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Review article

Conductive polymers and composites-based systems: An incipient stride in drug delivery and therapeutics realm

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ABSTRACT

Novel therapies and drug delivery systems (DDS) emphasis on localized, personalized, triggered, and regulated drug administration have heavily implicated electrically responsive DDS. An ideal DDS must deliver drugs to the target region at therapeutically effective concentrations to elicit a pharmacological response, resulting in better prophylaxis of the disease and the treatment. Biodegradable polymers are frequently employed for in-vivo long-term release; however, dose dumping can be anticipated. As a result, current DDSs can be tagged as dubbed "Smart Biomaterials" since they only focus on an on-demand cargo release in response to a trigger or stimulation. These organic materials have been recognized for their metal-like conductivity, as well as their mechanical stability and ease of production. These biomaterials can be programmed to respond to both internal and external stimuli. External pulsed triggers are required for extrinsic stimuli-responsive materials, whereas intrinsic stimuli-responsive materials rely on localized changes in the tissue environment. Furthermore, these materials have the ability to deliver active pharmaceutical agents at a varied concentration levels and across a broad spectrum of action. Drug delivery, biomedical implant technology, biosensor technology, and tissue engineering can be listed as a few prominent applications that have sparked immense interest for conductive polymers-based research and advancements in academia as well as in industry. This review comprehensively covers a cutting-edge collection of electrically conductive polymers and composites, and provide detailed insights of recent trends and advancements allied to conductive polymers for their potential applicability in an array of diverse meadows primarily focusing on drug delivery, biosensing and therapeutics. Furthermore, progressions in their synthesis, structural and functional properties have been presented in conjunction with futuristic directions for the smooth clinical translations.

1. Introduction

The word “Conductive” deciphers to the capability to transmit electricity or flow of charges. The polymers which own this property are called conductive polymers (CPs). Also, they possess semiconducting properties as well as being intrinsically conducting polymers. CPs are organic compounds that have metallic (such as better electrical and optical capabilities) and polymer properties (i.e., lightweight, flexibility in processing, and ease of synthesis). CPs are conductive in nature and they respond to electrochemical and electrical stimulation. Therefore, the entrapped compounds are released from the polymer. Shirakawa, Heeger, and MacDiarmid discovered in the late 1970s that iodine counter ions enhanced the conductivity potential of doped polyacetylene [1,2]. The conjugated system facilitates electron transit along the delocalized channel, which is the most prominent morphological feature of CPs. The electrical structure, which is made up of single and double bonds in an alternating pattern along the polymeric chains, determines its conductivity. The doping process aids in the formation of

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radical cations/anions known as polarons or dications/dianions known as bipolarons in the backbone of the polymeric material while the counter-ions that are within the solution, enter into the material to balance the produced charge [2]. Doping can be reversed in the case of poly(3,4-ethylenedioxythiophene) (PEDOT), a common biocompatible CP. It is well-established fact that the degree of doping boosts CPs' electrical conductivity (Fig. 1). (i.e., doping level).

Using oxidative chemical or electrochemical polymerization, approximately 25 different types of CPs can be produced. Because of their biocompatibility, stability, and outstanding electrical and electrochemical characteristics, polypyrrole (PPy), PEDOT, and polyaniline (PAni) (Fig. 2) are extensively and frequently used in the biomedical domain [3–7]. Brittleness, poor solubility or insolubility, non-biodegradability, rigidity, and difficulty in processability are all the key factors that limit its applicability. These limitations can be overcome by combining CPs with more biodegradable and flexible polymers, resulting in electroactive copolymeric combinations. The numerous promising properties and conductivity of commonly used conjugated CPs for medication delivery and biological applications are listed in Table 1.

In a number of applications, PEDOT and PPy have now been found to have high conductivity. In spite of that, mechanical qualities, processibility, and biocompatibility are typically deficient. A more effective technique to boost the mechanical strength of CPs is to make blends of CP or combine them with other polymers which inherit greater mechanical features for the predicted uses. They are referred to as CP composite/composites. Large-molecule doping can be utilized to increase the mechanical and biocompatibility of CP composites. However, the existence of insulating molecules inside the CP interferes with electron conjugation, which is a downside of the method [8].

In-vitro compatibility studies have been conducted on myoblasts [9], fibroblasts [10], keratinocytes [11], glial/endothelial [12], bone [13], neural [14], and mesenchymal stem cells to access the toxicity and tolerability of these CPs [15]. These CPs have been viable candidates for the use and assessment in biological systems since they were proven to be biocompatible in cell culture studies. Hence, the research in this area has blossomed. However, the toxicity of extra dopant ions, any

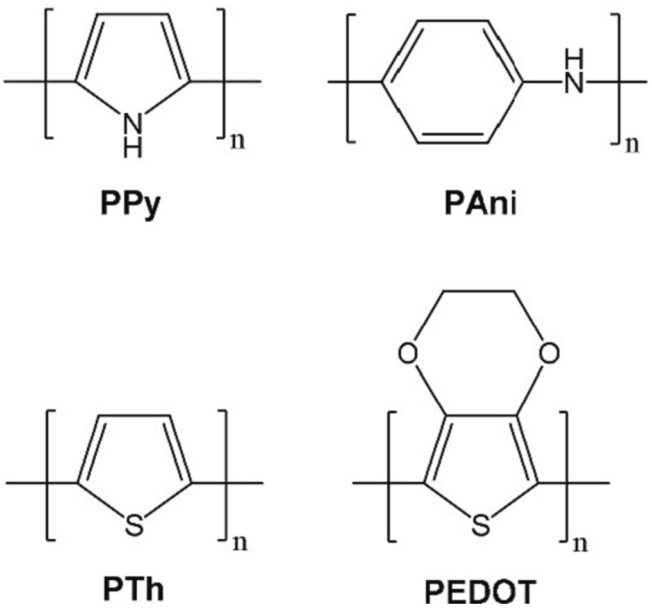

Fig. 2. Structures of most widely investigated CPs in biomedical applications.

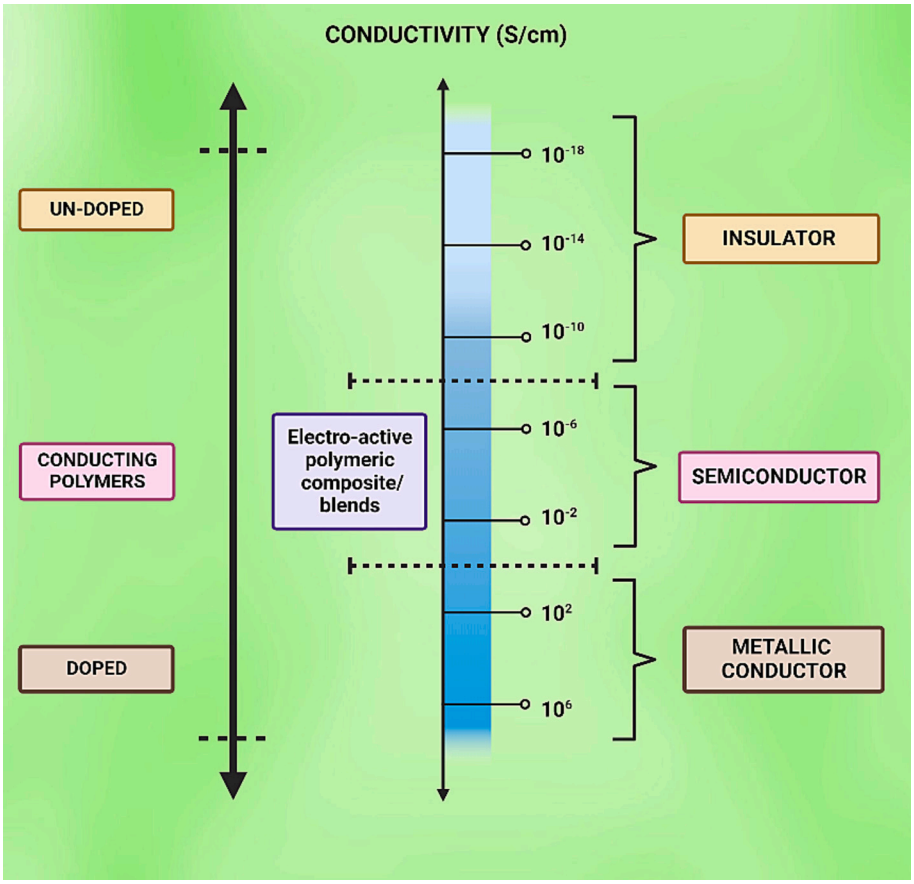

Fig. 1. Range of conductivity for CPs, CPs composites, and blends.

Table 1
Properties and conductivity of majorly used conjugated CPs implied for drug delivery and biomedical applications.

Polymer	Properties	Conductivity (S cm^{-1})	Type of doping	Drawbacks	Reference
Polythiophene	High electrical conductivity, ease of preparation, good optical property	$10–10^3$	p	Hard to process	[3,5]
Polyaniline	Diverse structural forms, environmentally stable, low cost	30–200	n, p	Hard to process, non-biodegradable, limited solubility	[3,7]
Poly(3,4-ethylene dioxythiophene)	Transparent conductor, environmentally and electrochemically stable	0.4–400	n, p	Limited solubility	[4,5]
Polypyrrole	High electrical conductivity, ease of preparation and ease of surface modification	$10–7.5\times10^3$	p	Rigid, brittle and insoluble	[6]

unreacted monomers, or residual solvents should be considered and scrutinized within biological systems [16,17]. Furthermore, nanoscale features of these materials may impact their toxicity levels and create negative side effects due to the large surface area accessible for the reaction [18]. Given the aforementioned considerations, periodic toxicity testing of CP-based materials is required to ensure their safety in biomedical and clinical applications.

Despite substantial advancements in technology and materials in the field of conducting polymer research, various obstacles and issues still exist. Two examples of such limitations are the stability of specific polymers and their susceptibility to certain climate variables. The stability, and ease of processing of these polymers, as well as their conductivity for drug delivery, are determined by surface tension and viscosity [19]. Lately, the use of CP-based composite materials for drug administration and delivery systems has been taken by storm. Despite the fact that several biodegradable CPs and CPs composites have been developed, high conductivity and adequate biodegradability remain difficult combinations to achieve, according to the literature. Dual

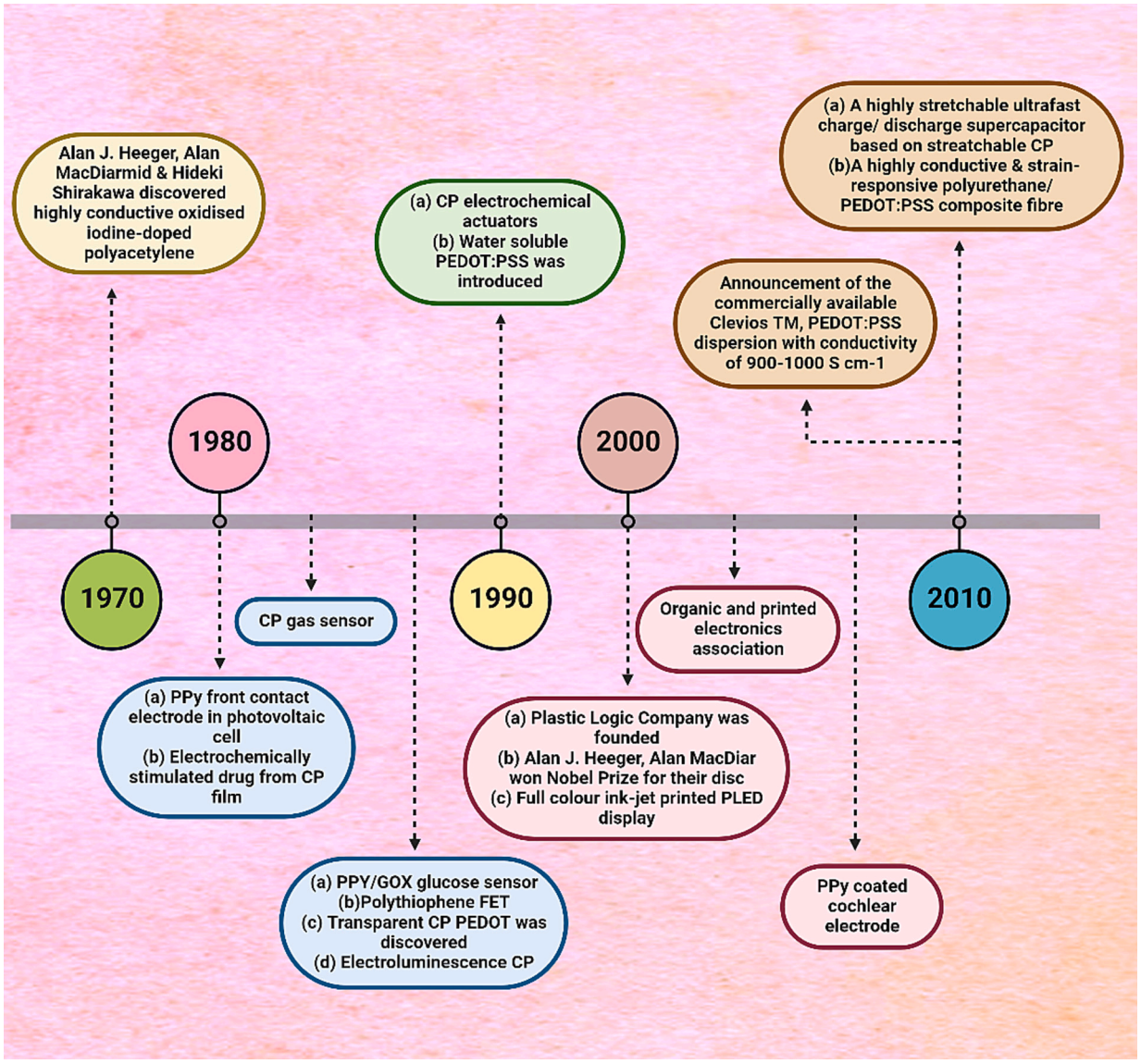

Fig. 3. A timeline detailing the evolution of CPs and their applications over past decades.

stimuli-responsive CP-based composites are also predicted to play a pivotal role in medication administration and delivery due to their precise and fine-tuned regulated release rate.

2. Importance in drug delivery

There has been a significant rise in the demand for advanced stimuli-responsive drug delivery systems as the concept of customized medicine has evolved tremendously [20–22]. To stimulate the release and enhance the localized concentration of the medication, several external triggering elements such as heat [23,24], ultrasonic [25,26], magnetization [27,28], lighting [29,30], and applied electric [31,32] can be employed. It can also be applied topically and consumed for enhanced target localization and rate release. Chemotherapy, implantation, anti-inflammatory activities [33,34], and hormonal problems [35] can all be addressed with specialized and tailored doses due to these qualities. Electrical impulses, notably have sparked a lot of attention among all other sorts of external triggering variables listed above. The rationale for this is the accuracy, precision, simplicity of signal creation, and ability to metamorphose into wire-free small implanted devices, all of which contribute to the improvement of clinical translation. Various initiatives and developments achieved in this domain, which led to a wide range of applications in a number of fields, are illustrated in Fig. 3.

Scaffolds that are made up of naturally obtained polymers such as chitosan, gelatin, and collagen alginate, as well as synthetically obtained polymers like PLLA (poly L-lactic acid), PLA (poly lactic acid) and PLGA (poly D, L-lactic-co-glycolic acid), have quite a wide array of therapeutic uses owing to their effortlessness of processing, biocompatibility and mechanical abilities [36]. Only a handful of these materials are employed for the stimuli responsive in drug delivery [37]. Electrical impulse-responsive drug delivery research can benefit from materials like graphene, carbon nanotubes, NPs, and CPs. However, the majority of electrically signal-mediated drug delivery technologies currently reported are based on CPs [38,39].

3. Types of conductive polymers and composites

3.1. Conductive polymers

3.1.1. Polypyrrole (PPy)

PPy has been employed as a CP in biological applications due to its simplicity of production, good conductivity, and surface modification abilities [40,41]. It helps a range of cell types adhere together and grow by providing environmental stability [42,43]. Tissue engineering [6,41], medicine delivery [44], biosensors [45], and bioactuators [46–49] are few examples of the biomedical uses of this CP. The biosynthesis may be adapted easily up to large volumes at ambient temperature, in either water or a variety of common organic solvents [50–53]. The biocompatibility of PPy has also been highlighted in a number of papers [12,54–56]. PPy NPs produced by oxidative polymerization have been shown to be lethal at higher dosages. These NPs, which are cell-dependent, prevent cell growth and survival.

3.1.2. Polyaniline (PAni)

Due to diverse structural forms, excellent ecological stability, reduced cost, and the potential to shift electronically between two states that are conductive and resistive through the use of a doping/developing process, this polymer is the second most widely investigated CP [40,57–59]. The polymer is found in varying forms liable on the degree of oxidation, as well as a fully oxidized pernigraniline base, half oxidized emeraldine base, and completely reduced leucoemeraldine base [60], with PAni emeraldine, is by far the most conductive and stable. PAni, on the other hand, is difficult to process due to its low solubility in most solvents [58].

PAni and its analogs are complex to use in biological applications due to low cellular compatibility, poor flexibility, and non-biodegradability [57,61]. Nonetheless, PAni's biological uses, such as brain probes, biosensing, controlled drug administration, as well as tissue engineering application, are being thoroughly researched for the prospect of promising results [16,60].

3.1.3. Polythiophene and derivatives

Polythiophenes (PTh) possess qualities that are identical and better than PPy [62,63]. Electroactive scaffolds used in cell culture, biological sensors, and brain probes [64–66] have been researched using PTh and its derivatives. PEDOT (poly (3,4-ethylenedioxythiophene)) is the most effective derivative of Polythiophenes because of its outstanding electroconductivity and inert chemical nature, allowing it to be utilized in biomedicine and biotechnology [67]. PEDOT's biocompatibility has been thoroughly demonstrated in research articles and publications. PEDOT, on the other hand, has a long track record of being produced into nanofilms, nanofiber mats, and nanorod arrays [68], besides other applications.

3.2. Conductive polymer composites

3.2.1. Composites based on conjugated CPs

Films of PPy-cellulose acetate (CA) with varying concentrations of pyrrole were produced by molding PPy-CA viscous solution on a plate made up of glass and soaking it in aqueous solution of ferric chloride. The generated films of CPs displayed extreme electrical conductivity of 3.6–101 S/cm with a 4.7 wt/percent PPy loading [69]. Chitosan and polypyrrole composites with radical scavenging capability were developed to be used in biomedical applications and food containers in a separate investigation. The synthesis utilizes chemical cross-linking of PPy in a chitosan solution with ammonium persulfate as an oxidizing agent [70].

Kim et al. have presented the production of composite materials of collagen and polyaniline nanofibers by using different ratios of PAni nanofibers dispersed in the collagen matrix. The electric conductivity of the collagen-polyaniline composite nanofiber film doped in HCI solution was retained, but there was a significant drop in conductivity when the quantity of Polyaniline in the composite was reduced [71]. Venkatraman and colleagues described the applications of poly (34-ethylene dioxythiophene)-coated microelectrodes with progressive systemic sclerosis as a cortical neural prosthesis. *in-vivo* chronic testing of microelectrode arrays rooted in the rat brain, (poly (3,4-ethylenedioxythiophene))-coated platinum-iridium electrodes outperformed platinum-iridium (Platinum-Ir) electrodes in charge injection and signal-to-noise recordings [72]. Cheng also observed that using Pt electrodes implanted in rat brains, the PEDOT-coated platinum-iridium (Pt-Ir) electrodes outperformed Pt-Ir electrodes in charge injection and signal-to-noise recordings. Cheng also observed that using composite films comprised of poly (3,4-ethylene dioxythiophene) and nanotubes of carbon (PEDOT/CNT), Pt electrodes implanted in rats' brains were more biocompatible. The cerebral response of rats injected with PEDOT/CNT composite film deposited on platinum implants was measured six weeks later. According to the findings, the coating increased the surface density of neurons and blood vessels surrounding to the platinum implants [73].

To produce synthetic brain conduits, Ateh et al. have utilized the method of dip coating from PPy/poly (d.l-lactic acid) (PDLLA) composite solution. The composite solution was created *via* polymerization of the emulsion of PPy in poly (d.l-lactic acid) solution. An aqueous solution of $FeCl_3$ was used to initiate the oxidative cross-linking of polymers. Nerve conduits were also created to bridge a 10mm defect in a rat's sciatic nerve utilizing a novel 5% PPy/PDLLA composite. After a period of six months, rats with PPy/ poly (d.l-lactic acid) conduits exhibited functional recovery that was identical and par to standard autologous nerve transplant and much improved than rats with poly (d. l-lactic acid) conduits [6].

3.2.2. Composites based on non-conjugated CPs

Adding NPs to nonconducting polymers increases their electrical conductivity. The use of CNTs, metal NPs, graphene, graphene oxide, and other conductive NP fillers are common. Graphene possesses superior mechanical properties, excellent electrical transport capabilities, and high insulation properties [74–78], all of which have elicited interest in its potential uses in a wide range of devices. In terms of thermal, electrical, and mechanical properties, graphene-based polymer composites surpass pure polymer [79]. This includes the generation of electrically conducting reinforced nanocomposites [80,81].

It has been demonstrated that oxides of graphene, which are more hydrophilic than carbon nanotubes, improve tissue adhesiveness at the surface of a biomaterial [82]. Despite CNTs' properties of high electrical conductivity, carbon-based CP composites are limited because of the difficulty in the homogeneous distribution of these carbon fibers throughout polymer materials [83,84]. The conductance of polymer composites is improved by filler particles that establish conductive channels in the polymer matrix [85]. However, variables such as conductive filler content and filler matrix interaction must be managed carefully as they impact the electrical properties of polymer composites.

4. Synthesis of conductive polymers and composites

Chemical and electrochemical synthesis are two ways of generating CPs, each with its own set of advantages and disadvantages that have been examined by researchers.

4.1. Conductive polymers

4.1.1. Electrochemical synthesis

One of the key advantages of the process is that it permits parallel doping and entrapment of molecules. However, removing the electrode coverings after manufacturing is problematic. CP covalent modifications are similarly challenging to achieve. Furthermore, the method is restricted to techniques in which the oxidized monomer is used to produce a radical ion that is reactive and it should also promote cross-linking of polymers [86].

4.1.2. Chemical synthesis

This synthesis approach is more difficult compared to electrochemical synthesis. The method expands the options for covalent CP backbone modification and simplifies post-synthesis modification. Electrochemical synthesis yields much thinner CP films than chemical synthesis. To recapitulate, both procedures are employed to develop commonly seen CPs (PEDOT, PPy, PTH, PAni, etc.). Chemical polymerization, on the other hand, can be used to create novel CPs by substituting different monomers [86,87].

4.2. Conductive polymers-based composites

4.2.1. Melt processing

This method does not require the use of a solvent. While the filler is still molten, it is mixed with the polymer matrix [84]. In mixing, high-temperature extrusion and injection molding are employed [88]. The technique is suitable for industrial operations due to its simplicity and rapid production. Illustration of melt processing method for the synthesis of CPs composites is shown in Fig. 4.

4.2.2. Mixing

A suitable polymer solution is created in this procedure, and the nanofiller is distributed in the solution using sonication (Fig. 5). The procedure is advantageous because graphene sheets or nanotube dispersion separation is simple [89–91].

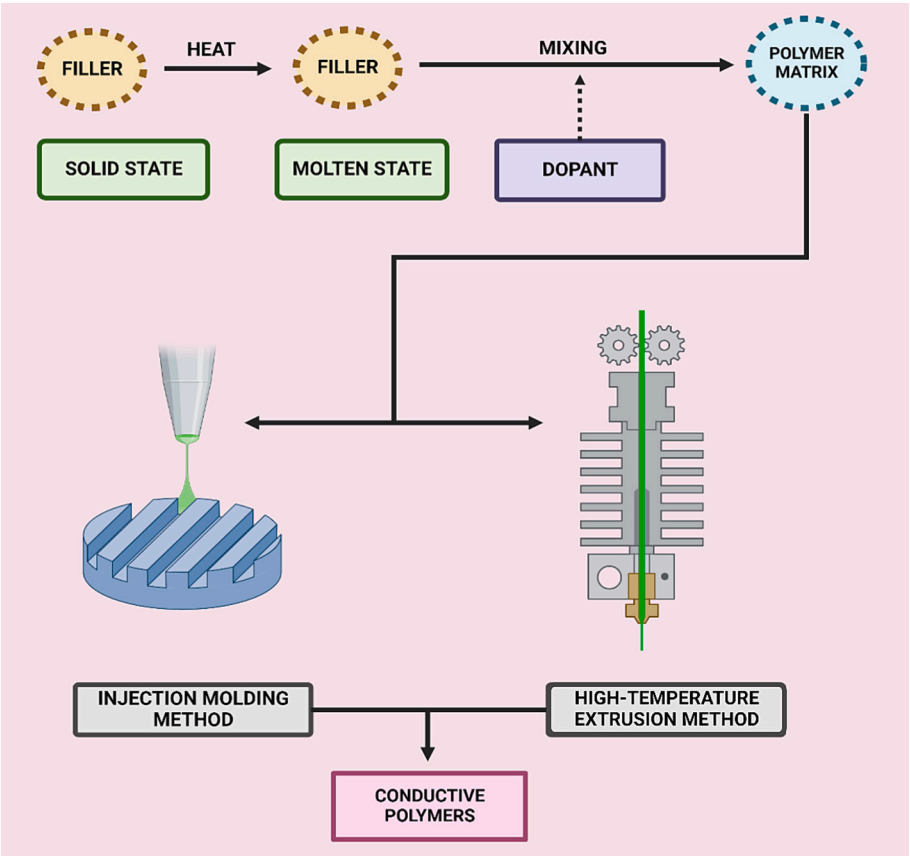

Fig. 4. Overview of melt processing method for the synthesis of CPs composites.

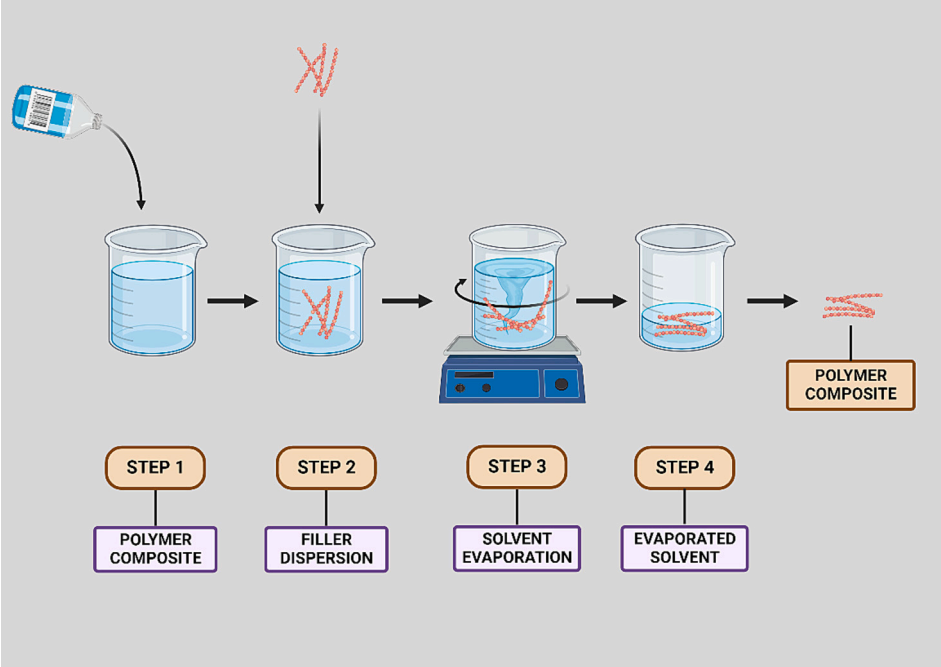

Fig. 5. Overview of solvent mixing method for the synthesis of CPs composites.

4.2.3. Latex technology

The technology makes graphite and carbon nanotube-based polymeric materials in a straightforward method. It offers several benefits, including ease of use, scale-up, and evenly scattered fillers in the polymer matrix. It also enables you to directly add individual chemicals to a thick polymer matrix. Three steps make up the procedure: a) make a colloidal aqueous dispersion of the nanofiller, b) combine the polymer matrix with the nanofiller, and c) dry the obtained colloidal mixture to make a composite. Carbon nanotube, polymer nanocomposite, and graphene polystyrene nanocomposite are recently produced using this

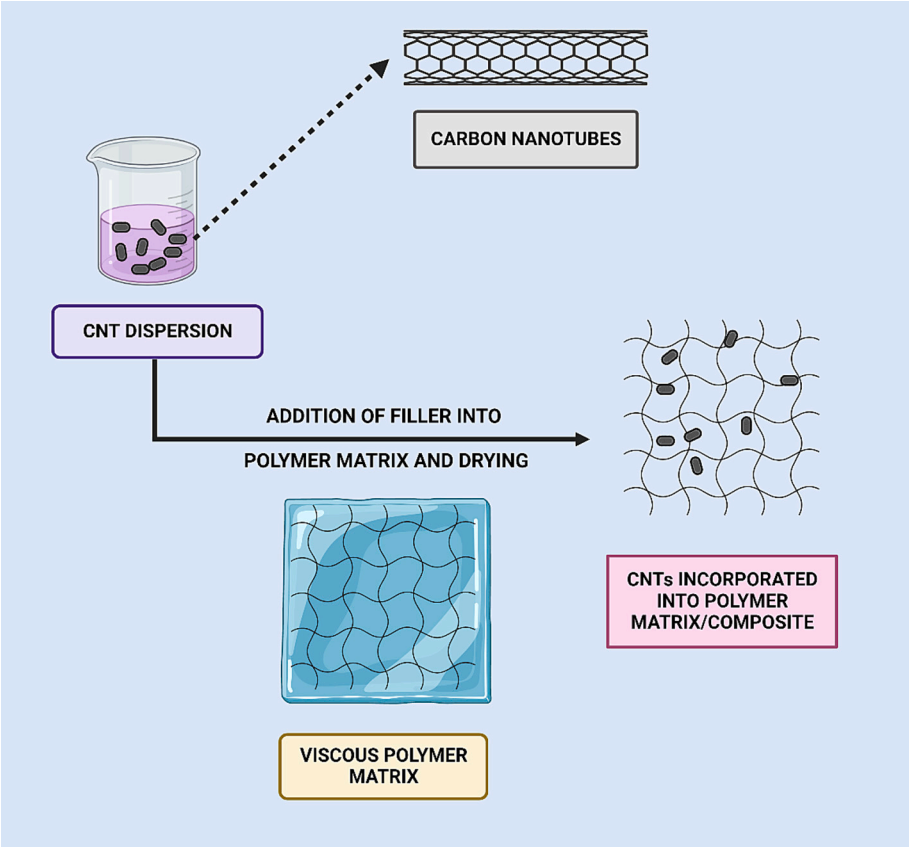

Fig. 6. Overview of latex technology for the synthesis of CPs composites.

method [92]. Fig. 6 illustrates latex technology method for the synthesis of CPs composites.

4.2.4. In-situ polymerization

The polymerization process is initiated using radiation or heat [93]. Following the increase in the filler present in the liquid monomer, the initiator diffuses across the liquid monomer. Due to the simplicity of creating covalent connections, this approach forms CNT polymer nanocomposite through covalent bonding between the matrix and CNT (Fig. 7). This method can be employed to introduce carbon nanotubes into a polymer composite [90].

5. Applications of CPs and composites

5.1. CP architects for drug targeting and drug delivery

5.1.1. Polymeric films

The simplest and most common form of CPs is electrochemically generated thin films, and the electropolymerization of CPs has been a well-established process for adjusting film thickness while adding biomedically active drugs as doping agents. As a result, electrochemically generated polymer films for drug release on demand are frequently employed. To enable controlled release, drugs with varying chemical properties, such as methotrexate [94], dexamethasone [95], heparin [96], sulfosalicylic acid [97], chlorpromazine [98], and risperidone [99], are incorporated into CP films. Only a handful of examples include films constructed of PEDOT, poly(N-methyl pyrrole) (PNMPy), PPy oligoaniline, oligoaniline-PEG, oligolaniline-PCL, and oligoaniline-alanine.

Krukiewicz et al. have discovered that films made up of PEDOT containing the physiologically active chemical botulin demonstrated high cytotoxicity against Michigan cancer foundation-7 and KB cell lines, with cell death increasing dramatically following botulin release due to the potential difference across them. As a result, local chemotherapeutic uses in such matrices are more likely [100]. Investigation into the recording of neuronal activity using an electrode installed in the rat's hippocampus, as well as to control local inflammation using CV-triggered weekly delivery of dexamethasone was incorporated into PEDOT film and their release in a controllable environment was examined. After a 12-week assessment period, the test electrodes that released the drug had neurons closer to those electrodes compared to the reference electrodes [101].

Mattoli and colleagues employed a modified supporting layer technique to develop available conductive PEDOT and PSS nanofilms. PEDOT (poly (3,4-ethylenedioxythiophene)): PSS nanofilms can be tailored, doubled, and also unfolded numerous times in water without breakage, disaggregating, or losing its conductivity properties, enabling for its use in sensing and actuation as well as medical applications such as smart scaffolds for cell culture [68]. The researchers also created a curved actuator by placing a thin PEDOT: PSS coating of a polymer on the exterior of a monodomain nematic liquid single crystal elastomer (LSCE) film [102] made of polysiloxane in another study. In comparison to metals or inorganic NPs, LSCE improved the mechanical characteristics of PEDOT: PSS, allowing for the construction of an all-polymer dependable millimeter-scale actuation composite [102].

A novel poly(diketopyrrolopyrrole-alt-3,4-ethylenedioxythiophene) (PDPPEDOT) and poly(N-isopropylacrylamide) PNIPAM hydrogel which is a narrow-bandgap semiconducting polymer that responds to near infra-red (NIR) light containing Doxycycline was developed by Yingjie Wu et al. [103]. Under the influence of NIR laser irradiation, the hydrogel's shrinkage and the drug release pattern of produced hydrogel systems were successfully demonstrated. The temperature of the system rose when composite hydrogels of PDPPEDOT/PNIPAM were exposed to irradiation of NIR laser, causing the hydrogel to shrink and hastening the

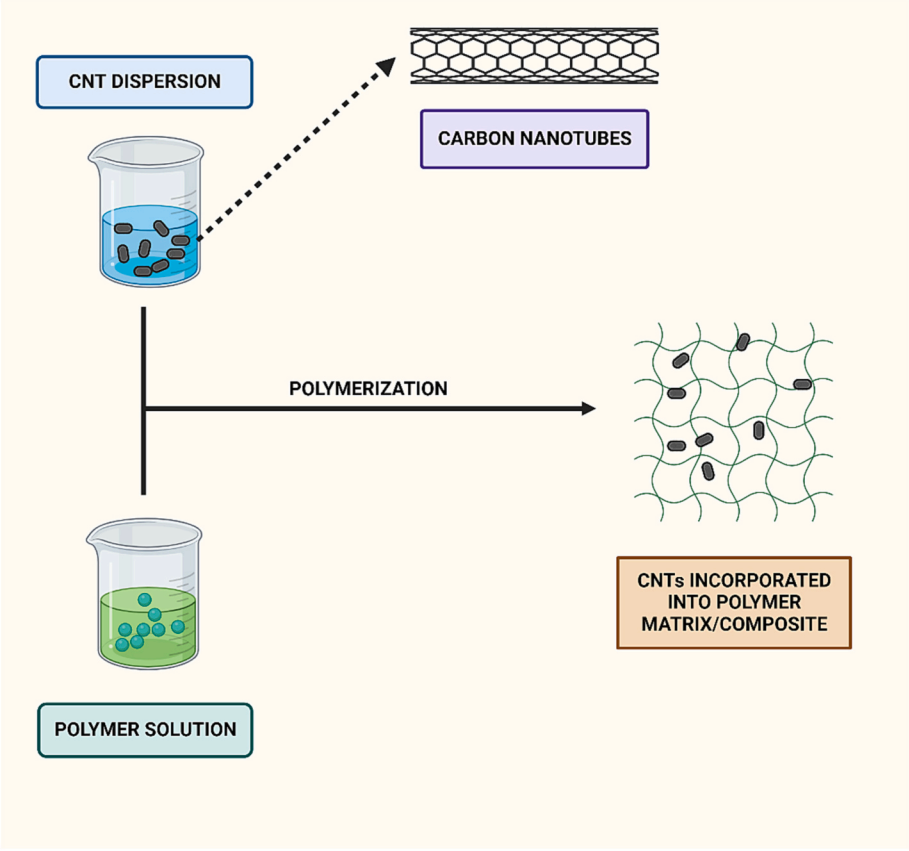

Fig. 7. Overview of in-situ polymerization method for the synthesis of CPs composites.

rate of loaded drug release. The produced hydrogel composites can release medications on-demand, continuously, and remotely over extended times, in contrast to conventional hydrogels. A variable spatial/temporal control over the target position, dose quantity, and duration is possible using a remote-triggered drug release device. These hydrogels with photothermally responsive properties can be used as skin therapeutic patches and films or as implants with spatially and temporarily controlled release of the drugs.

Electrophoretic Deposition (EPD) is one unique technique for producing nanomaterial-hydrogel-based composite films at the oil/water interface. Carbon nanotubes (CNTs) electromigration occurs at the oil/water interface wherein the cross-linking of polymer was stimulated to generate hydrogel film composite *via* interfacial EPD. The main advantage of this technique is that CNTs can be incorporated into the hydrogel because polymerization takes place far away from the solid substrate while being surrounded by both oil and water. The feature of EPD is to regulate the composite hydrogel film, configuration, and polymerization parameters, enabling commercial production without any sophisticated apparatus. Doped hydrogels for drug delivery are an example of the potential use of interfacial EPD technique because numerous materials, such as carbon materials, ceramics metallic particles, and microbes possess finite surface charge while dispersed in dielectric liquids [104].

5.1.2. Polymeric nanoparticles (NPs)

The creation of NPs from CPs for electro-responsive drug delivery requires chemical synthesis as well as surfactants to promote colloidal stability. The NPs possess better functional properties, scalability, and drug entrapment than electrochemically produced films. A recent study using CPs found that 51 % of the overall weight of the drug can be loaded, which is much higher than the amounts generally achieved using polymeric films [105].

The biggest problem with CP NPs is the setup necessary to induce their release. The oxidation and reduction of nanoparticles in a solution of an electrolyte must be studied since their mobility from the bulk of the fluid to the surface of anode is limited. Ge et al. have used a PLGA-PEG-PLGA gel with 1% Polypyrrole nanoparticles affixed to the surface of the electrode, and in vivo delivery of fluorescein was achieved by administering a 1.5 V/cm electric field *via* two needles for 40 seconds in each stimulus. An increase in the release of fluorescein from PPy NPs was observed [106]. Similarly, in another investigation, PPy NPs coated electrodes have been drop-casted with 0.05 weight percent chitosan in 0.1M HCI to avoid separation during electrostimulation [107].

In another research work, formulation of hydrogel/NPs-loaded with small hydrophobic drugs for controlled release was developed by polymerization of two polymers, a naturally occurring polymer poly (-glutamic acid) (PGGA) composed of glutamic acid linked between amino and carboxylic acid groups by an amide linkage, and poly(3,4-ethylenedioxythiophene) (PEDOT) which possess high electrochemical activity. Specifically, during the crosslinking reaction, Curcumin (CUR) was used as a drug candidate, and curcumin-loaded PEDOT (PEDOT/CUR) NPs were then integrated into the hy1drogel composed of PGGA. The rate of drug release of the PEDOT/CUR hydrogels and PGGA/PEDOT/CUR hydrogels were evaluated in both the presence and absence of electrical stimuli at the voltage of −0.5 V for 15 min every 24 hours. The electrochemical, chemical, and morphological characterization was done in great detail. Despite the fact that CUR was relatively slow in drug release profiling in both situations owing to its poor water solubility and hydrophobicity, the results demonstrated that the release rate was more than twice as high for developed PGGA/PEDOT/CUR electrically stimulated systems. Hence, researchers proposed use of developed hydrogels when therapy requires slow, sustained and/or controlled release of drug [108].

Using the drop-casting technique on a gold substrate, poly 2-(diethylamino)ethyl methacrylate (PDEA) NPs with PPy as the conductive component were combined to produce a 3D conductive PEDA/PPy hybrid film. The hydrogel NPs were then electrochemically used to create PPy as a semi-interpenetrating polymer network. Through pH switching, Doxorubicin (DOX) was incorporated into the hydrogel NPs, entrapping them while they are in a collapsed state, and then releasing them when an electrical stimulus is applied. DOX was released much more quickly at +0.65 V anodic potentials than at −0.6 V cathodic potentials. This was due to protons being liberated from PPy in its oxidized state, resulting in pH change, swelling of the hydrogel NPs, and the release of DOX. For E=+0.65 V, the highest amount of drug release was reported at 240 minutes. With the exception of cathodic potentials (0.65 V), the release kinetics analysis showed that DOX release was regulated by Fickian diffusion. This research outcomes depicts that the developed hybrid PDEA/PPy semi-interpenetrating network can be employed for electro-stimulated drug administration and targeted drug delivery, and has the capacity to encapsulate and distribute diverse drugs *via* a simple pH switch approach [109].

Furthermore, electrical stimulation of NPs trapped in the dialysis bag was demonstrated inside the electrochemical cell, indicating that medication can diffuse through the dialysis bag and is released from the NPs after electrostimulation [110]. Curcumin release from PEDOT NPS coupled to a glassy carbon surface was described similarly [111]. Table 2 projects overall procedures for the production of electrosensitive NPs including the release of electro-stimulated CP which is based on NPs [106,107,110–112].

5.1.3. Polymeric nanofibers, nanowires, and nanotubes

CPs have brought together several varieties of tubular micro-and nanostructures. Nanowires made out of elongated entangled nanotubes that form a mesh have been studied using PPy. It can also be prepared in a variety of ways, including using functional compounds [113–115], seeded growth [53], and interfacial polymerization [116]. Although their effectiveness in biosensing and energy storage has been thoroughly examined [117], nothing much is known regarding their application as DDSs.

ATP was used as a morphology-directing agent as well as a model delivery drug, and the findings demonstrated a considerable difference in release (around 53% for traditional PPy morphologies compared to 90% for the PPy nanostructured wires post 45h of electrical stimulation). Conductive voltammetry demonstrated more electroactivity of PPy nanowires than standard PPy forms, while electrochemical impedance spectroscopy studies revealed much lower material resistance [118]. Alternatively, Lee et al. used an anodic alumina oxide membrane with 0.2 m as pore size as a sacrificial template and a mixture of biotin as a dopant and pyrrole monomers as an electrochemical deposition to form arrays of nanowires. The encapsulation efficacy has been reported to improve when the DOX (doxorubicin) molecules are linked with biotin dopant. The quantity of medication released by the application of electrical stimulation was far greater than the quantity released using unstimulated controls, where the major driving force was diffusion [119].

Drugs can even be integrated or absorbed into PPy nanowires without causing CP doping agents to become ineffective [120]. Jiang et al. employed nano- and micro-gaps created between nanowires as drug storage reservoirs in their research, and their findings showed that the volume to be loaded and drug charge aren't the key factors in loading capacity. To prevent drug leakage and to allow the controlled and sustained release of the drug, a subsequent coating of the mesh with a polypyrrole layer was given which resulted in a sandwich-like stable form [121].

Regulating the breakdown of PLGA/PLA or activating the surfaces of CPs with an electrical field are two further options for drug delivery. Chen et al. used a PEDOT shell to encapsulate diclofenac-loaded bacterial cellulose (BC) microfibers. PEDOT shrank as a result of the electrical stimulation, creating an electric movement that pressed on the BC microfibre, boosting drug release (as illustrated in Fig. 8) [122]. Another work reported the action of CPs to release drugs from curcumin-loaded electrospun PCL microfibers (MF) and PEDOT NPs. PCL/PEDOT/CUR

Table 2
Summary of several drug delivery systems incorporating CPs based NP. The entries are classified by the drug charge at a neutral pH.

Active ingredient	Polymer used	Type of dopant used	Synthesis procedure	Release stimuli	Reference
Daunorubicin (1–2 mM) and fluorescein	Anionic and cationic PPy	Decanol (0.236 M) and Dodecyltrimethylammonium bromide (0.162 M)	Polymerization in aqueous solution is achieved by using $FeCl_3$ as oxidant agent and adding the surfactant and the drugs to the reaction medium	Daunorubicin: Constant potential at 0.5 V for 10 s (applied every 5 min) Fluorescein: Constant potential at −0.5 or −1.5 V for 10 s (repeated every 5 min)	[106]
Fluorescein sodium salt and methotrexate (1–2.2 mM)	PPy	Sodium dodecyl sulfate (0.1 M) (SDS)	Different oxidizing agents (H_2O_2, $HAuCl_4$ and $FeCl_3$) were employed to prepare PPy NPs. Drugs were added to the reaction medium before the particle formation process	5 stimuli at a constant potential of −0.5 V for 20 s (applied every 3 min)	[107]
Insulin (5 mg/mL)	PPy	Sodium dodecyl sulfate (SDS) (0.1 M)	PPy NPs were prepared using H_2O_2 as oxidizing agent. The encapsulation was achieved by adding the insulin into the dispersion of NPs	Constant potential of −1 V (for 20 min)	[110]
Curcumin (0.027 M)	Neutral PEDOT	Sodium dodecyl sulfate (SDS) (0.009 M)	Chemical polymerization by the addition of ammonium persulfate in the aqueous solution containing the drug, monomer and surfactant	Constant potential at 0.50, −0.50, −1.00, and −1.25 V (for 3 min)	[111]
Fluorescein, piroxicam and insulin (3 mg/mL)	PPy	Sodium dodecyl sulfate (0.1 M) (SDS)	Chemical polymerization is achieved in aqueous solution incorporating the drug to the reaction medium	Constant current at −50, −100, −200 and −300 μA	[112]

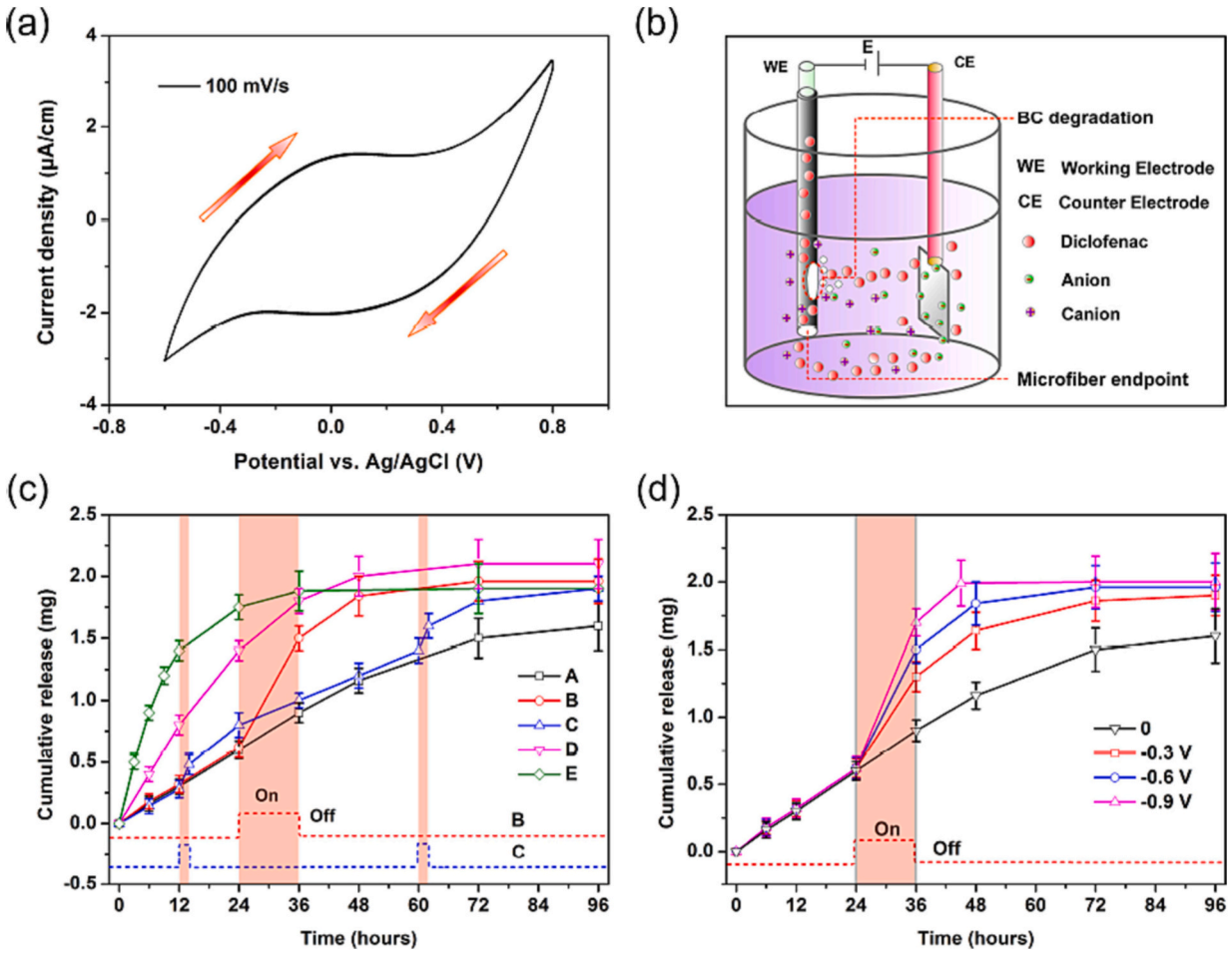

Fig. 8. (a) BC/PEDOT microfibre CV curve in 0.1M PBS buffer solution; (b) Schematic of electrically stimulated microfibers; (c) Electrical stimulation of drug-loaded BC/PEDOT microfibers, (A) Diclofenac sodium release patterns from microfibers without electrical stimulation as a control, (B) With a 12 h stimulation after 24 h, (C) With 2 h stimulation at the interval of 12 h and 60 h, (D)/ With a continuous stimulation from the beginning, (E) Drug loaded BC microfibers without electrical stimulation; (d) Diclofenac sodium cumulative amount released from the microfibers into distilled water as a function of applied electrical current, the electrical current was switched on and off at intervals of 24 hours. Reproduced with permission from reference [122].

MFs have been efficiently fabricated by electrospinning and exhibit tangible advantages for electrically modulating curcumin release. Changes at the MFs are caused by the migration of PEDOT NPs from the interior to the surface when potential pulses are introduced. The drug release scales linearly with the number of potential pulses. This is a prospective method for developing programmable drug delivery systems [123].

Amoxicillin-loaded PAni nanofibers were encapsulated in polyacrylamide hydrogel to construct a viable drug delivery system. Due to the presence of PAni nanofibers, acrylamide polymerization, and reticulation enables more even circulation of conductive fillers, resulting in a 3D continuous polyaniline network of nanofiber backed up by hydrogel matrix [124]. Amoxicillin was pre-loaded into PAni fibers to prevent drug release within the hydrogel system itself. The hydrogel's pattern of drug release from the composite demonstrated an "ON-OFF" cyclic pattern of drug release from cathodic electric stimulation application/removal owing to activation/deactivation of polyaniline *via* electrochemical reduction. This substance is a good alternative for the electrostimulated administration of drugs because of its potential to serve as a low-voltage switch delivery and low cytotoxic property against fibroblast cells of the mouse (noted viability 80%). The majority of transdermal drug delivery solely relies on the transportation of ionized drugs by means of electromigration. Owing to the redox intrinsic characteristics of CP filler in the study, drug release through polyacrylamide/PAni hydrogel *via* electrostimulation was achieved. The prepared hydrogel also has the potential to be used when the drug is in either a neutral state or model conditions.

A novel mesoporous hybrid silica (MS)-coated with carbon nanotubes (CNTs) nano platform was developed by Bing Li et al. for phototherapy and drug release mediated by the stimulation of near-infrared (NIR) laser. The anticancer drug Doxorubicin (DOX) has an exceptionally significant drug loading ability of up to 80% (weight) when it is chemically grafted onto the responsive CNT@MS. The human serum albumin (HSA) shell's absorption serves as a biocompatible interfacial system. It has been demonstrated that the drug only releases into solution after photothermal stimulation and separates itself from the nanocomposite. It has also been shown that such intelligent platforms can deliver medication in response to a variety of pulsatile NIR excitations with controlled temperature profiles. In regards to the antitumor activity, researchers demonstrated that the fundamental factor responsible for cancer cell toxicity was the photothermic impact of the nanocomposites caused by NIR light and that DOX administration through the NIR light boosts toxicity, enabling a synergistic effect to apoptosis of tumor cells. Finally, when nanocomposites were encapsulated in a hydrogel that replicates the extracellular matrix, the resulting smart responsive scaffolds effectively released DOX to cells situated above the composite hydrogel in response to NIR light [125].

Wet-spinning procedure to produce PEDOT: poly(styrene sulfonate) (PSS) fibers, which were then used as a template to electropolymerize the PPy outer shell layer was utilized. Ciprofloxacin HCl was employed as a dopant during PPy synthesis, and the release of the drug was measured when the PPy layer was lowered. Electrical stimulation enabled the ciprofloxacin hydrochloride to be released under controlled conditions. The antibacterial efficiency of the integrated and released ciprofloxacin was established against Gram-positive and Gram-negative bacteria. This demonstrates the stability of the drug's antibiotic characteristics during processing and the drug release mechanism employed. Additionally, tests on the fibers in cell culture revealed that neither the fibers' presence nor any released compounds from the fibers had an adverse effect on B35 neuroblastoma cells (as illustrated in Fig. 9) [126]. Table 3 summarises the processes utilized to create and electro-stimulate the production of nanofibers, nanowires, and nanotubes.

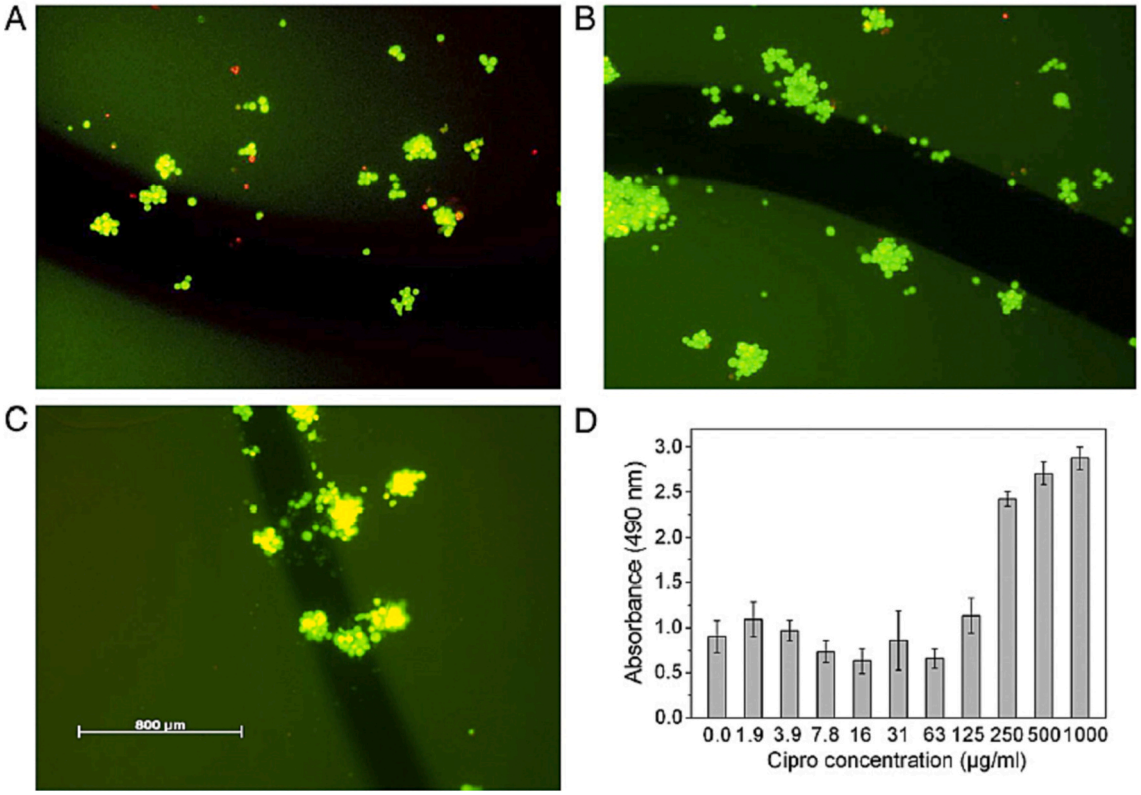

Fig. 9. B35 neural cells cultured on PEDOT:PSS-CHI (A), PEDOT:PSS-CHI-Ppy.Cl (B) PEDOT:PSS-CHI-Ppy.Cipro (C) fibres over a period of 72 h (scale bar 800 µm). Calcein AM/PI staining generates a strong fluorescent green in metabolically active cells and red in membrane compromised cells, respectively. (D) illustrates the findings of an LDH release cytotoxicity study on the impacts of a dilution series of Cipro on B35 cells after 48 hours of incubation. Reproduced with permission from reference [126].

Table 3
Summary of several drug delivery systems incorporating CPs based nanowires, fibers and nanotubes. The entries are classified by the drug charge at a neutral pH.

Active ingredient	Type of polymer used	Type of dopant used	Synthesis procedure	Release stimuli	Reference
Dex (3.75% w/v)	PEDOT	PBS 1x	Polymerization by coating CP onto PLGA nanofibers core loaded with the drug at 0.9 mA/cm2 for 30 min. The PLGA core was dissolved in dichloromethane for 10 min	Constant potential at 1 V (for 10 s)	[43]
ATP (0.20 M)	Anionic PPy	$LiClO_4$ (0.07 M) and drug	First layer: CA with $LiClO_4$ at 1.0 mA cm^2 for 150 s Second layer: ICP nanowires with the drug and $LiClO_4$ at 1.0 mA cm^2 for 600 s	Constant potential at −0.80 V for 45 h. The surface was coated with a Mg layer to induce self-powered release	[118]
DOX (0.0018 M)	Cationic PPy	Biotin (1 mM) and PSS (0.01 M)	Biotin with PSS nanowires at 1 V for 6, 12, and 18 minutes. Thereafter, the biotin carboxyl residue was activated, and the system was incubated in a drug solution at 4°C overnight	Constant potential at −1 V for 1 min	[119]
Diclofenac	PEDOT	$FeCl_3$ (0.154 M)	PEDOT core-shell microfibers obtained by immersing diclofenac-loaded bacterial cellulose microfibers into a monomer solution of ethanol with $FeCl_3$	Constant potential at −1 V for 1 min	[122]
Curcumin (0.5 mM)	Neutral PEDOT	DBS (0.01 M)	Electrospun PCL fibers loaded with PEDOT NPs (10 mg/mL) and curcumin (1.04 mg/mL)	1, 3 and 5 pulses of 1.0 V (each pulse lasts 60 s) with a time lapse of 5 s in between	[123]
Ciprofloxacin hydrochloride (0.05 M)	PEDOT	Drug	PEDOT:PSS fibers were coated with PPy layer doped with Ciprofloxacin hydrochloride. The latter was obtained by CP at 0.5 or 2.0 mA/cm^2 for 10 or 20 min	Constant potential at 0.3 V and reduced at −0.26 V	[126]
ATP (0.01 M) and Dex (0.005 M)	PPy	p-Toluene sulfonate (0.085 M)	CP nanowire network with p-toluene sulfonate at 0.477 mA/cm^2 for 1600 s. The drug was achieved by dropping it onto the nanowire network. Finally, another PPy layer with p-toluene sulfonate was deposited	CV from −0.9 V to 0.6 V	[127]

5.1.4. Polymeric nanosponges and nanoporous films

Nanoporous sponges and nanofilms are created to improve medicine retention while also achieving enhanced and controlled drug release features. Preparing porous surfaces is an effective way for increasing the outermost area to achieve desired properties. While medicines can be embedded into the polymeric bulk during the polymerization of CP, many additional medications can be incorporated into nanopores (not always as dopant agents), and these pores can be opened [128] or closed [129] by a thin topmost layer of CP. Because drug size and charge are not considered restrictions, in this case, the latter technique produces CP-based DDSs with greater loading capacity. Hard templates, such as Poly (methyl methacrylate) (PMMA) and PSS beads dissolved in a suitable solvent, that be used to achieve porous morphologies [128–132].

Sharma et al. have developed a novel method for producing sponge-like structures by electropolymerized PPy around a PMMA hard template after dispersing PMMA beads over a stainless-steel substrate in a dispersion crystal. PMMA particles were then dissolved in a 1:3 v/v of toluene: acetone mixture before being applied dropwise onto sponge-like Polypyrrole sheets and air-dried overnight at 20°C. For drug entrapment, a thin layer of Polypyrrole was electrically polymerized. The maximum release of the drug was seen when the films were reduced to 0.6 V because of an increase in drug diffusion when the space between nanopores was extended [131].

Jeon et al. have employed CPs as actuators that control the opening and shutting of artificially made pores, which increased ion transport across the porous membrane when open and suppressed it when closed. In the reduced state, the pore size was smaller, whereas, in the oxidized state, it was larger. DBS/PPy was utilized as an electrically sensitive material because its volume fluctuates dramatically depending on the electrochemical state. Polypyrrole doped with dodecylbenzene sulfonate (DBS/ PPy) was electrically polymerized over an aluminum oxide membrane which is porous, and topped with a thin layer of gold (up to 35 percent). These developments have been influenced by several parameter among which movement of solvated ions is one quite important parameter. In has been experiential that polymer matrix expand and contract as solvated ions enter and depart from the polymer matrix [133].

In another research attempt, to overcome the material constraints of biologically active electrodes, modified silica nanoparticles were incorporated into conducting polymers as dopants. Precursors of silica were used to produce thiol-modified particles (TNP). It was subsequently oxidized to produce sulfonate-modified nanoparticles (SNPs). Hexadecyl trimethylammonium bromide is added, and this permits the selective synthesis of nonporous and porous SNPs. Fluorescein and rhodamine were utilized as model-drug candidates. Nonporous nanoparticles doped with (PEDOT) hydrogel film offer higher stability during stimulation and charge injection (4.8 mC cm^2), and lower interfacial impedance when compared to PEDOT/PEDOT films (styrenesulfonate). The variety of therapeutic choices is substantially increased to accommodate both electroactive and cationic compounds using SNP dopants while preserving their bioactivity. Drug loading capacity and drug release were increased by 16.8 times. The practicality and its potential application in doping conducting polymers with specific nanoparticles are demonstrated in this study, providing a wide range of possibilities for creating composite materials that will improve chemical sensing, electrical stimulation, and on-demand drug delivery [134].

5.1.5. 3D hybrid structures

DDSs have recently been manufactured employing hybrid materials aimed to enhance properties and multitasking capabilities. Feiner et al. have created a hybrid cardiac matrix that captures electrical inputs from cells while also administering drugs. They were constructed from SU-8 epoxy mesh and a thin gold layer covered in a rough titanium nitride nanoscale layer. Following that, the electrospinning technique was utilized to pour PCL-gelatine fibers onto the electronics, smoothing the adherence of the heart cells (Fig. 7). Fibers were added for multiple purposes, including enhanced cell adhesion, drug diffusion, polymer delamination, and avoidance from the surface of the electrode, with the ultimate aim of the material being able to gather electrical signals from the surrounding cardiac cells. Determining when to initiate the electric stimuli for the drug release is an important consideration [135].

Carbon nanotubes (CNTs) were used as a core component as well as thermal and electrical conductors in a study conducted by Sang-Yu Park et al. The hydrophilic dispersion of chitosan (Chit) was used as the shell unit, and poly(N-isopropyl acrylamide-co-BBVIm) (pNIBBIm) was used as a temperature-sensitive copolymer and drug carrier. The construction

of the CNT sponge framework from the produced CNT core units and Chit shell units ensured connectivity of the CNTs and the uniform distribution was enhanced. The CNT sponge based on 3D hydrogel, specifically the 3D framework of CNT-Chit/pNIBBIm hydrogel, showed a better ability to be utilized in smart transdermal drug delivery in the coming years. In this study, 37% of the drug (Ketoprofen) was delivered to treat musculoskeletal pain, with about 30% shrinkage in the hydrogel after thermal and electrical "ON/OFF" switches. Due to the 3D frame, the hydrogel of nanocarbon possesses excellent mechanical, physicochemical, thermal, electrical, and biocompatible properties resulting in phenomenal thermal and electrical stimulus-responsive character that is capable of controllable and/or controlled drug delivery approach for an array of medical and biomedical application [136].

For efficient drug delivery, a personalized dose is necessary for Warfarin because it has a narrow therapeutic index which is impossible to achieve with commercially available products at the moment. Furthermore, geriatric and paediatric patients may have trouble ingesting solid oral dosage forms. Taking these facts into consideration, a group of researchers aimed to investigate the use of semisolid/hydrogel extrusion 3D printing to create orodispersible films containing Warfarin in order to address these concerns. Using extrusion 3D printing, translucent, smooth, and thin orodispersible films loaded with the drug Warfarin for therapeutic use were effectively produced (3.9–7.4 mg). Semisolid/hydrogel extrusion 3D printing is a potential technique for generating orodispersible warfarin films with personalized doses since excellent linearity (R^2=0.9996) was established between prescribed drug concentration levels and the size of the films. It is a one-step procedure that employs disposable and non-reusable syringes to prevent the printing materials from coming into contact with the 3D printer used for printing, offering it a viable technique for in-hospital compounding on demand [137].

5.2. For regenerative medicine and tissue engineering

The most often used CP for regenerative medicine and tissue engineering applications is PPy. Schmidt and colleagues devoted a significant amount of time and effort in investigating the potential applications of PPy and similar systems in regenerative medicine. Fonner et al. provided a unique combinatorial computational technique in which the properties of chlorine-doped derivative (PPyCl) and native undoped CP (PPy) were thoroughly examined and their compatibility with human tissues was anticipated. They observed that doping improved backbone flexibility and that the total charge (approximately 80%) in the PPyCl derivative was focused on the PPy rings nearest to chlorine. A variety of PPy derivatives can be synthesized and proposed for application in tissue engineering and regenerative therapy based on flexibility and charge present on the surface [138].

Hydrogel wound dressings exhibiting conductivity, antibacterial, and antioxidant properties were developed by Shen Wang et al. [139]. To construct the hydrogel, dopamine was added to an alkaline solution, in which it is polymerized to form polydopamine (PDA). PDA was then utilized to convert $AgNO_3$ (silver nitrate) into Ag nanoparticles (AgNPs) to produce a composite of PDA and AgNPs (PDA@AgNPs). To prepare PDA@AgNPs-PPyGel-Fe hydrogels, polypyrrole-grafted gelatin (PPy-Gel) was dissolved in a PDA@AgNP solution and cross-linked with ferric ions. The hydrogels that are created contain pores that range in size from 20 to 50 μm and are soft and ductile. The hydrogels' high water absorption rate suggests that they have the capability of absorbing wound exudates. In order to efficiently transfer bioelectric impulses for skin regeneration, PPy and Fe^{3+} furnish the hydrogels with slightly greater conductivity than that of skin tissue. Hydrogels were capable of self-healing and the self-healing mechanism can be accomplished in a short period of time owing to ionic interactions and hydrogen bonding. While AgNPs provided hydrogels with strong antibacterial properties, PDA facilitated them with strong antioxidant properties. The hydrogels exhibited good swelling ability, increased blood compatibility, and cytocompatibility and exhibited porous architectures with tunable pore sizes. While PDA promotes antioxidant properties, PPy boosts conductivity.

A significant barrier to wound healing is infection. Dressings having antibacterial properties are greatly desired to accelerate wound healing. Oxidative coupling of catechol groups utilizing horseradish peroxidase (H_2O_2/HRP) catalysis was employed to achieve adhesive, antibacterial, antioxidant, and conductive properties of the dressings [140]. Gelatin-grafted-dopamine (GT-DA) and polydopamine-coated carbon nanotubes (CNT-PDA) were polymerized to obtain GT-DA/chitosan/CNT hydrogel composite and Doxycycline was added to attain the antibiotic effect to treat infected wounds. Furthermore, CNT-PDA equipped the prepared hydrogel with superior photothermal effects, resulting in efficient antibacterial activity against bacteria both in-vitro and in-vivo. The PDA and catechol groups contributed to the adhesiveness of wounded tissues. By altering the CNT-PDA concentrations, the hydrogels' swelling, porosity, mechanical, rheological, and conductive properties, and degradability were all precisely controlled. The high biocompatibility of these hydrogels was confirmed by testing for haemolytic and cytotoxicity using L929 fibroblast cells. These hydrogels had excellent effects on full-thickness skin wounds in mice, as denoted by the deposition of collagen, wound closure, immunofluorescence staining, and histomorphological examination outcomes (Fig. 10). Briefly, the developed conductive and adhesive antibacterial GT-DA/chitosan/CNT hydrogels demonstrated incredible capability as well as versatile wound dressings for augmented healing of infected wounds.

In order to create unique and adaptable bioinks for bioprinting FRESH (freeform embedding of suspended hydrogels) extrusion with practical benefits in bioelectronics. Paola Sanjuan-Alberte et al. have proposed a new-fangled method [141]. A decellularized extracellular matrix, which is the major component of this bioink, offers a favourable environment for the development of cells with specialized biochemical signalling pathways. Successfully produced 3D bioprinted constructs that included human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) while retaining high cell viability. MWCNTs (multiwalled carbon nanotubes) were deposited into the hydrogel's matrix, increasing the electrical and morphological characteristics of 3D printed decellularized extracellular matrix (dECM) hydrogels, and to further investigate the actuating and sensing potential of the prepared conductive material, electrical stimulation was used. The researchers' findings demonstrated that using an electrically CP in association with external electrical stimulation can cause the rate of contractions to resemble those of pathophysiological conditions. This illustrates the material's potential for usage in the fabrication of smart conducting hydrogel scaffolds for applications in actuating and/or biosensing. Results from RT-PCR showed a considerable improvement in the maturation markers of hPSC-CMs and a downregulation of Ca^{2+} L-type currents, which are frequently seen in pacemaker heart cells and it may even suggest that the cell profile is more similar to that of the myocardium. All these outcomes propose multifunctional and versatile applications of CPs and their composites in treating cardiovascular diseases with the implication of regenerative medicines and tissue engineering.

5.3. For physiologically significant molecular sensors

Biosensors identify molecules such as antigens, carbohydrates, neurotransmitters, hormones, and antibodies, at incredibly low quantities [6,142–145]. CPs have gained significant attention in recent years for their application in a range of biosensors. Biosensors are employed in the creation of microelectronic sensing devices since they perform well even under adverse conditions. CPs-based electrochemical sensors have immobilized numerous biomolecules with promising efficiency while also allowing for fast transfer/exchange of electrons [146,147]. Polysaccharides and proteins, which are anionic biospecies, are typically used in CPs for biological applications. These biosensors sense touch, force, or pressure and function as sensory and/or electrochemical

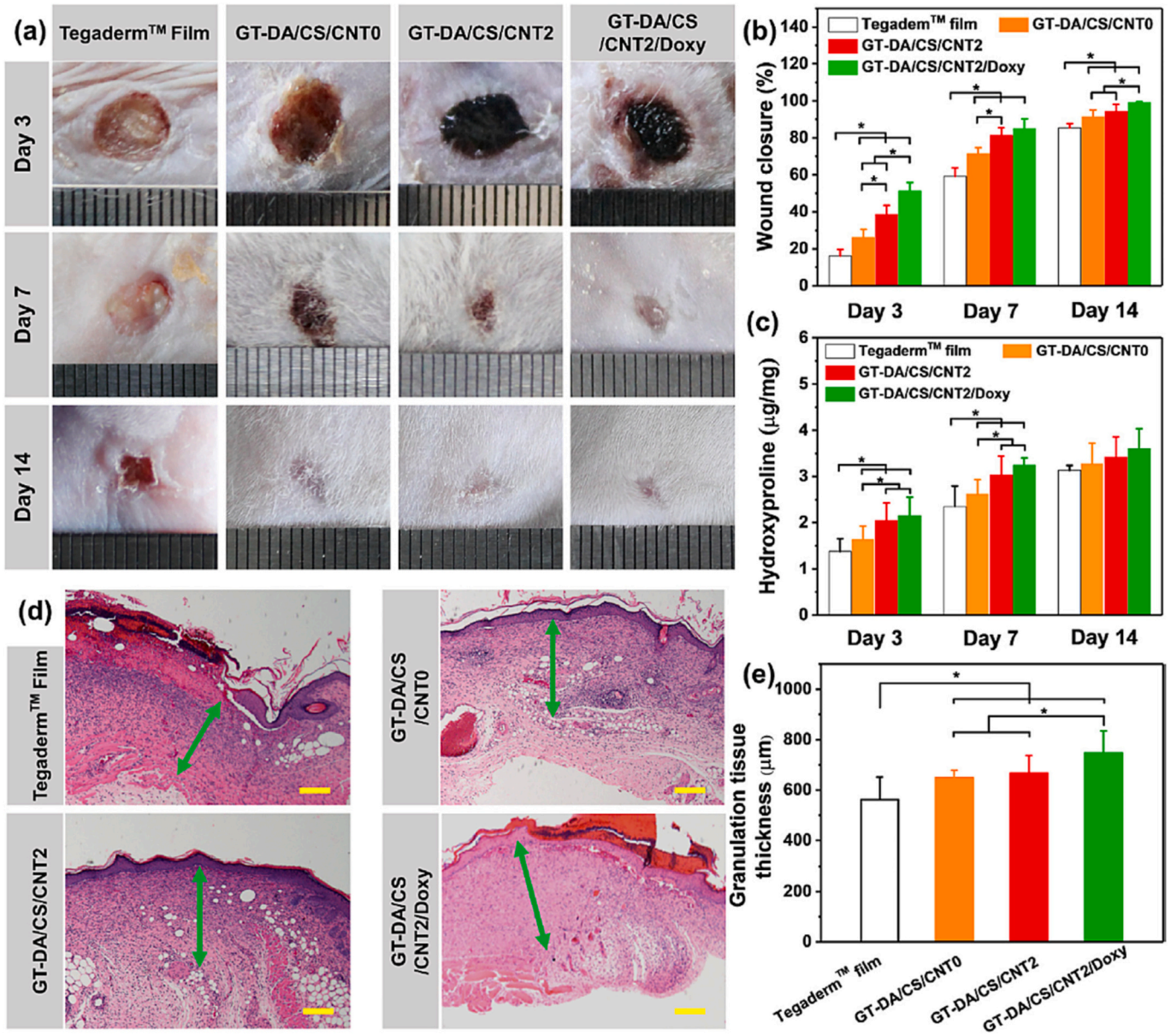

Fig. 10. (a) Images of wounds at 3rd, 7th and 14th day treated with Tegaderm™ film, GT-DA/CS/CNT0, GT-DA/CS/CNT2, and GT-DA/CS/CNT2/Doxy hydrogel; (b) Wound closure percentage in each group (*$P<0.05$); (c) Newly formed skin tissue hydroxyproline concentration (*$P<0.05$); (d) Skin tissue granulation light microscopic images on the 7th day (indicated using green arrows, scale bar: 200 μm). (e) Granulation tissue thickness for each group on the 7th day (data shown as the means±SD, $n = 5$). Reproduced with permission from reference [140].

sensors, or they can sense heat and thus function as thermal sensors [148]. In recent years, incredible developments and discoveries in biosensor clinical testing have occurred. PPy is a prospective electrical conductor that is stable in water and air. Its synthesis is simple and rapid and uses electrochemical or chemical processes. As a result, PPy is commonly utilized to design and develop biosensors [149,150].

When antibody-modified polymer and antigen interact, changes in ion flux out of and into the CP membrane generate signals. Gobi et al. presented an immunosensor for insulin detection based on surface plasmon resonance in a similar way of detection. High sensitivity and specificity for the detection of insulin were achieved by the immunosensor system using the indirect competitive immunoassay method. This was the first of-its-kind regenerable immunosensor providing a quick, label-free, and completely automated analytical system that has been used to report a low detection limit of 1 ng ml-1 insulin with a response time of less than 5 min [151]. Tarabella and colleagues investigated the sensitivity and monitoring capabilities of organic electrochemical transistors (OECTS) which is based on (poly (3,4-ethylenedioxythiophene)): PSS as a real-time biosensor for the monitoring of liposome dynamics, identifying the formation of liposome and evaluations in electrolyte solutions *via* ion-to-electron amplified transduction [152].

Although the majority of sweat glucose sensors are intended to use during physical activity and other activated stimulation-induced sweating. On the other hand, natural sweat and/or sweating offers a convenient alternative that has no impact on users. It can be accessible during inactivity without interfering with one's way of living, and maintains a relationship between blood glucose and sweat glucose. In the absence of external activities that cause sweating, a sweat glucose biosensor with the non-invasive approach of simple hydrogel patches for quick collection of natural sweat was developed (Fig. 11). The wearable hydrogel patch acts as a medium for electrochemical sensing and quickly absorbs natural hand perspiration. The hydrogel-based patch contains poly(3,4-ethylene dioxythiophene) nanocomposite (PEDOT NC) doped

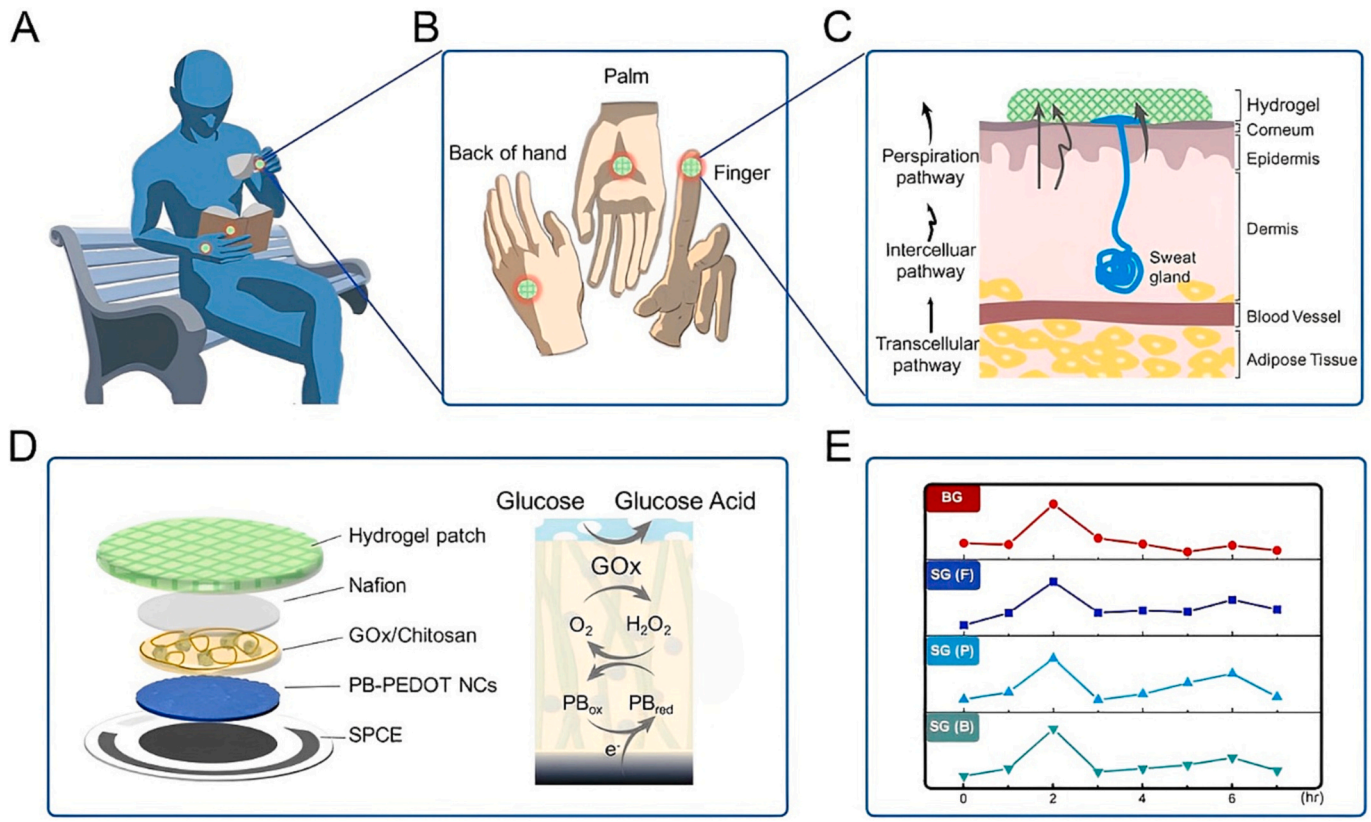

Fig. 11. Schematic representation of the design, mechanism involved, and the usage of natural sweat as a sample for glucose sensor. (A) The hydrogel patch can be placed at different positions on the body for the sampling of sweat during resting time. (B) The positions to place the patch on the hand for sweat collection are the palm, back of the hand, and fingers. (C) The favourable glucose sweat sampling pathways for natural sweat hydrogel patches. (D) Schematic representation of the multiple layers in PB-PEDOT NC enzymatic electrode of the sweat glucose monitoring device and the working mechanism GOx with the PB probe. (E) The sweat glucose monitoring device can identify sweat glucose levels without externally applied stimulation or high-intensity physical activity at various locations such as the palm, back of the hand, and finger. Reproduced with permission from reference [153].

electrode with Prussian blue (PB) resulting in PB-PEDOT NC; which offers a low-cost, reliable electrocatalytic activity for measuring sweat glucose. By focusing on parts of the hand with a high density of sweat glands during everyday routine labor, even for inactive activities, this sensor enables the quick assessment of sweat glucose uptake. It is more realistic for patients with diabetes to routinely test their blood glucose levels. The non-invasive sweat glucose measurement is significantly enhanced by the PB-PEDOT NC electrode's tailored surface, which also provides good stability and electrocatalytic activity [153].

Using electroconductive hydrogel composed of three-component namely carrageenan, polyvinyl alcohol, and PEDOT:PSS (poly(styrenesulfonate)) incorporated into the stent as a biofuel cell (BFC) electrode was investigated by Christina G. Antipova et al. [154]. The produced composite hydrogel's mechanical stability was due to its conventional double-network of the produced hydrogel. The hydrogel's mechanical behavior was compared to that of a vein since its intended purpose involves integration into the circulatory system. Constructive models were selected for the purpose of obtaining analytical parameters of deformation curves that are relevant to both hydrogel and vein. The deformation curves are well-fit by the Ogden and Gent models. The hydrogel's shear modulus was found to be comparable to the veins. This indicates PEDOT: PSS-based material is adequate enough for stable and safe operation under the mechanical impacts caused by typical blood flow in addition to having strong cycle stability. Electrochemical investigation showed that such a device is capable of 3.98 x 10 5 W of power. By modifying the stent material while taking into consideration of its functions as a BFC cathode, the cathode portion can be enhanced, allowing for an even larger boost in power. Thus, it's feasible to develop a biofuel cell incorporated within the stent for cardiovascular surgery that enables the implantation of such power-generating devices using all stenting alternatives.

5.4. *In the neural interfacing systems*

The intricacy of the nervous system originates from the numerous networks of neurons and accompanying cells that engage together to analyze internal and external information that governs moods, speech, motion, sight, and hearing. To better understand the nervous system, researchers are curious to learn about the mechanics of neural networks and how to treat certain neurological ailments. The neural interface acts as a link between neural tissues and electrical devices, creating a link between electronic and biological systems. This allows researchers to investigate and manipulate brain networks that support both healthy and pathological states. Neural electrodes can be used to study nerve networks and their reactivity to bioactive chemicals. Neuronal electrodes implanted in the brain enable the recording of neuronal impulses, which assists in the research of brain systems and gives efficient stimulations to degraded brain areas to cure neurological illnesses including epilepsy, blindness, Parkinson's, deafness, and movement problems. As a result, having reliable data acquired from the brain for accurate neural system analysis and precise stimulations is crucial for neurological research. A brain electrode with excellent conductance, good biocompatibility, and low resistance is required for clinical diagnosis. Noble metal neural electrodes may not be suitable for implantation for longer duration and recording of the signal due to the mechanical hurdle between the stiff metal electrode of Metal = 74–530 kPa [196] and soft neural tissue of the brain = 2.1–3.7 kPa [155], spinal cord = 3–6.3 kPa [156], and Peripheral nerve = 576–840 kPa [157,158].

A significant foreign body response (FBR) can occur at the electrode-neural tissue contact, leading to the electrode and surrounding tissue malfunction. The current focus of the research is on making stable, tiny, and high-density microelectrodes that can enhance recording and stimulation specificity in both in-vivo and in-vitro uses. Brain electrodes with smaller geometrical sizes have been widely employed to perform precise and selective neural electrode implantation, lowering the risk of injury to neural tissues and microelectrodes. The tiny geometrical size of these microelectrodes restricts their electrical functions in contrast to the bulkier ones, resulting in increased resistance and reduced charge injection capabilities. To overcome this deficit, the surface of microelectrodes that is geometric can be reduced to obtain porous, conductive, and bio-supportive nanostructures [159].

Microelectrodes which are rough in nature and microelectrode coatings on common planar microelectrode substances like platinum and gold are being researched as ways to increase the electrochemical surface area while keeping the required geometric area. These gold, silver, and platinum metal electrodes are coated with materials that are conductors using chemical and electrochemical deposition. Conducting materials include graphene and its oxide [160], iridium oxide (IrOx) [117], nanotubes of carbon [161], and carbon polymers (CPs) [162]. CPs have been recommended as a potential electrode material for the next brain electronics with decreased neural interface impedance due to their high conductivity, exceptional charge transport capacity, and acceptable biocompatibility. Many researchers have focused on coating CPs such as Polypyrrole [163], PAni [164], and PEDOT [165] on the surface of these electrodes for efficient characteristics.

The susceptibility of modified neural electrodes is lower than that of bare metal electrodes because of the improved surface area which is electrochemically active following the deposition of CPs. Zhou et al. used potentiostatic or galvanostatic electrochemical accumulation procedures to coat a Poly (3,4-ethylenedioxythiophene) and multiwall CNTs composited thin film onto platinum microelectrodes. The PEDOT/multiwall CNT film formed using the galvanostatic method has a porous morphology consisting of twisted rods of smaller diameters than the coating created using the potentiostatic method (50 nm). These two techniques produced PEDOT/multiwall CNT-coated microelectrodes with impedances almost two orders less than bare platinum microelectrodes at 1 kHz [166].

The endurance of CP coating on the microelectrodes is significant especially for persistent observation of brain tissues. Researchers have sought to solve these challenges by doping inorganic and organic chemicals in the CP coating, which enhances the adhesion of the CP films to the substrate and the bio-supportive action of the electrodes that correspond to brain tissues. To polymerize Poly (3,4-ethylenedioxythiophene): tetrafluoroborate onto the platinum neural electrode, Bodart et al. utilized three different solvents for doping. The composite electrodes' mechanical and electrochemical stability was examined. According to the findings, Poly (3,4-ethylenedioxythiophene)/12BF4 coatings coated on Pt-Ir microelectrodes in organic solvents were physically durable after five minutes of sonication and could retain >80 % of their charge storage capacity. After 2–3 minutes of sonication, coatings created in de-ionized water detached off the Pt-Ir microelectrodes. After 2 weeks of immersion in a solution of Phosphate buffered saline of pH 7.4, the resistance of Poly(3,4-ethylenedioxythiophene)-coated microelectrodes was enhanced when prepared using propylene carbonate compared to acetonitrile which resulted in lower than the Pt-Ir electrode alone. The Pt-Ir electrode coated with the Poly (3,4-ethylenedioxythiophene : BF4 film from organic solvents was more stable following sonication [167]. Cui et al. polymerized PPy and a biomolecule (a silk-like polymer containing fibronectin fragments and nonapeptide (CDPGYIGSR) on neutral probe gold electrode sites electrochemically. Aside from improved electrical properties, the Polypyrrole/SLPF-coated gold electrodes generated more cells of 1:250:6 cells per site than the uncoated gold electrodes. Furthermore, neuroblastoma cells from humans chose predominantly seeded onto the Polypyrrole/CDPGYIGSR-modified electrode over the electrode covered with Polypyrrole/CH_3-COO. Cell activities on neural electrodes can be controlled to induce the creation of integrated tissue-electronic interconnections as a result of additional doping of different kinds of biomolecules in the CP coating applied to the neutral electrode [168].

Carmena and colleagues have investigated the applications of (poly (3,4-ethylenedioxythiophene)) (doped with PSS) covered microelectrodes as cortical neural prosthetics in a study [72]. When compared to Pr-Ir electrodes, electrodes that are coated with PEDOT demonstrated greater signal-to-noise recordings and also improved charge injection during in-vivo prolonged testing of microelectrode arrays transplanted in the brains of the rats. Feng et al. created nanofibers of PEDOT mats using electrospinning and in-situ interfacial crosslinking which uses $FeC1_3$ as an oxidant [121]. Nanofibers of PEDOT mats possessed fairly good mechanical properties, were flexible, had an electrical property of 7.80+0.4 S cm1, and were biocompatible with cell culture plates. Sui et al. have investigated the electrochemical properties of PEDOT: PSS coatings coupled with a layer of dopamine on the electrodes made of platinum in-vitro and in-vivo. The (poly (3,4-ethylenedioxythiophene)): PSS/dopamine-covered electrodes were installed into the striatum area of rats' brains for in-vivo investigations. When platinum electrodes were electrically stimulated, the PEDOT: PSS/dopamine coatings were shown to lower the electrode impedances, enhance the charge storage capabilities, and release substantial quantities of dopamine. PEDOT: PSS/dopamine-coated implant electrodes might be utilized to treat Parkinson's disease, according to the findings [169].

Poly(N-isopropylacrylamide-co-N-isopropylmethacrylamide) (P(NIPAm-co-NIPMAm) and P3HT6S were utilized in order to develop novel conductive semi-IPN (interpenetrating polymer network) hydrogel. The chemical structure of polythiophene was altered and synthesized in order to ensure water solubility, which was necessary to promote the formation of the hybrid hydrogel. Investigating the poly[6-(3-thienyl)-hexanesulfonate] (P3HT6S) concentration and its influence on the morphological features of P(NIPAm-co-NIPMAm) hydrogel formulation revealed similarities to hydrogels with P3HT6S concentrations till 2%. The P(NIPAm-co-NIPMAm)/P3HT6S hydrogel's chemical and thermal properties were evaluated and compared. Concerning the conventional hydrogel formulation, the proposed hybrid hydrogel's mechanical, electrochemical, and electrical properties were significantly improved. Thereby, it was demonstrated that the developed formulation has the ability to enhance neural electrical signal conduction in physiological conditions and optimum mechanical integration into the brain tissue/neurons (Fig. 12**)**. Additionally, it was shown that neural progenitor cells (NPCs) grown on P(NIPAm-co-NIPMAm)/P3HT6S hybrid hydrogel enhanced the survival of two primary cell types present in the central nervous system which are astrocytes and neurons [170].

In applications like nerve conduits and neural probes, electrical and biological impulses must be incorporated with the neurons. Following the integration of a co-dopant such as nerve growth factor (NGF) in the electrochemical deposition of CPS, Polypyrrole and (poly (3,4-ethylenedioxythiophene)) were tested for their ability to bring forth distinct biological interactions with neurons [171,172]. PC12 (rat pheochromocytoma) cells connected to Nerve Growth Factor-modified substrate with stretched neurites on both PPy and (poly (3,4-ethylenedioxythiophene)), demonstrating that the Nerve growth factor in the polymeric matrix is physiologically active. This technology might be useful to make materials that are suitable for both physiological and electrical stimulation [172].

6. Conclusions

Since CPs and CP-based composites subsume metallic and polymeric properties which combine the flexibility of polymers with the conductivity of metals, are exhilarating prospects for drug delivery applications

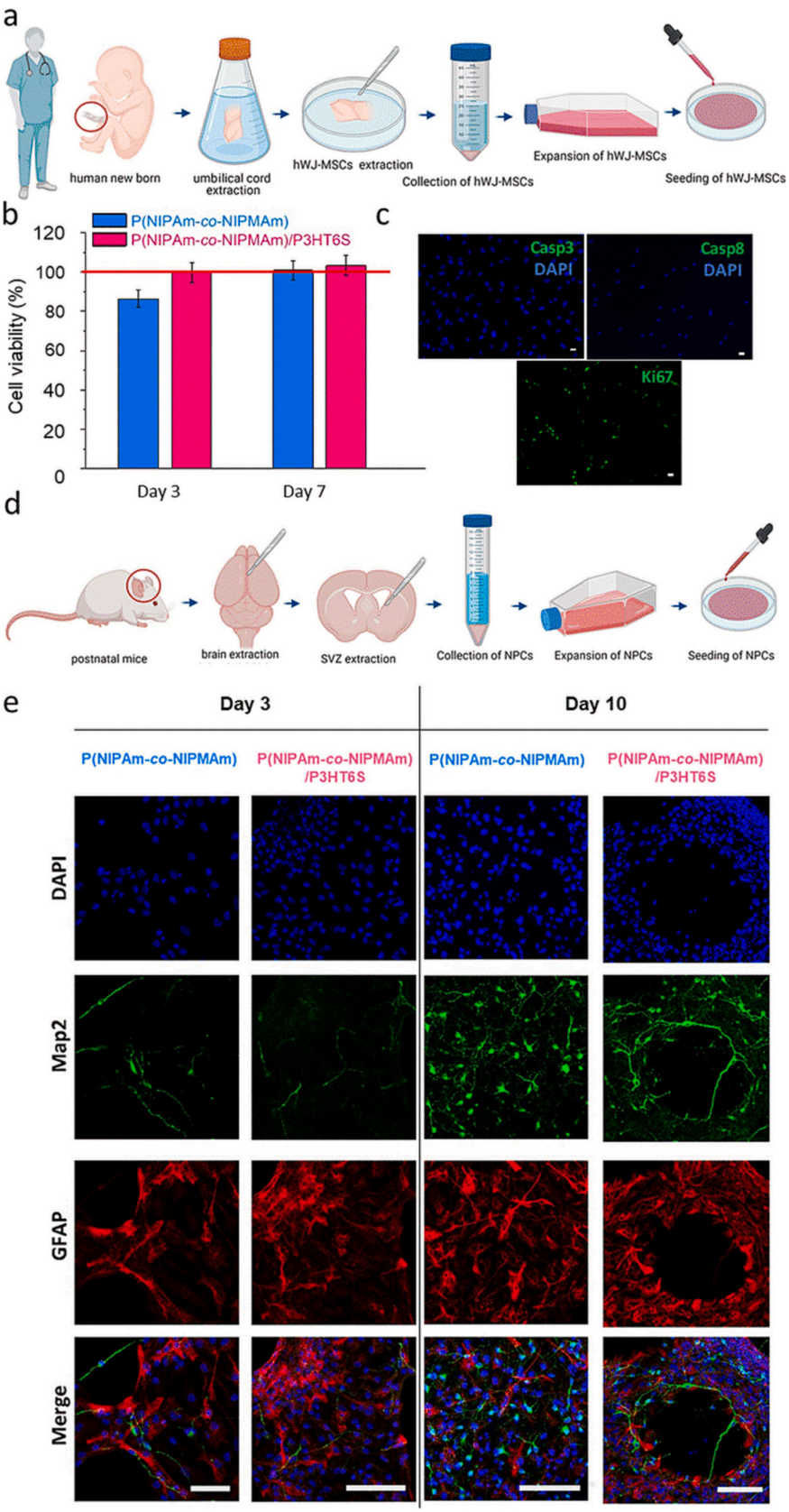

Fig. 12. In-vitro cell studies outcomes on P(NIPAm-co-NIPMAm)/P3HT6S and P(NIPAm-co-NIPMAm) hydrogels. (a–c) hWJ-MSC culture: (a) Schematic depiction of cell isolation from the human umbilical cord; (b) At each time interval tested, the cell viability for both hydrogels were found to be high in the conditions. Data are normalized to control condition (TCP, red line) and expressed as relative percentages; (c) Captured confocal images for Casp3, Casp8, and Ki67 expressed in green color *via* culturing hWJ-MSCs on the P(NIPAm-co-NIPMAm)/P3HT6S hydrogel demonstrated the absence of Casp3 and Casp8 apoptosis markers, while demonstrating the presence of the Ki67 proliferation marker (green). DAPI nuclear stain (blue). Scale bars: 10 μm. (d, e) NPC culture: (d) Depiction of cells isolation from mice subventricular zone. (e) Confocal images of hydrogel substrate cultured with neurospheres at time intervals of 3 and 10 d.v.i, depicting the maturation of Map2-positive neurons (green colour) and GFAP-positive astrocytes (red colour) during the culture time. DAPI nuclear staining (blue). Scale bars: 100 μm. Reproduced from reference [170]: available *via* license Creative Commons Attribution-Non-Commercial-No Derivatives 4.0 International.

and implants. They're appealing because of their biocompatibility and ability to be precisely targeted, controlled, and fine-tuned for constructing new drug delivery systems. They can also be loaded into hydrogels and metallic electrodes to form a composite material for tissue diagnostics, medicine delivery, and electrical stimulation. High-efficiency brain recording electrodes with considerably increased biosupportive nature and sensitivity may be prepared by coating nanostructured CPs onto metallic electrodes. Polymers are coated on the surface by CPs utilizing a variety of procedures like inkjet printing, photolithography, and electrodeposition to create flexible electronics that adapt to the epidermis of tissues. Polymeric photoresists can also be used in conjunction with metal electrodes to create ultra-flexible CP-based composites with mesh and thread-like morphologies. Injectable electronics with these ultra-fine CP-based composites are conceivably employed for neurological monitoring, chronic tracking, and single-neuron brain mapping. The mechanical function and sturdiness of these technologies could be enhanced further for clinical translation. However, there have been various red flags concerning the biosafety of implantables and injectables due to certain components used in their fabrication, such as metallic chromium and highly cross-linked nondegradable SU-8, which have both been associated with toxicity.

7. Way forward and challenges

CPs offer exciting prospects for implantable devices and delivery systems in biomedicine and therapeutics, ranging from electrode-related coverings for high brain stimulation to scaffolds for tissue regeneration purposes. Bioabsorbability, on the contrary, is one of the paramount limitations due to its high natural inclination to degradation or break down. However, further substantial in-vivo examinations are necessary to advance to the next level of study. Importantly toxicity testing and toxicological profile are also necessary before a breakthrough in human clinical trials. CP research for utilization in human beings is still in its cradle phase and a bright future is just around the corner.

Optimal designing of micro or nanoparticles for therapeutic applications is essential to maintain a tight balance in manufacturing time, intricacy, efficacy, and price. The fabrication of CPs films is the most basic and straightforward procedure. Nonetheless, these CPs films are quite often fragile and have poor structural performance. Drug retention can also be improved by raising the surface volume ratio for drug entrapment. High-end CPs that require electrical and/or electrochemical cues to induce controlled release have recently been created. So far, the most impressive DDSs have to be self-powered devices based on magnesium substrates since they do not require expensive and sophisticated electrical components for detecting real-time environmental changes and initiating drug release. Future devices will be able to extend their mechanical stability to attain flexible electronics, allowing for more efficient integration into the human body. Besides, a system with better sensing capabilities for stimuli like pH, neural activity, heat, and mechanical forces can be utilized to decide the amount of medicine to be administered. Future technologies will be able to extend in terms of remote drug activation owing to the utilization of CPs as nanoreservoirs. It may also be regarded as the ability of the self-regulating system to maintain a feedback mechanism without the involvement of an operator. A well-known example of high demand is self-regulated insulin delivery, which would revolutionize anti-diabetic therapy by substituting daily injections with monthly self-regulatory injections, improving patient compliance, and changing the lifestyles of millions of diabetes patients. As a result, a better knowledge of the body's electrophysiology is necessary for a personalized and precision-based delivery system.

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Declaration of Competing Interest

Authors declare no conflicts of interest.

Data availability

Data will be made available on request.

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