility, cell proliferation, antibacterial, non-toxicity, etc. To adjust the desirable properties, special attention is required for altering the structure of PEDOT:PSS material. PEDOT:PSS offers excellent antibacterial properties against both gram-positive and gram-negative bacteria. Moreover, PEDOT:PSS demonstrates an important role in sensing human body humidity, pressure control, glucose detection, as well as employed in human sweat sensors. Besides these, PEDOT:PSS has been studied as a scaffold for endothelial cell preservation. There are several issues which need to be resolved in the future, such as improved biocompatibility and stability to explore the PEDOT:PSS based composite materials in biomedical applications. However, a related review article is lacking, directed on the PEDOT:PSS biomedical applications, namely, antibacterial, tissue engineering, and biosensing. Therefore, the current article summarizes importance of PEDOT:PSS for

biomedical applications, and main emphasis is given to its recent advances, challenges and perspectives.



Keywords: PEDOT:PSS, antibacterial, biosensors, tissue engineering, biocompatibility

1. Introduction

Across the world, there has been a tremendous rise in the human population suffering from various diseases and severe illnesses that sometimes may lead to death. The requirement of health safety for an individual in the world is one of the major concerns of a scientific community. The ample medicines, antibiotics, and medical devices are available in the market for helping, curing, and thus improving the quality of life to some extent.[1] Infectious diseases caused by different microorganisms are inevitable and have become a topic of discussion. Many bacterial and viral diseases have been treated, but the threat of occurrence of new infections is unavoidable and their prevention and treatments are necessary.[2,3] Bacterial diseases such as tuberculosis, typhoid, cholera, etc., are considered some of the deadly infectious diseases that affect millions of the world's population each year. According to World

Health Organization, in 2019 globally 1.4 million deaths were reported and around 10 million people, consisting of 1.2 million children suffering from tuberculosis.[4] Every year, around 1.5–4.0 million people are falling ill due to acute disease, cholera, and 100,000 deaths are reported around the world.[5] Penicillin, the first antibiotic to treat bacterial infection was discovered in the early twentieth century and later ceftaroline, tetracyclines, quinolones, etc., were also applied. A bacterial infection is a major challenge as these bacteria may cause different diseases, consequently leading to allergies and ultimately death, and is considered as one of the most expensive treatments.[6] The prevention of growth of these bacteria is a major concern, and in the last two decades, many materials have been developed and introduced as antibacterial.[7] To these classes, a variety of inorganic nanomaterials such as titanium (Ti)[8], silver (Ag)[9], copper (Cu)[10,11], gold (Au)[12], etc., and metal oxides nanoparticles including zinc oxide (ZnO)[13], magnesium oxide (MgO)[14], and calcium oxide (CaO)[15], etc. were used throughout the centuries as antibacterial materials and applied in biomedical devices. [16,17,18,19,20,21] However, despite their successful antibacterial results, the high cost of Ag and Au nanoparticles restrict their widespread applications.

Besides inorganic materials, polymeric materials, due to their tunable structures turned out to be a desirable antimicrobial materials[21.] In general, polymers can be categorized into natural polymers with intrinsic antimicrobial properties and polymers whose surface can be modified to impart antimicrobial activity [22]. The development and designing of antimicrobial polymers are essential for the food industry, water treatment and countless biomedical and health care sectors. With the growing use of numerous biomaterials and external devices used in human body, there is a risk of bacterial infection. Mostly, polymeric materials exhibit antimicrobial properties and have a positive charge, whereas a negative charge is carried by the bacterial cell walls. Thus, the interaction between the cationically charged polymers and anionically charged bacterial cell membrane, results in the destruction of the bacterial cell growth [23 , 24]. Additionally, polymer scaffolds are considered one of the most extensively studied materials which enable cell proliferation for engineering or regeneration of human tissues. The complicated arrangement of tissues in the human body can sometimes lead to diseases and thus, establishing novel devices or strategies for the damaged tissue repairment has become necessary. The scaffolds should provide not only a large surface area but should have the ability to attach to the cells.[25] Chitosan (CS), glycogen, and polyethyleneimine are some of the most frequently used materials [20,26] in tissue engineering. The increased use of medical devices in humans has also arisen the risk of bacterial infection. Indeed, polymeric materials owing to their intrinsic antimicrobial properties, have successfully gained attention in the fabrication of medical devices. Biosensors are one such extensively studied device because of the advantages such as low cost, sensitivity, and selectivity, thus making their contribution to forthcoming generation health care sectors.[27] Conducting polymers are one of the class of polymers that possess antibacterial and antifouling properties. This expects them to be promising candidates in biomedicine. Conducting polymers based material is considered to be applied to various antifouling coatings or antifouling biomaterials, tissue engineering and biosensors.[28]

2. Importance of conducting polymers in biomedical applications

The conducting polymers comprise alternate single and double bonds, which are responsible for their semiconducting properties, and can even behave as conducting metal. The presence of covalent, Van der Waals, electrostatic forces and dopant make conducting polymers flexible and soft, thus making them different from inorganic materials.[29] Moreover, compatibility with the biological entity is an important factor for commercialization in the field of clinical application. Limitless efforts have been made in the development of conducting polymers with emphasis on the ease of synthesis, low cost, environmentally friendly, and biocompatibility. The facile modification in the π backbone or by side group substitution can tune the optical, electronic, biological, stability, solubility and mechanical characteristics etc. of the conducting polymers.[30] Simultaneously, structural modification is also a subject of concern for researchers to improve the mechanical strength, chemical stability, optical and electronic properties for their diverse applications.[31] Other relevant properties such as antibacterial, non-toxicity, and electrical stimulations enable conducting polymers potency in the biomedical field (Figures 1a and 1b).

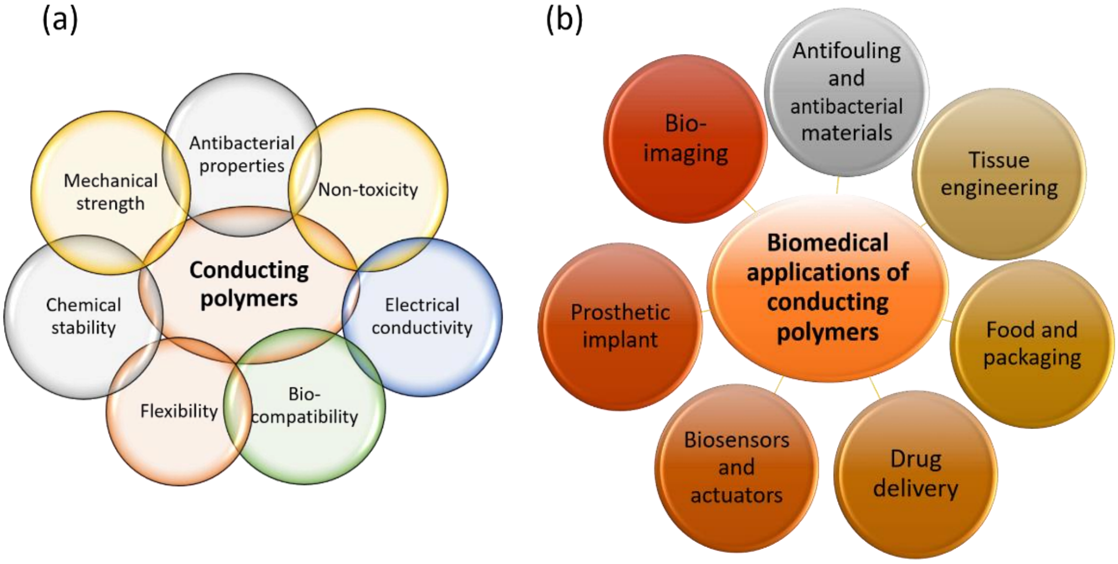


Figure 1. (a) Properties and (b) applications of conducting polymers in biomedical field.

2.1 Properties required for antibacterial activity

The structural properties of bacteria play a crucial role in describing the antibacterial effect. In general, bacteria consist of a cell wall, based on which bacteria can be categorized into gram-positive and gram-negative. Gram-positive has comparatively a thicker cell wall than gram-negative bacteria, and both the bacteria have cytoplasmic membranes. These membranes are phospholipid sheets having anionic lipids which are responsible for negative charge on the bacteria. For the eradication of bacteria, cytoplasmic membranes are considered as an efficient target.[23] The antibacterial mechanism is generally explained by the electrostatic forces acting between the polymers and the bacterial cell wall. Cationically charged antibacterial agent enters into the bacterial cell membranes, and this disturbs the integrity of membrane, ultimately killing the bacteria[28] (Figure 2). The conducting polymers such as polyaniline (PANI)[32], polypyrrole (PPy), poly(3,4-ethylenedioxythiophene) (PEDOT)[33], and their composites [34,35,36]with metal or metal oxides such as Ag [37,38], Au[39], palladium (Pd) [40], copper oxide (CuO) [41] and ZnO [42] for imparting antibacterial properties are well reported in the literature.[43,44,45] For instance, a composite of polypyrrole with dextrin exhibited antibacterial activity against the gram-positive and gram-negative bacteria.[34] Also, enhancement in antibacterial properties of PPy synthesized via chemical polymerization of pyrrole in the presence of acriflavine hydrochloride dye was reported.[46] Further, the antimicrobial activities of PPy or PANI coated fabrics with the help of

Ag nanoparticles and PPy aerogels in composition with the cellulose were demonstrated.[47,48] Similarly, functionalized polyaniline was examined for the antibacterial properties against Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus) bacteria as reported by Robertson et al[49]. They proposed that via hydrogen peroxide production, hydroxyl radicals formation take place which can be responsible for perturbing bacterial cell growth. For this study, the PANI surface was functionalized using poly(3-aminobenzoic acid) and then ATP synthase was targeted. This promoted oxidative and acid stress, which further reduced the cell viability.[49]

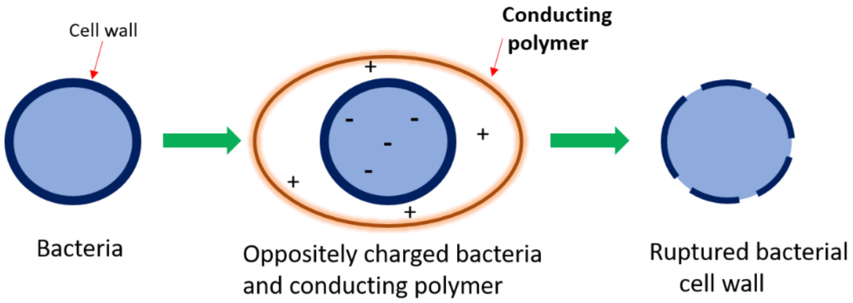


Figure 2. Antibacterial action of conducting polymers.

2.2 Properties required for tissue engineering

Tissue engineering is a branch of biomedical sciences. It aims in maintaining, repairing and replacing a variety of tissues by connecting reparative cells, biological molecules and scaffolds, etc.[50,51] These scaffolds have biodegradability and compatibility with the host unit, showing suitable mechanical properties and salient features for the transfer of the nutrients or removal of toxic wastes.[52] Classically, biomaterials include ceramics and polymers for scaffold fabrication in tissue engineering. Extensively used ceramics materials, such as tricalcium phosphate and hydroxyapatite (HA), were reported for bone tissue regeneration as they possess mechanical stiffness and bio-compatibility. However, the brittleness offered by the ceramics limits their usage in modelling for implantation, and thus could not be used for clinical purposes. Polymers such as collagen, gelatine, chitosan, polyurethane, polycaprolactone (PCL) are some of the natural and synthetic polymer scaffold materials.[53,54] Polymers allow easy structure tailoring and are biologically active, which make cell adhesion possible and exhibit biodegradability. However, the poor mechanical stiffness of polymers hampers their orthopaedic applications, and thus the introduction of ceramics was proposed to prepare composite scaffolds using polymer.[55] For example, the composite scaffold of poly(D,L-lactic-co-glycolic acid) with HA, demonstrated excellent mechanical properties, with promising cell growth.[56,57]With the progress in tissue engineering, conducting polymers based scaffolds were also applied to restore, replace and repair injured or damaged tissues.[58] Studies showed that conducting polymers, due to their electroactivity, can provide the regeneration for cardiac, bone, or nerves via cell growth, proliferation, adhesion, migration, or differentiation. [59] Additionally, the highly conductive conducting polymers composites were investigated as they provided nanostructures similar to naturally occurring materials.[60,61] Furthermore, with the introduction of carbon based biomaterials such as carbon nanotube (CNT), graphene, etc., superior properties, such as high conductivity and mechanical strength were achieved by conducting polymers for tissue regeneration.[62] Conducting polymers suffer from limitations, such as the rigid structure of PPy and its poor solubility, which constraint their widespread biomedical application.[63] PANI is also another most studied polymer and its composites with Ag, Au, and CNT, etc., were also tested for applications in a variety of biomedical disciplines, but the poor processability and non-biodegradability are the serious concerns of PANI.[64,65]

2.3 Properties required for biosensors

Biosensors are analytical devices mainly comprising of two components.[66] The first component includes cells, enzymes, nucleic acid, antibodies, etc. These are sensitive and interact with the chemical species in a living body under examination. The second component, the transducer helps in recording the interaction between the biological part with the analyte in the form of signals such as electrochemical, thermal, or optical. [67] The conducting polymers[26], carbon-based materials such as CNT[68], graphene[69,70]and metal nanoparticles[71] are used as electrodes in biosensing applications. The flexibility, solution processability, and low cost are the advantages of conducting polymers materials. Moreover, the conducting polymers have exceptional π bonding, responsible for the delocalization of electrons and provide a path for the charge mobility, contrarily to their inorganic counterparts. The conducting polymer is used as an electrode in an electrochemical biosensor and an analyte under examination is fixed on the conducting polymer's surface. The recognition element is attached to the conducting polymer electrode, and the physical adsorption between the molecules and the conducting polymer surface plays a significant role to work it as a sensor. The aforementioned properties exhibited by conducting polymers assure extensive applications in biomedicine.

3. PEDOT:PSS for biomedical applications

PEDOT and its derivatives have shown huge interest in biomedical applications due to their excellent properties such as conductivity, stability, electrochemical, biocompatibility and, easy preparation.[72,73] The well-known *p*-doped PEDOT, i.e PEDOT:PSS is water soluble, which allows its facile and environmental friendly synthesis and thus is one of the commercialized materials that have gained attention in different fields[74]. As a polymeric material, PEDOT:PSS has been well-studied as hole transport layer (HTL) in organic light emitting diode (OLED) [75,76], organic/perovskite photovoltaic [77,78,79,80], electrochromic materials [81,82,83], capacitors[84],[85], as well as is being explored in biomedical applications.[63,86,87 ,88 ,89,90]

Conducting polymers including PPy, polythiophene, PANI, and their derivatives because of their rigid π conjugated backbone and the stacking force in between the molecules enable them hard to dissolve and even their degradation becomes difficult below their melting point. Indeed PEDOT is highly conducting in a doped state, but its insolubility restricts several applications. [91 , 92] However, EDOT unit with the electrolyte PSS by oxidative chemical polymerization results in a solution-processable blue coloured polymer known as PEDOT:PSS. The chemical structures of PEDOT, PSS and PEDOT:PSS are shown in Figure 3. The PSS is a colorless negatively charged polymer, which assists in balancing charge as a counter ion. It also helps in the dispersion and stabilization of PEDOT moieties in water, in contrast to its insulating character. Different processing techniques were used to enhance the conductivity by eliminating surplus insulating PSS. This provided not only separation of phases but also tunable morphology. Acids, polar solvents or ionic liquids helped in increasing the electrical conductivity of PEDOT:PSS.[93] In addition to its promising conductivity, its flexibility and chemical stability make it substituent for conventionally used materials in biomedical applications. The metal electrodes of Al, Ag, and Cu are rigid, robust and suffer from surface oxidation which is responsible for conductivity loss.[94] Previous report demonstrated Au electrodes for skin applications due to its biocompatibility and ductility, but its high cost is one of the major disadvantages.[95] Conducting polymers, specifically PEDOT:PSS is an extensively used material for biomedical applications due to its diverse advantages. Firstly, the cytocompatibility and biocompatibility of PEDOT:PSS in vitro were demonstrated, for example, poly(ethylene glycol)diglycidyl ether (PEGDE), an efficient anti-immunogenic and cross-linking agent was used in combination with PEDOT:PSS, subsequently leading to the higher conductivity and improved hydrophilicity of PEDOT:PSS. Also, PEGDE helped in enhancing biocompatibility. [96] Another study revealed the interaction of epoxy moiety of glycidoxy propyltrimethoxysilane with PSS units of PEDOT:PSS, for potential applications in bioelectronics, flexible and electrochemical devices. [97] Jeong *et al.* reported the high conductivity of PEDOT:PSS films via hydrothermal treatment approach that can contribute to bio-signals monitoring medical devices.[94]

In this review, we have provided an overview of the recent development in PEDOT:PSS based materials for biomedical applications. Figure 4 shows the number of research articles published from 2016 to 2021 (keywords used; antibacterial, tissue engineering or biosensor PEDOT:PSS) via a web of science. As for PEDOT:PSS based materials, a lot number of articles were published in optoelectronics, however, there are very few reviews on biomedical applications [98,99, 100,101]. The current article is aimed to cover this gap. The article is divided into three major sections, comprising of antibacterial, tissue engineering, and biosensing applications. The recent advances on PEDOT:PSS based materials and its potential properties such as biocompatibility, mechanical strength, cell proliferation, antibacterial, non-toxicity, etc., are described. It is presented that special attention is a prerequisite for tuning the structure of PEDOT:PSS to adjust the desirable properties.

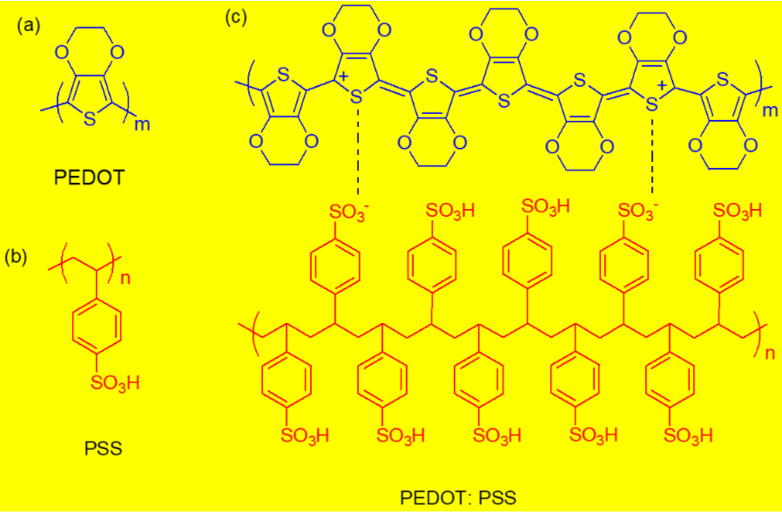


Figure 3. Chemical structure of (a) PEDOT, (b) PSS and (c) PEDOT:PSS.

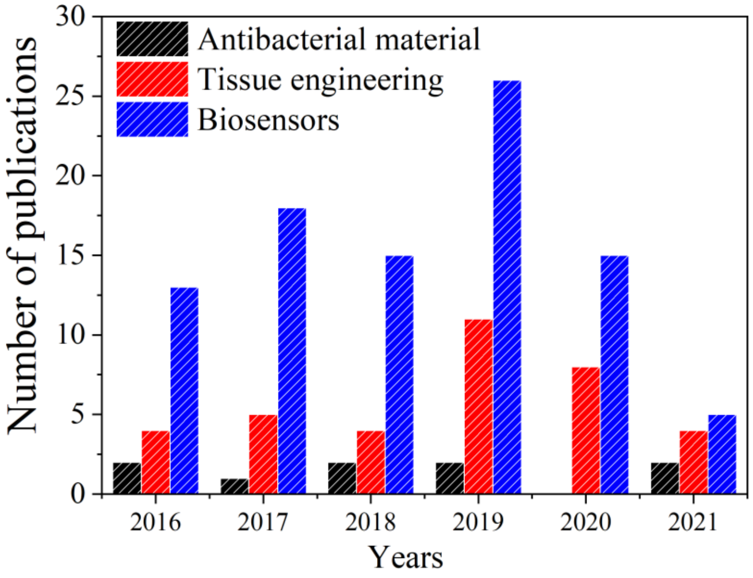


Figure 4. The number of publications of PEDOT:PSS in biomedical applications in the last 6 years searched via a web of science.

3.1 PEDOT:PSS based Antibacterial Materials

Given the many advantages of conducting polymers in section 2, they reveal promising properties for antibacterial applications, by the support of biopolymers like gelatin, dextran, chitosan, agarose, cellulose etc. or by the carbon based materials practice.[102,103, 20]A detailed synthesis technique, properties and the bacterial action of PEDOT and PEDOT:PSS composites are summarized in Table 1. Chang and Sultana [104] reported an eco-friendly polymer composed of polylactic acid (PLA) and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) for the bactericidal studies. The electrospinning method was adopted to fabricate the polymer membrane with various molar ratio of the two molecules. Further, the circular shaped polymer membranes were soaked in the PEDOT:PSS solution dissolved in isopropanol for half an hour. Finally, the dipped membranes were oven dried at 40 °C for 3 h and were characterized for antibacterial activity via a zone inhibition test. The analysis was performed by immersing the PEDOT:PSS coated polymer membrane in tetracycline hydrochloride as a drug and the results showed that drug immersed PLA/PHBV membrane coated with PEDOT:PSS against the S. aureus as gram-negative bacteria and E. coli as gram-positive was effective. Recently, Lin *et al.* have studied the effect of oxidant, monomer and textile pattern on the electrical properties of the PEDOT:PSS coated fabrics. Different fabrics such as polyethylene terephthalate (PET) woven fabric, PET mesh cloth, cotton woven or knitted fabric were used. Among them, PEDOT:PSS deposited PET fabric composite with the highest conductivity has shown the best antibacterial activity of 71% against E. coli and hence meets the standards of antibacterial textile. [105]

Table 1. Preparation of polymer PEDOT/ PEDOT:PSS based antibacterial material.

Year	**Antibacterial Material**	**Synthetic route**	**Bacteria**	**References**
2016	PEDOT:PSS/CS	Mixing and drying	S. aureus	[106]
2017	PEDOT:PSS/PLA/PHBV	Electrospinning	E. coli, S. aureus	[104]
2018	PEDOT/Fe_2O_3 nanoparticles	Vapour phase	S. aureus	[33]
2019	PEDOT:PSS/MWCNT/PANI	Dipping and drying	E. coli	[107]
2019	PEDOT/(P(Py-1,4-P))	Electropolymerization	S. aureus, E. coli	[108]
2019	PEDOT:PSS/Agarose	Mixing and gelation	S. aureus, E. coli	[109]
2021	PEDOT:PSS coated fabric	___	E. coli	[105]

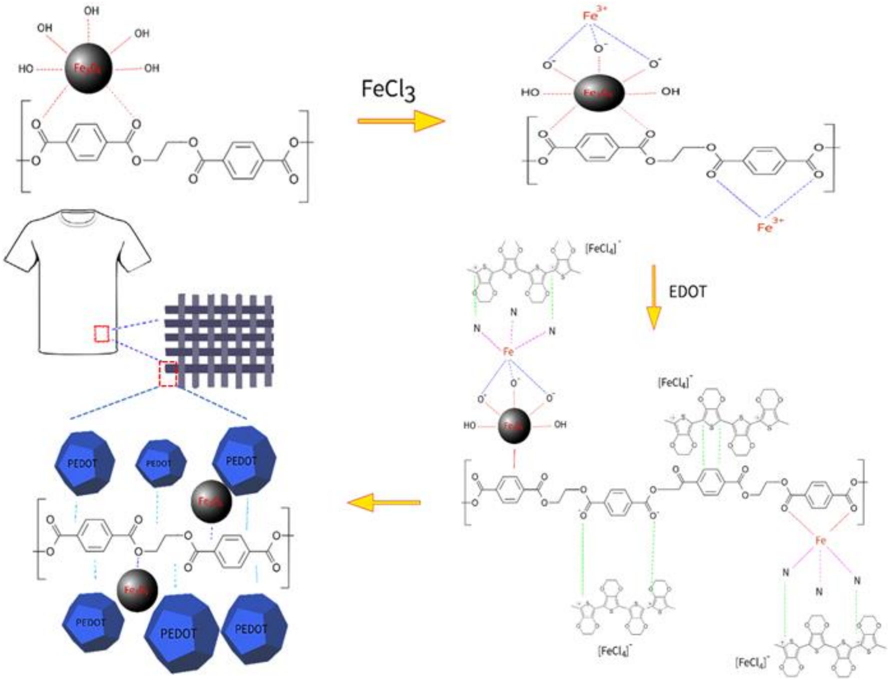


Figure 5. Schematics representation of in situ Fe_2O_3 incorporated into PET substrate and synthesis of PEDOT (Reproduced with permission. [33] Copyright 2018, Elsevier).

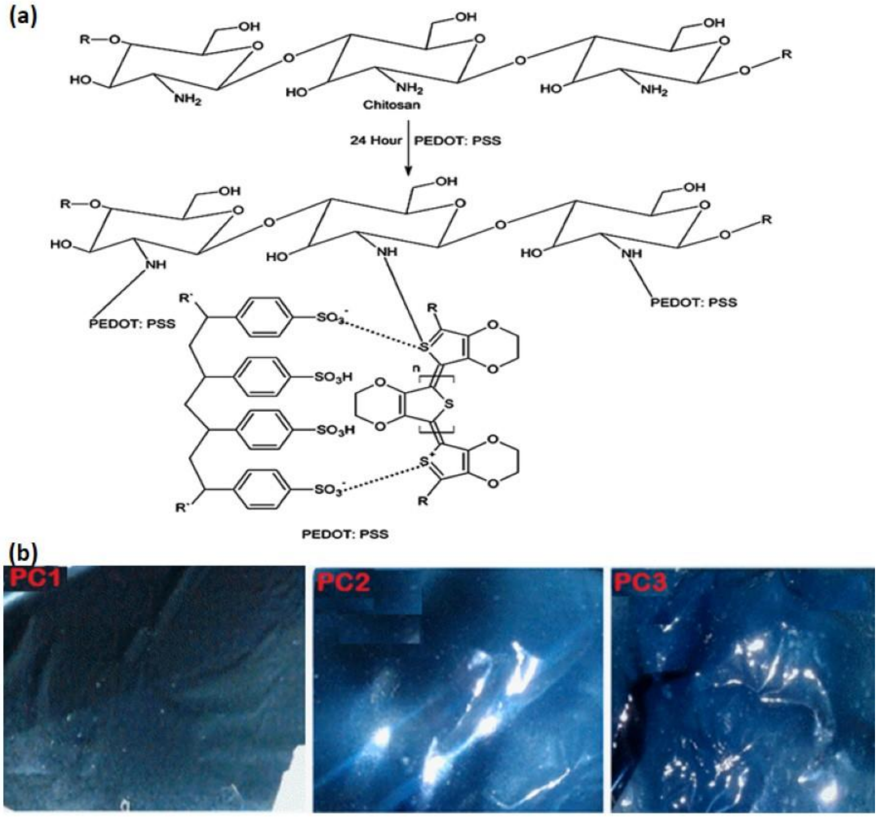


Figure 6. (a) Synthesis mechanism of PEDOT:PSS/CS films, (b) PC1 (1:1), PC2 (1:2) and PC3 (1:3) fabricated bio-hybrid films (Reproduced with permission.[106] Copyright 2016, Elsevier).

Sedighi *et al.*[33] prepared the Fe_2O_3 nanoparticles doped PEDOT film on the textile based flexible substrate PET, which shows the antibacterial properties. The film preparation was a two-step process. The first step involved in-situ synthesis and simultaneously coating of Fe_2O_3 nanoparticles on the PET. The PET was dipped in iron (III) chloride ($FeCl_3$) solution and then the Fe (III) interacted with oxygen ions and formed the complex, as shown in Figure 5. In the next step, the EDOT was adsorbed and polymerized on the Fe (III) via vapour phase route to obtain PEDOT. The PEDOT has a positive charge which is stabilized by a counter ion, $[FeCl_4]^-$. The PEDOT films incorporated with Fe_2O_3 nanoparticles revealed promising antibacterial activity against S. aureus bacteria. The Fe_2O_3 nanoparticles are responsible for the formation of reactive oxygen species (ROS), and enable electrostatic interaction between bacteria and the nanoparticles. As a result, these ROS helps in the eradication of 99 % of gram-positive bacteria. The Fe_2O_3 nanoparticles incorporation helped in enhancing the tensile strength of PET textile and the protection against UV radiation was observed by PEDOT assistance. It is important to mention that the PET fabric, due to its flexibility and stretchability, other than magnetic and electrical properties, extends its applications in energy storage devices, bio-sensor and textile industry. [33]

Furthermore, Smith *et al.*[107] have established an easy dipping and drying technique for the fabrication of conductive, flexible cotton fabric using PEDOT:PSS and multiwalled carbon nanotubes (MWCNT) followed by electrodeposition of PANI to achieve bactericidal properties.[107, 110]One of the latest experiments in which Sánchez-Jiménez *et al.* [108]have reported the antibacterial efficiency of *n*-doped PEDOT when poly(pyridinium-1,4-diyliminocarbonyl-1,4-phenylene-methylene chloride) (P(Py-1,4-P)) was used as a reducing agent. This is a rare example as only a few research studies have been investigated for *n*-doped, unlike *p*-doped PEDOT. The results showed the electropolymerized PEDOT is biocompatible with non-cytotoxic characteristics. The comparison studies were also performed with *p*-doped and de-doped PEDOT and it revealed the bactericidal properties against S. aureus and E. coli.[108] The contact angle measurements results showed the improvement in hydrophilicity of *p*/*n*- doped PEDOT. Thus, the affinity towards water has increased with doping of PEDOT with P(Py-1,4-P) and suggested few P(Py-1,4-P) molecules remain stuck to the surface. The antibacterial activity against E. coli and S. aureus for de-doped, *n*-doped, and *p*-doped PEDOT films were compared to controlled conditions. The fraction of adhered bacteria on the film surfaces revealed the best results with *n*-doped polymer. Khan *et al.*[106] reported the preparation of CS introduced PEDOT:PSS along with its antibacterial activity (Table 1). Their group synthesised

PEDOT:PSS by oxidative polymerization method using ammonium peroxydisulfate as an oxidant. The next step involved the synthesis of hybrid PEDOT:PSS and CS film (Figure 6a) by varying the two in 1:1, 1:2 and 1:3 volume ratio, named as PC1, PC2 and PC3, respectively. Figure 6b shows the film images, and dark blue color indicates the stability of PEDOT polymer. For improving the mechanical properties, the crosslinker polyvinyl alcohol (PVA) was added to the above mixture to form H-bond and were investigated against S. aureus and E. coli for 12 h using disk diffusion test. In disk diffusion test, the effect of antibiotics is studied with the ring formation around the plate by using agar plate cultured with bacteria and the minimum inhibition concentration (MIC) is calculated, which is defined as the minimum amount of antibacterial agent to stop the bacterial growth. It was found that pristine PEDOT:PSS was ineffective against the two bacteria. On the other hand, with the incorporation of CS, the antibacterial activity of PEDOT:PSS was observed for gram-positive bacterium with MIC value of 0.044 mg/L. This could be explained due to the electrostatic interaction of the cationic charged amino units in CS with the negatively charged species in the bacterium. As a result, the CS incorporated PEDOT:PSS, i.e. PC1, PC2 and PC3 showed more effective bactericidal properties than the pristine PEDOT:PSS.[106] By mixing PEDOT:PSS with polysaccharide agarose, Ko *et al*.[109] developed hybrid nanocomposite and it displayed both photothermal and antibacterial properties. A free-standing film of PEDOT:PSS combined with agarose was prepared to completely inhibit or execute bacterial growth by near-infrared (NIR) radiations. NIR covers the range of 700-1100 nm and it has particular advantage in biological fields such as to combat bacterial infection as well as cancer treatment. It is nearly harmless to living tissues and can be deeply penetrable into tissues. The NIR radiations owing to their penetration property in tissues, enable minimum absorption of haemoglobin and water as a result exhibit considerable interest in photothermal activities[111]. Moreover, in the rapid thermal killing of pathogenic bacteria, the NIR light works as a key component. A photothermal agent can emit the photothermal heat after absorption of the NIR (650-900 nm) light through non-radiative mechanism. In PEDOT:PSS/agarose, the strong NIR absorption occurs due to the formation of polaron and bipolaron states in PEDOT:PSS, and the absorption was gradually improved after increasing the PEDOT:PSS concentration. The NIR irradiation increased the PEDOT:PSS/agarose temperature and for the highest PEDOT:PSS concentration (40 v/v%), there was a sharp rise in the temperature from 25.7 to 50.2 ^{o}C after exposure of NIR irradiation for 100 s. It suggests rapid photothermal conversion. The content of PEDOT:PSS in PEDOT:PSS/agarose hybrid was varied from 5 to 40 v/v%, and then the obtained mixture was allowed to cool down to form a gel at room temperature. The prepared solution represents a reversible sol-gel transition of the hybrid films, which are homogeneous as well as stable as a result, gelation formation with the blue colour change could be clearly observed. This colour change became darker as the concentration of the PEDOT:PSS was altered. The bending and twisting properties of coated film were also demonstrated, which are essential for flexible devices. Figures 7a and 7b demonstrate the consecutive damage and healing images of the PEDOT:PSS/agarose films after exposure to NIR irradiation. On the PEDOT:PSS/agarose surface, a cut of approximately 500 µm was made with the help of scalpel blade, and the cut was cured after NIR irradiation for 1 min at damaged sites. The PEDOT:PSS/agarose was partially melted by the photothermal conversion phonemenon to heal the damage. The NIR-triggered temperature was localized to the particular region and it made it appropriate for diverse biomedical applications. For antibacterial testing, the bacterial strains comprising of E. coli (Figure 7c) and S. aureus (Figure 7e), were studied on agarose and PEDOT:PSS/agarose hydrogel and irradiated with NIR light. The S. aureus and E. coli were used to represent gram-positive and gram-negative bacteria, respectively. Both bacteria were unaffected by NIR irradiation for agarose alone. Whereas, the NIR irradiation time improved the bactericidal activities of PEDOT:PSS/agarose. The absorption of NIR caused a sudden rise in temperature within 2 min and led to the death of bacteria (Figures 7d and 7f). It was found that agarose alone was unperturbed, whereas PEDOT:PSS introduced agarose showed quite strong absorption, most probably due to generation of polaron and bipolaron states. Also, increase in absorption is directly proportional to the PEDOT:PSS content, and therefore best antibacterial activity was observed in case of 40 v/v % of PEDOT:PSS concentration with complete eradication of bacteria.[109]

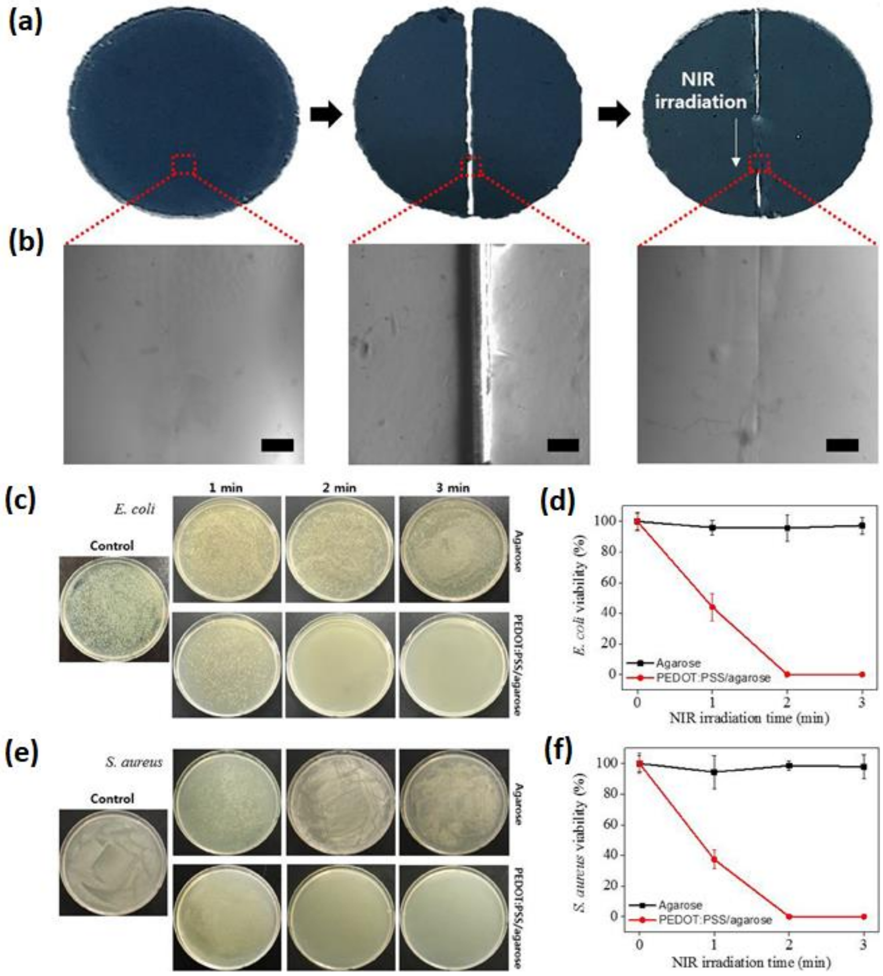


Figure 7. (a) The 40 v/v% PEDOT:PSS/agarose film photographs, and its (b) microscopic images presenting the self- healing of damaged region after NIR laser applied. (c, e) *E. coli* and *S. aureus* colonies in agarose and PEDOT:PSS/agarose solution and (d, f) the bacterial viability percentage depending on the NIR exposure time (Reproduced with permission. [109] Copyright 2019, Elsevier).

3.2 PEDOT:PSS in tissue engineering

With the progress in tissue regeneration, designing new biomaterial that can show promising interaction with the host tissue has become a demand. Several conducting scaffolds materials, such as graphene, CNTs, metal nanoparticles, etc., are explored in tissue engineering, but unfortunately, non-biodegradable and toxic issues restrict their applications.[112] Due to intrinsic characteristics features such as biocompatibility, cell adhesion, non-toxicity, etc., possessed by conducting polymers, they are extensively used as scaffolds biomaterials in tissue repairing and engineering. However, when practised in vivo, the degradation process acts as a limitation, which can occur either by hydrolysis or enzymatic. This produces smaller fragments and then further the material dissolution at tissue and material interface takes place. Despite this, some attempts were made to obtain biodegradable conducting polymer materials, for example, Shi *et al.*[113] proposed PPy nanoparticles composite with polylactide and demonstrated low content of PPy was introduced in body, to investigate the stability and degradability of the PPy. Another effort by Rivers *et al.*[114] offered an alternative method by copolymerization of pyrrole and thiophene attached with ester, and found that electrically conducting materials can undergo degradation via ester bond cleavage. Other reports demonstrated that in sequence of cells, L929 fibroblasts, RSC96 Schwann cells, MC3T3-E1 cells, etc., conducting polymers based materials can improve the property of cell adhesion and helps in proliferation.[115,116] The properties of PEDOT:PSS, including conductivity, flexibility, easy preparation, non-toxicity, and tunable structure modifications, are investigated for applications in tissue engineering [117]. Table 2 describes the properties, synthetic route and potential application of PEDOT:PSS scaffolds.

Table 2. Preparation, properties, and proposed applications of PEDOT: PSS scaffolds in tissue engineering.

Year	**PEDOT: PSS scaffold**	**Preparation**	**Properties**	**Proposed applications**	**References**
2015	PEDOT:PSS/BC	Freeze drying	Biocompatible, cell proliferation, non-toxic	Biosensors, neural implants and artificial tissue engineering	[118]
2016	PEDOT:PSS/CS/ nHA	Freeze drying	Conductive, porous, three-dimensional, mechanical strength	Tissue engineering	[86]
2017	PEDOT:PSS/ dodecylbenzenesulfonic acid	Freeze drying and annealing	Conductive, porous, mechanical strength	Bone tissue engineering	[119]
2017	PEDOT/ hyaluronic acid / PLLA	___	Biocompatible, electrochemical stable	Neural tissue engineering	[120]
2018	PEDOT:PSS/ PLA/ PHBV/ HA	Electrospinning and coating	Conductive, bioactive	Bone tissue engineering	[121]

2018	PEDOT:PSS/ gelatin Or PEDOT: PSS/ alginate	Solvent casting technique	Conductive, better cell response	Endothelial cell regeneration	[122]
2019	PEDOT:PSS/ CS/PVA	Electrospinning	Mechanical and electrical properties, non-toxic	Cardiac tissue engineering	[123]
2019	PEDOT:PSS/CS/ nHA/ PCL	Freeze drying	Highly porous, mechanically stable	Tissue engineering	[87]
2019	PEDOT:PSS/ MWCNT	Sonication and freeze drying	Highly porous, mechanically stable, conductive	Tissue engineering, electronic implants	[124]
2019	PEDOT:PSS/ PEGDA	Freeze drying	Electrochemically active, non-cytotoxic, printable	Signal recording device, drug delivery device, neural tissue regeneration	[125]
2020	PEDOT:PSS/ Au	Coating	Long term stable, electrochemical active	Tissue engineering, drug delivery	[126]

Khan *et al.* [118] published a report on bacterial cellulose (BC) incorporated PEDOT:PSS (BC-PEDOT:PSS) and attained biocompatibility, eco-friendly, and also high conductivity for possible application in tissue engineering. The biocompatibility of the BC-PEDOT:PSS was investigated against animal fibroblast cells and it also showed the excellent cell adhesion, filopodia formation and interconnectivity during 3 days of incubation. Furthermore, the non-toxic nature and biocompatibility of BC- PEDOT:PSS composite could be useful for biosensors, drug delivery, tissue engineering as well as neural implants.[118] The application of PEDOT:PSS as a conductive scaffold for bone tissue engineering was also studied. Guex *et al.* [119] designed first time the PEDOT:PSS porous scaffold with 53.6 µm pore diameter and evaluated its performance in vitro using MC3T3-E1 osteogenic precursor. The MC3T3-E1 gene expression levels were significantly improved within 4 weeks of study and it exhibited PEDOT:PSS suitability for bone tissue engineering. Figure 8a displays the MC3T3-E1 cultured on PEDOT:PSS scaffold and extracellular matrix layer covering the entire scoffold structures between day 1 and day 28th. The scanning electron microscopy (SEM) image shows the increase of cell numbers, with a densely formed tissue construct. Another report presented the synthesis of nanocomposite PEDOT by conventional oxidative polymerization route doped with hyaluronic acid/poly(l-lactic acid) (PLLA)[120]. The cytotoxicity test revealed the good cell adhesion by PEDOT composite film, and enhanced cell viability was symbolised by MTT assay. MTT is defined as an assessment for cellular metabolism, where the oxidoreductase enzymes via reduction of 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) dye form insoluble purple coloured formazan.[127] Also, an impact of electrical stimulations on neurons was shown by Wang *et al.*[120], with the help of hyaluronic acid and PLLA doped PEDOT. The PEDOT composite films, due to their biodegradable and conducting nature were applied in tissue engineering. To examine the electrical stimulation effect, films were subjected to various current intensities, as a result neurite length and cell viability were improved. This fact was explained by the release of hyaluronic acid from the films, which in turn helped in cell adhesion along with neurite growth. Additionally, the balanced electrical form of a cell membrane was perturbed with the stimulations and led to cell differentiation and proliferation.[120]

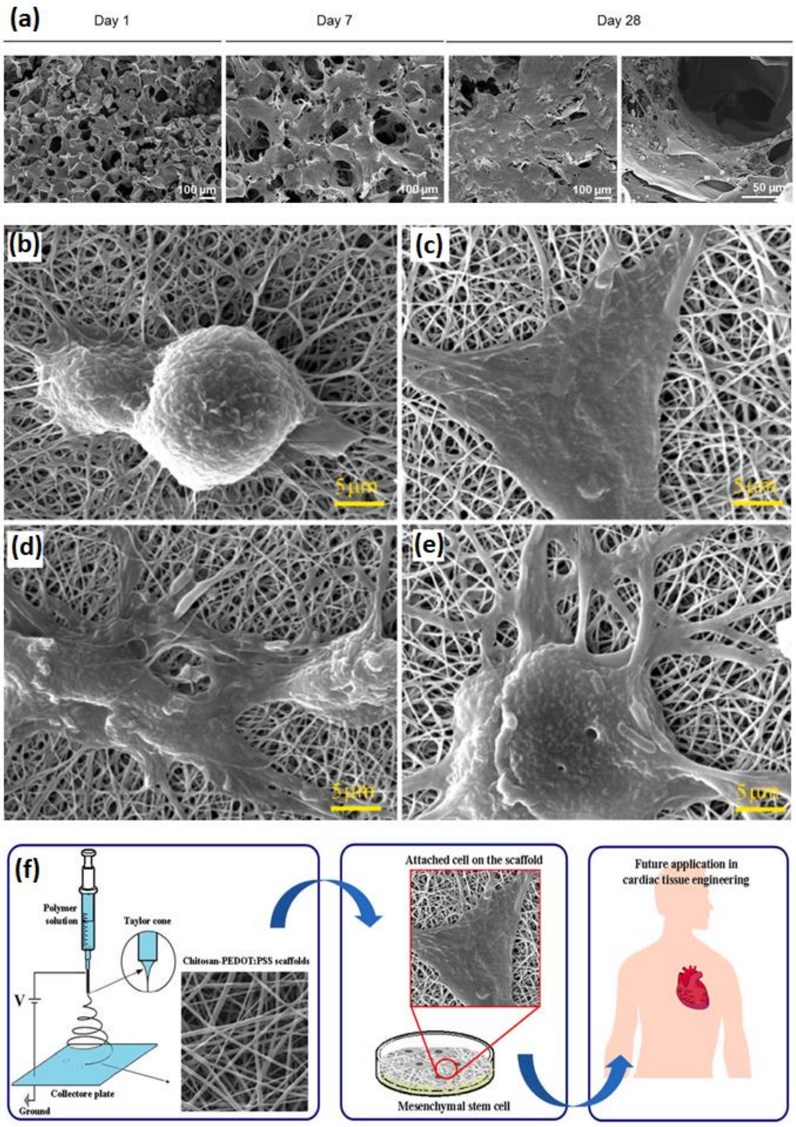


Figure 8. (a) The scanning electron microscopy (SEM) micrograph of MC3T3-E1 cells cultured on PEDOT:PSS scaffold for 28 days (Reproduced under the terms of the Creative Commons CC-BY license 4.0.[119] Copyright 2017). SEM images of: (b) CS/PVA, (c) CS/PVA/PEDOT:PSS (0.3), (d) CS/PVA/PEDOT:PSS (0.6), (e) CS/PVA/PEDOT:PSS (1) on day 3 of cell culturing. (f) Illustration of the scaffolds added PEDOT:PSS for potential in cardiac tissue engineering application (Reproduced with permission.[123] Copyright 2019 Elsevier).

Hassan *et al*.[121] demonstrated an electrospun membrane of PLA/PHBV/HA coated with PEDOT:PSS for the enhancement of the conductivity. The biomineralized membranes exhibited superhydrophilic surface, which reveal potential application in the area of bone tissue engineering. The ability of HA entities to form apatite with Na$^+$, Cl$^-$, Ca $^{2+}$, K$^+$ etc., lead to higher diffusion rate by interaction with hydroxyl groups present in membrane, as a result, enhance the cell proliferation. Mahmoudinezhad *et al.*[122], reported that PEDOT:PSS scaffolds comprising of either gelatin or alginate can act as a good candidate for endothelial cell preservation. The conductive composite scaffold was prepared by increasing the percentage of PEDOT:PSS from 0.1 to 1.0 % by a solvent casting technique and were cultured on human umbilical vein endothelial cells to observe certain stimulations. Significant cell proliferation was observed after seven days for various concentrations and suggested futuristic endothelial applications. Abedi *et al.*[123]also developed the PEDOT:PSS/CS scaffolds via electrospinning method, with enhanced mechanical strength and electricconductivity. The content of PEDOT:PSS was differed from 0.3 to 1 wt% in the PEDOT:PSS/CS composites and PVA with a weight ratio of 3:1 related to the composite was introduced, which are represented as CS/PVA, PEDOT:PSS/CS/PVA (0.3), PEDOT:PSS/CS/PVA (0.6) and PEDOT:PSS/CS/PVA (1). By examining the cell viability, an improvement in cell growth was observed in the scaffolds prepared with PEDOT:PSS. The cell division activity is presented by the SEM on day 3 of bacteria culturing (Figure 8b-e). The reduction of fiber diameters and increase in local curvature results in promoting the cell attachment, especially in scaffold containing PEDOT:PSS (Figure 8e). However, the surface roughness can be effective in describing the cell attachment. Figure 8f depicts the electrospinning technique for the fabrication of scaffolds. The enhanced cellular response on incorporation of PEDOT:PSS, in addition to improvement in the electrical and mechanical properties of the resulting scaffolds, enables applications specifically in cardiac tissue engineering.[123] In cardiac muscle tissue, electroconductivity is prerequisite property responsible for electrical signals transmission and thus PEDOT:PSS based scaffolds can be applied wherever conductivity and cell viability can be correlated.

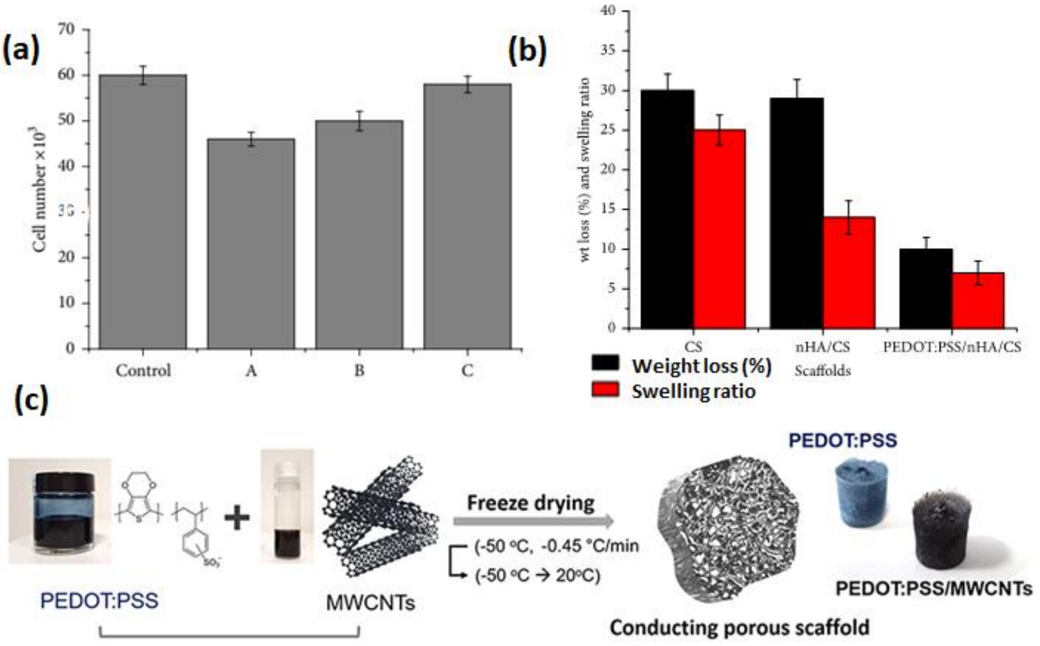


Figure 9.(a) The cell growth on scaffolds: (A) CS, (B) CS/nHA, (C) PEDOT:PSS/CS/nHA compared to controlled condition (tissue culture plate), (b) The CS, nHA/CS, and PEDOT:PSS/nHA/CS scaffolds weight loss and swelling ratio analysis (Reproduced[86] Copyright 2016). (c) Schematic process used for the fabrication of the 3D conducting scaffolds based on PEDOT:PSS and PEDOT:PSS/MWCNTs (Reproduced under the terms of the Creative Commons CC-BY license 4.0.[124] Copyright 2019).

The chitosan and nano-hydroxyapatite (nHA) are well-known for great compatibility and mechanical stability [50]. Lari *et al.*[86] prepared three dimensional, porous composite of CS and nHA with the introduction of PEDOT:PSS. The free drying and lyophilisation method was adopted for the synthesis. Figure 9a clearly shows more cell growth in the PEDOT:PSS scaffold containing CS and nHA. The suitable mechanical properties in the scaffold due to PEDOT:PSS ensured improvement in cell adhesion and binding properties. An increase in the cell growth was observed as a consequence of the mechanical strength. The PEDOT: PSS/nHA/CS scaffold reduced the water uptake and also exhibited slower weight loss and which are the favourable response for tissue engineering. Figure 9b shows the swelling ratio and weight loss behaviour of the scaffolds examined in phosphate buffered saline (PBS). It presents that after 24 h incubation in PBS, at 37 ^{o}C, the water uptake of PEDOT:PSS/nHA/CS has shown reduction than nHA/CS scaffolds, however pure chitosan exhibited the highest water uptake. After incorporation of nHA and PEDOT:PSS into chitosan, the porosity and pore size were decreased, as a result, the swelling ratio is also reduced for PEDOT:PSS/nHA/CS scaffold. After a month, the 10% weight loss was observed for PEDOT:PSS/nHA/CS scaffold, whereas CS and nHA/CS scaffolds had shown 30% loss in the weight. Moreover, their extended work[87] demonstrated the role of PCL in PEDOT:PSS/ nHA/CS/PCL for further improving the mechanical properties. Also, the cell viability of polymer scaffold revealed 85% non-toxic nature and therefore shows futuristic tissue engineering applications.

Jayaram *et al.*[124] examined enhanced cytocompatibility of PEDOT:PSS in the presence of MWCNTs, and obtained 3D nanoporous structure. The PEDOT:PSS and MWCNT solution was mixed at different ratio (1:1 and 3:2) to obtain the hybrid materials. To form the scaffold, resultant solution was pipetted into a 96-well plate and it was placed for freeze drying at -50 ^{o}C, as demonstrated in Figure 9c. The sample was heated at 70 ^{o}C in order to allow crosslinking formation in the scaffolds. Also, the PEDOT:PSS scaffolds were investigated for biocompatibility and superb cytological compliance with the incorporation of MWCNTs. The telomerase immortalized fibroblasts (TIFs) were cultured upon the surface of scaffolds and evaluated for their cytotoxicity. The optical images captured after 2 days showed the spread of the TIFs over the entire scaffold, as a result these scaffolds of PEDOT:PSS can be employed as hosts in cell culture applications such as tissue simulations.[124]

Heo *et al.* [125] reported the PEDOT:PSS based printable and conductive hydrogel crosslinked using polyethylene glycol diacrylate (PEGDA) with improved electrochemical properties and reduced cytotoxic effect. The cytotoxicity assessments of PEDOT:PSS hydrogels in culture with dorsal root ganglion were examined at an interval of 24 h for three days. The results revealed no cytotoxic response and an increase in the cell proliferation was observed over the cell culture duration. Further, the group fabricated 3D printable, conductive and square shaped architecture based on PEDOT:PSS hydrogel with varied pore size. Additionally, LED circuits were successfully lighted utilizing the conducting hydrogels, as a result can be served in bioelectrical applications like signal recording, biosensors and tissue engineering. Electrophysiology studies the heart's electrical activities, which involves the use of electrodes for stimulation of cells/tissue and data recording. The stability is required of electrode materials for long term application. PEDOT:PSS as a coating layer on microelectrodes array is widely reported in order to reduce the impedance in vivo and electrophysiology in vitro, and has shown adequate stability for variety of applications such as drug development, toxicology, and tissue engineering.[125] Dijk *et al.*[126] presented a stable as well as favourable performance of spin coated PEDOT:PSS over the gold electrodes for vitro bioelectronics applications. This is one of the reports showing the long term stability of electrodes composed of PEDOT:PSS using electrochemical impedance spectroscopy. Herein, the PEDOT:PSS deposited electrodes were tested in cell cultured system containing fetal bovine serum for a period of four months. The constant electrochemical impedance measurements show that PEDOT:PSS electrodes in cell cultured medium can show enough stability upto four months and are related to electrophysiology such as tissue engineering and drug delivery system.

3.3. PEDOT:PSS based biosensors

The properties of conducting polymers are very important for their conductive interfacial interactions with cells or tissues, proteins, etc. Their conductive surfaces facilitate electronic signals with cells or tissues, and they can also act as a biological probes and electrochemical sensors by investigating the electrical signals.[22] In addition to this, they are currently being examined for therapy, such as brain stimulation, neural tissue engineering or pain treatment. Conducting polymers applications in organic biomedical and bioelectronics are gaining significant attention, which can be major because of their inheritant mechanical properties, unlike their inorganic counterparts and were raised in many prior reports.[7, 20, 25]The soft characteristics of conducting polymers or carbon based materials, allow the fabrication of stretchable, flexible and conformable organic bioelectronic and also enable biosensing technology.[128] The biocompatibity of conducting polymers is beneficial for bioelectrodes interfaces as they possess dual, ionic and electronic charge carriers. For example, in biosensors, immobilized enzymes are applied to form a selective conducting polymer architecture.[22, 129]

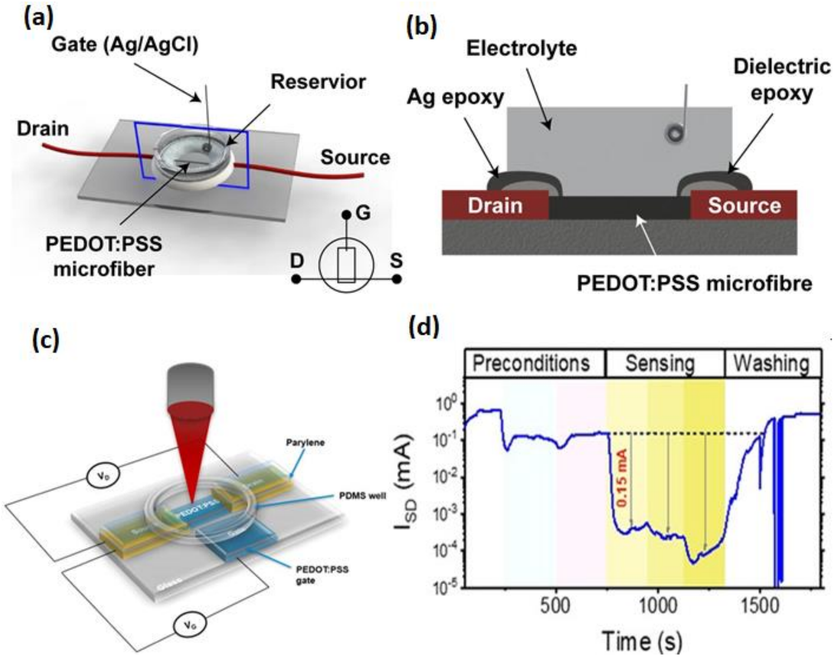


Figure 10. (a) The OECT schematic diagram of PEDOT: PSS microfiber for cation concentration sensing, (b) OECT cross-sectional view. (Reproduced under the terms of the Creative Commons CC-BY license 4.0.[130] Copyright 2018). (c) The representation of OECT glucose sensor device and the mechanism of glucose interaction with the enzyme, (d) OECT sensor log scale recording plot of chronopotentiometric for the glucose sensing with a ferrocene mediated. (Reproduced with permission.[131] Copyright 2019, John Wiley and Sons).

Considering PEDOT:PSS, in the field of electrochemical biosensors, a few papers have been published, which are summarized in Table 3. Sui *et al.* [132] have investigated CS incorporated PEDOT:PSS deposited electrochemically on the Pt electrode surface. Moreover, using dexamethasone as a biosensing material, PEDOT:PSS/CS deposited electrodes were applied in electrochemical biosensors and showed stability in phosphate buffer solution. Kim *et al.* [130] presented an easy wet spinning method to obtain a fibrous PEDOT:PSS and used it for the fabrication of novel wearable devices called sweat sensor, which measures the ion concentrations in human sweat. The spinning technique was used to form the rough shaped solid of PEDOT:PSS in which the PEDOT:PSS solution is injected by syringe and then treated with sulphuric acid. Moreover, these microfibers showed sufficient tensile and mechanical strength which is enough to be sewn it into cotton fabric with a needle. The sulphuric acid treatment induced the removal of PSS and a significant rearrangement in the PEDOT:PSS improving its crystallinity [133]. The conductivity of microfiber PEDOT: PSS was improved with the increase in the concentration of acid. Further, microfiber PEDOT:PSS was used in the fabrication of organic electrochemical transistor (OECT) for sensing small cation (Na^+, K^+, Ca^{2+}, Cu^{2+}, etc.) concentration. Figure 10 a-b show three terminal fabricated OECT device and its cross-sectional view. In the OECT fabrication, PEDOT:PSS microfiber was connected with dielectric epoxy as a sourse and drain connections. The copper wires with dielectric epoxy were used for electrical insulation and Ag epoxy provided sufficient mechanical adhesion and good reproducibility with 5-7 mm as the channel length. In the microfiber PEDOT:PSS OECT, the electrical connections of both source and drain electrodes were made using source meter and changes in the current were observed at the drain voltage of -0.1 V. Then the gate bias was applied onto Ag/AgCl electrode dipped in NaCl electrolyte reservoir which worked as a artificial human sweat. The PEDOT:PSS consists of PEDOT which is hydrophobic and is doped with the hydrophilic PSS unit, as a result the gate bias could push small ions into or out of the microfiber PEDOT:PSS network. This helps in the doping or de-doping of PEDOT which is altered by positive or negative gate bias, with respect of ion concentration present in the solution. As a result, the source and drain current through the PEDOT:PSS microfiber is observed. The PEDOT:PSS microfiber based OECT was developed for cation sensing ability in artificial and human sweat. The small size and flexibility of OECT allowed for their easy fixation on a human arm or a wrist.[130] Also, PEDOT:PSS deposited via ink printing onto a diaper as a substrate has been utilized for cost effective humidity sensor for detecting liquids. This technique is advantageous due to minimal use of material with improved sensitivity [134].An electroactive bacterium, Shewanella oneidensis embedded PEDOT:PSS was electrochemically prepared on a carbon substrate for biosensors. Herein, the encapsulation of bacterium to form bacterial composite film with higher current density was presented. The flow through method was implemented to incorporate bacteria in the PEDOT:PSS. These biofilms provided better cell viability and multiple times current enhancement, along with easy transfer of electrons to PEDOT:PSS. The bacteria embedded films are eco-friendly which enable futuristic applications in biosensors. [135] PEDOT:PSS was used in the fabrication of cost- effective and miniaturized screen printed ion selective electrode for the detection of traces of acetylcholine ion. The PEDOT:PSS film was drop-cast on a screen printed platform with carbon layer for the preparation of acetylcholine selective membrane sensors. The chronopotentiometric technique was used to study the potential stability of the electrodes and further compared to the electrodes made in the absence of PEDOT:PSS. The PEDOT:PSS introduced sensors showed accuracy, reproducibility, sensitivity and selectivity.[136] For the first time, the application of PEDOT:PSS, as a metabolite sensor was demonstrated by Tan *et al.*[131] They tuned the structural, electrical properties and doping level of PEDOT:PSS by crosslinking with (3-

glycidyloxypropyl)trimethoxysilane (GOPS). The different concentrations of glucose such as 0.02 mM, 0.04 mM and 0.06 mM were used to study the biochemical interactions. Figure 10c demonstrates the 3-terminal OECT device configuration with an electrolyte encapsulated by the polydimethylsiloxane (PDMS) well, and it works on a ferrocene mediator mechanism [131,137]. Figure 10d shows the chronopotentiometric recording plotted for glucose sensing. The components involve in electrolyte for electron transfer reactions are glucose, glucose oxidase (Gox), and ferrocence (Fc). The mechanism shows the interaction of glucose with Gox, as a result the enzyme gets reduced, electrons are transferred to the acceptor Fc and charge transport takes place in PEDOT:PSS solution. Consequently, PEDOT:PSS acts as an electrochemical sensing electrode in an OECT device. The reaction at electrode changes the electrolyte potential and further adding of glucose is expected to decrease the drain current output (I_{SD}). The further introduction of glucose de-doped the PEDOT:PSS due to glucose and Gox interaction. As recorded chronopotentiometric plot shows the dropping of I_{SD} from 0.6 to 0.15 mA and more addition of glucose dropped the I_{SD} up to 0.38 μA. After washing of the electrolyte with PBS solution and recovering of current, demonstrates the reversibility of the OECT. The OECT probe exhibited good sensitivity to glucose detection for measuring glucose levels within blood samples.[131] Recently, researchers focus has been shifted towards the flexible pressure sensors, particularly for monitoring and controlling biomedical instruments. The dominated pressure sensor technologies are based on piezoresistive, piezoelectric, and capacitive pressure sensors. Among them, the piezoresistive based pressure sensors have shown high sensitivity and low cost. The dominated materials for fabricating piezoresistive pressure sensors are silicon-based thin film, conductive polymers and bonded metal. [138] In conductive polymers, the PEDOT:PSS have shown excellent piezoresistive property, as well as high thermal and electrochemical stability. There are a few techniques which have been introduced to improve the piezoresistive characteristics of PEDOT:PSS such as nitrogen plasma treatment of PEDOT:PSS film. [139] Beside it, the incorporation of gold nanoparticles also have been reported to improve the PEDOT:PSS piezoresistive characteristics.[140]Recently, graphene oxide (GO) has also been proposed as a doping agent into PEDOT:PSS for flexible pressure sensor. Wang *et al.* [141] introduced the GO doped PEDOT:PSS composites and proposed it for monitoring of the pressure on rat's brain surface without any major damage. Figures 11a-e demonstrate a fabrication of piezoresistive pressure sensors by combining two parts, "A" and "B". The part A composed of patterned indium tin oxide (ITO) and part B, made of the PET substrate coated with PEDOT:PSS/GO. The miniaturized pressure sensing devices were fabricated using scaled masks as shown in Figure 11f. Figure 11g shows an image of intracranial surgery in a skull of a male rat using pressure miniaturized sensor of 0.2 cm diameter composed of PEDOT:PSS composite. The application of pressure up to 5 kPa through a device, showed the pressure sensing ability in a rat's brain without any disturbance (Figure 11h). This device has also shown potential use in detection of sound vibrations for hearing aid applications. The devices having a size 0.2 cm can be applied inside a human ear implantation for sensing sound because of similar size of an ear drum as shown in Figure 11i-k. For hearing aid applications, the miniaturized device can be used in ear implantation, which can help in sensing sound in the absence of any extra accessories. Figure 11l clearly displays a performance of device in detecting sound vibrations of different music styles, either classical or heavy metal, placed inside the ear. Their pressure sensor was able to detect the classical music with a sudden decrease and then back to original high resistance. Whereas, in case of heavy metal music, comparatively lower resistance was observed throughout the process, and this might be due to heavy vibrations recognized by the sensor. This shows a outlook in biomedical field for pressure regulations and sound detection. Most recently, Ren *et al.* [142] have published Ppy and PEDOT:PSS hybrid conductive hydrogel with significantly improved biocompatibility for bioelectronics. A simple solution mixing technique was adopted to prepare Ppy-PEDOT:PSS based hydrogel with porous structures. The attractive forces between negatively charged PSS unit and positively charged Ppy facilitated the formation of hybrid hydrogel. The conductivity was found to be around 860 S/cm, which could be attributed to the conducting PEDOT:PSS and also delivered cross linking properties other than serving as a dopant. For sensing performance of hybrid based electrochemical biosensor, dopamine was chosen as a detection object and for enhancing the sensitivity, Au nanodots were selected as catalysts which were electrochemically deposited over the hydrogel. The cyclic voltammetry studies suggested the higher current response of Ppy-PEDOT:PSS hydrogels as compared to bare glassy carbon electrode due to the promising capacitive properties of PEDOT:PSS. However, a slight increase in the current was observed in case of Au deposited hydrogel probably due to the enhanced electron transfer. Further, for the inspection of the hydrogel in biosensors, impedance spectroscopy was carried out for the Ppy-PEDOT:PSS hybrid hydrogel cultured with PC12 cells. The rise in the impedance as the culture time was extended, shows the well cell growth on the Ppy-PEDOT:PSS hybrid hydrogel as a result enables monitoring of the cell proliferation. Also, scanning confocal microscopy was used to detect the position of PC12 cells and results indicated the attachment of PC12 cells on the surface and also migration into the pores, facilitating the cell culture. The promising biocompatibility of conducting Ppy-PEDOT:PSS hydrogels allows their potential in the electrochemical biosensors.[142]

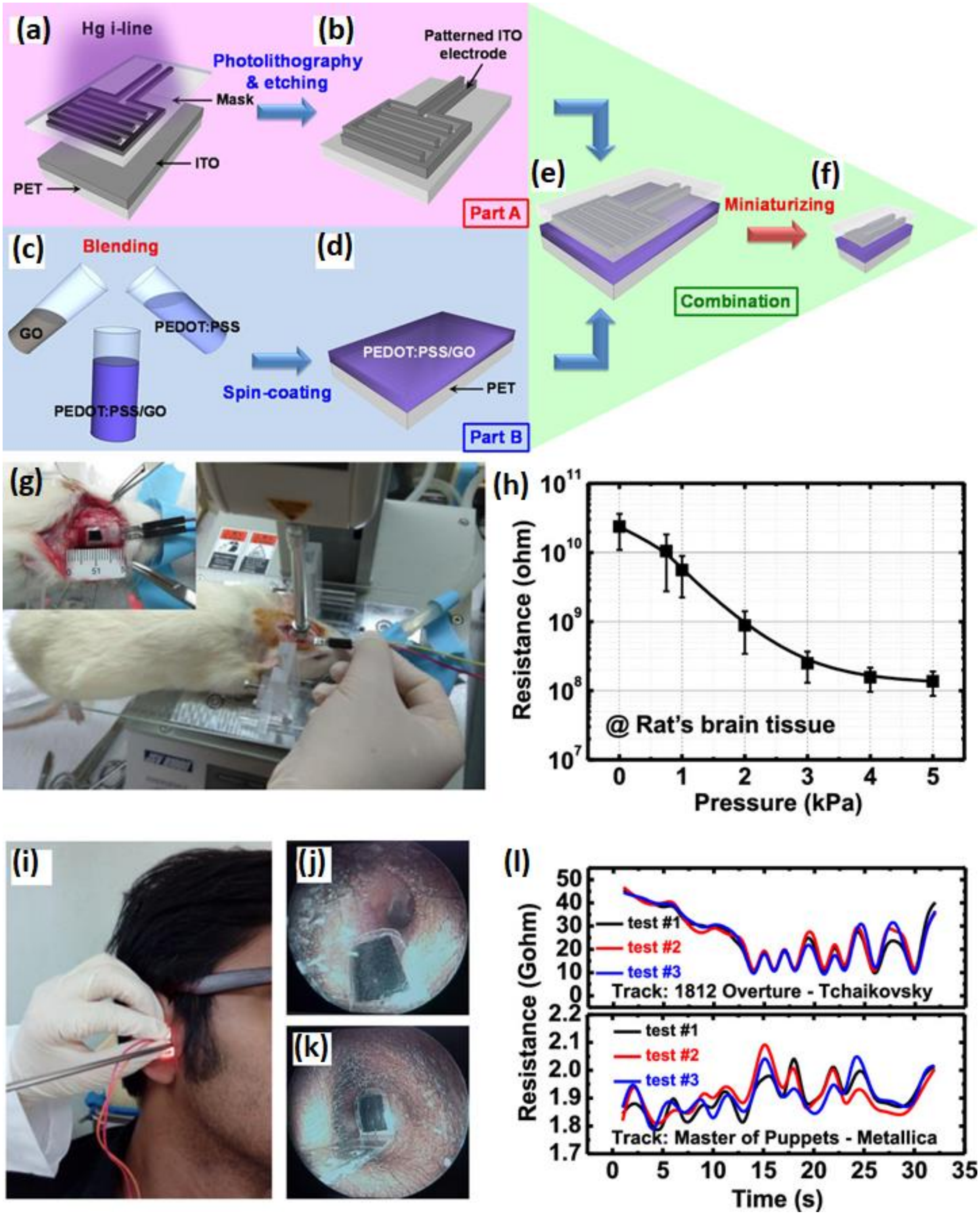


Figure 11. A schematic (a-f) fabrication procedures of piezoresistive pressure sensors, (g) image of intracranial surgery of a rat with the fabricated PEDOT:PSS/GO pressure sensing device, (h) Resistance-Pressure curve of a fabricated pressure sensor, (i) the PEDOT: PSS/GO based piezoresistive pressure sensor and sound detection photograph, attached fabricated device in the (j) ear canal and covered in the (k) ear drum. (l) Different styles of music detection, classic (upper) and heavy metal (lower). (Reproduced with permission.[141] Copyright 2019, American Chemical Society).

Table 3. Preparation, properties and potential applications of PEDOT: PSS composites as biosensors.

Year	**Polymer Composite**	**Preparation**	**Properties**	**Potential Applications**	**References**
2017	PEDOT: PSS/CS	Electrochemical polymerization	Electroactive, low cost, highly sensitive	Electrochemical biosensors	[132]
2018	PEDOT: PSS/ sulphuric acid	Wet spinning process	Free standing fibers, simple, human friendly	Human sweat sensor	[130]
2018	PEDOT: PSS	Printing technique	Cost effective, sensitive	Humidity sensor	[134]
2018	PEDOT: PSS/ bacteria	Flow through method	Conductive, viable	Biosensors,energy yielding devices	[135]
2019	PEDOT: PSS	___	Conductive, potentially stable,	Acetylcholine sensors	[136]
2019	PEDOT: PSS/GO	___	Miniaturized, flexible	Pressure sensor, hearing aids	[141]
2019	PEDOT: PSS/GOPS	Sonicated and spin coated	Mechanically stable, sensitive	Glucose sensor	[131]
2021	PEDOT: PSS/ PPy	Solution mixing technique	Conductive, porous, biocompatible	Hydrogel-based electrochemical biosenor	[142]

4. Current challenges and future prospects

PEDOT:PSS is evolving as a good candidate with promising biomedical properties, there are number of issues which need to be scrutinized in the future to explore the PEDOT:PSS based composite materials in terms of long term biocompatibility and stability. One of the main issues of PEDOT:PSS is its hygroscopic and acidic nature which lead to degradation of films upon contact with aqueous or organic solution. Also, the optimization of the PEDOT:PSS properties in terms of uniformity of the films in medical devices is another challenge. Moreover, the attention should be paid to post treatment methods to avoid non-homogeneity of the conductive fims. Despite these issues, further advancement in PEDOT:PSS's properties namely cytotoxicity, biocompatibility, mechanical strength, electrical stimulations and antibacterial action is necessary for taking into account of implications in vivo. This will help in filling the void from laboratory scale to futuristic commercialization in medical sectors.

Conductive materials in different nanostructures are currently being explored for tissue scaffolds and wound healing. There should be balance between the complicated arrangement of tissues in the human body and implantable electrodes before testing on living beings. Recently, the self healing properties of PEDOT:PSS in combination with flexibility has shown potential aspect in flexible wearable bioelectronics.[143] Studies have demonstrated the morphological impact on tissues/ cells behaviour and their feasibility for therauptic effect and in drug detecting devices. By modulating the self-healing properties with the morphology in addition to the antibacterial properties can give new sight for development of wearable accessories in clothing.[144]

Additionally, the combined effect of structure and properties of PEODT:PSS suffer huge challenges. To adjust the desirable properties, special attention is still required for altering the structure of PEDOT:PSS materials by different functionalization or substitution techniques Also, selection and distribution of numerous additives is very important for altering the structural properties of PEDOT:PSS.[145] In the future, it is important to develop high performance and cost effective techniques and processes for commercialization.

5. Summary

PEDOT:PSS is considered a successful polymer because of its low cost, considerable stability, high conductivity, biocompatibility, and mechanical strength. Most importantly, easy aqueous solution processability makes it more attractive than other conducting polymers in medical applications. In recent years plentiful work has been conducted to explore the PEDOT:PSS for different applications, and the current article summarizes recent advances in PEDOT:PSS based materials in biomedical applications. PEDOT:PSS in composition with different additives such as CS, PLA, MWCNT or agarose can enhance its antibacterial action against both gram-positive and gram-negative bacteria. The composites of PLA, PHBV, HA, CS, etc., induced PEDOT:PSS were largely described for fighting against bacterial infections. The techniques used for preparing the PEDOT:PSS scaffolds and composites include electrospinning, electropolymerization, gelation, lyophilisation, wet spinning process and inkjet printing. A considerable research in the tissue engineering area with PEDOT:PSS is under process. The properties like electrochemical activity, high conductivity, and mechanical stability play an important role in presenting PEDOT:PSS scaffolds's significant advancement in neural, cardiac and bone tissue engineering. In the last few years, PEDOT:PSS based biosensors has captured considerable attention because of their biocompatibility, inexpensive and miniaturized fabrication method, and are successfully used as electrodes for different biosensor devices, such as sensing humidity, pressure and glucose detection in the body, also employed as human sweat sensors. Prevalent studies have been explored mainly in vitro, and in future studies, human trials for the existing materials should be considered.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

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