Electroactive biomaterials: Vehicles for controlled delivery of therapeutic agents for drug delivery and tissue regeneration

DOI:
10.1016/j.addr.2017.12.012

Document Version
Accepted author manuscript

Elsevier Editorial System(tm) for Advanced Drug Delivery Reviews

Manuscript Draft

Manuscript Number: ADDR-D-17-00149R1

Title: Electroactive biomaterials: Vehicles for controlled delivery of therapeutic agents for drug delivery and tissue regeneration

Article Type: SI: Wound healing & Scar war

Keywords: Piezoelectrics; Conductive polymers; Photovoltaics; Electrets; Electric signals; Drugs; Wounds

Corresponding Author: Professor Sarah H Cartmell, PhD Bioengineering

Corresponding Author's Institution: School of Materials, University of Manchester

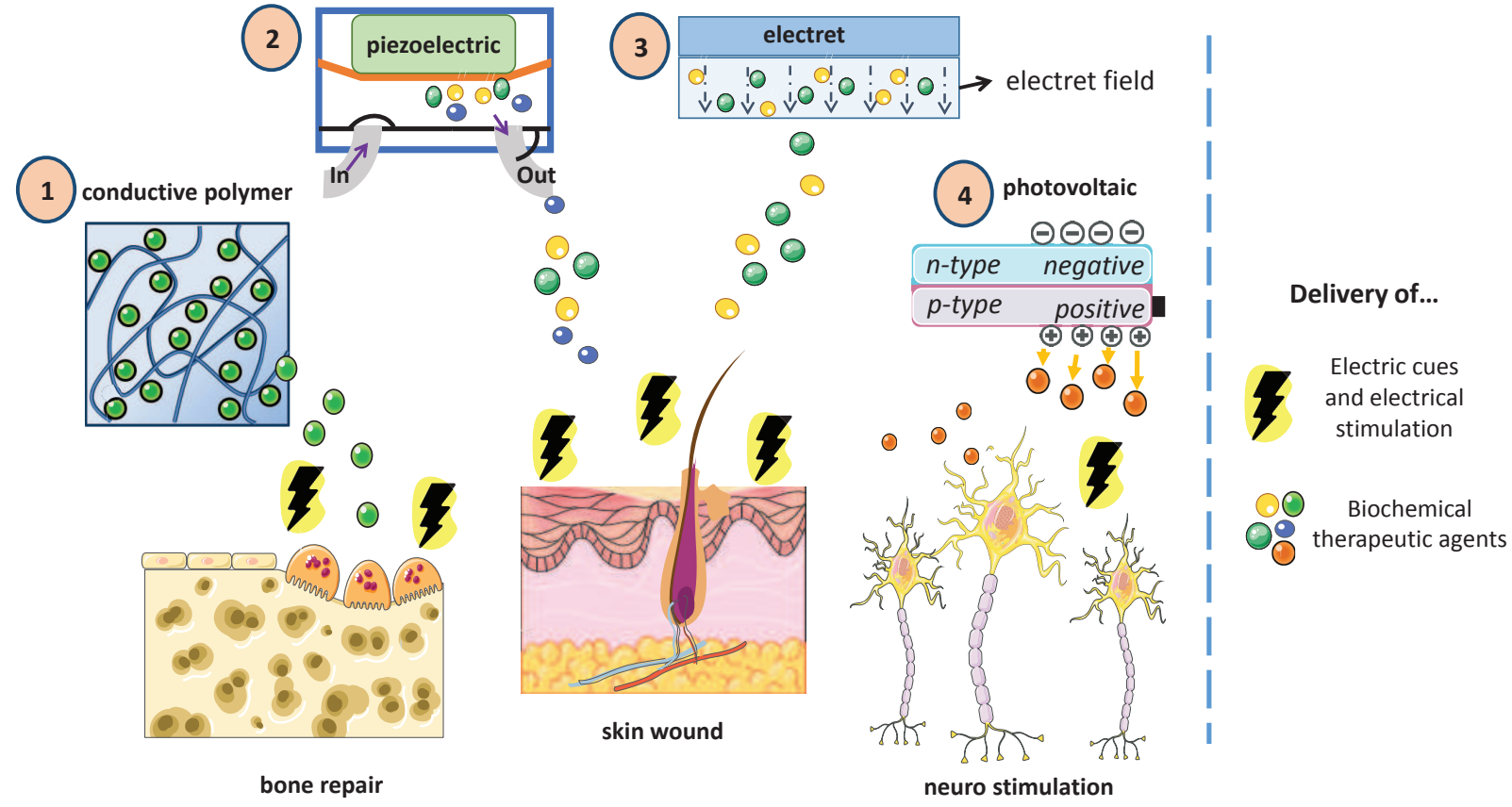
First Author: Biranche Tandon

Order of Authors: Biranche Tandon; Adrian Magaz; Richard Balint; Jonny J Blaker; Sarah H Cartmell, PhD Bioengineering

Abstract: Electrical stimulation for delivery of biochemical agents such as genes, proteins and RNA molecules amongst others, holds great potential for controlled therapeutic delivery and in promoting tissue regeneration. Electroactive biomaterials have the capability of delivering these agents in a localized, controlled, responsive and efficient manner. These systems have also been combined for the delivery of both physical and biochemical cues and can be programmed to achieve enhanced effects on healing by establishing control over the microenvironment. This review focuses on current state-of-the-art research of electroactive-based materials towards the delivery of drugs and other therapeutic signalling agents for wound care treatment. Future directions and current challenges for developing effective electroactive approach based therapies for wound care are discussed.

*Graphical Abstract

Click here to download Graphical Abstract: Graphical abstract.pptx



Electroactive biomaterials: Vehicles for controlled delivery of therapeutic agents for drug delivery and tissue regeneration

Biranche Tandon[a,b], Adrián Magaz[b], Richard Balint[a], Jonny J. Blaker[a,b], Sarah H. Cartmell[a,*]

[a]School of Materials, The University of Manchester, Manchester, M13 9PL, UK

[b]Bio-Active Materials Group, School of Materials, MSS Tower, The University of Manchester, Manchester, M13 9PL, UK

*Corresponding author at: School of Materials, The University of Manchester, Manchester, M13 9PL, UK; e-mail: sarah.cartmell@manchester.ac.uk

Abstract

Electrical stimulation for delivery of biochemical agents such as genes, proteins and RNA molecules amongst others, holds great potential for controlled therapeutic delivery and in promoting tissue regeneration. Electroactive biomaterials have the capability of delivering these agents in a localized, controlled, responsive and efficient manner. These systems have also been combined for the delivery of both physical and biochemical cues and can be programmed to achieve enhanced effects on healing by establishing control over the microenvironment. This review focuses on current state-of-the-art research in electroactive-based materials towards the delivery of drugs and other therapeutic signalling agents for wound care treatment. Future directions and current challenges for developing effective electroactive approach based therapies for wound care are discussed.

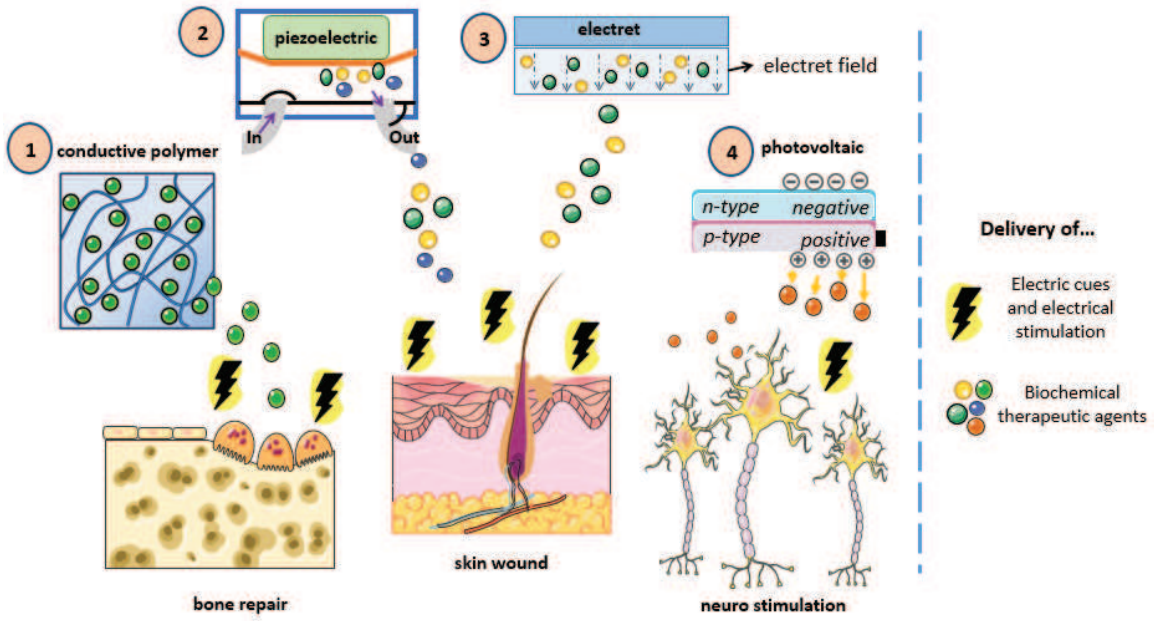
Keywords

Piezoelectrics; Conductive polymers; Photovoltaics; Electrets; Electric signals; Drugs; Wounds

Abbreviations: CP, conductive polymers; PPy, polypyrrole; PEDOT, poly(3,4-ethylenedioxythiophene); PANI, polyaniline; PLLA, poly(L-lactide); PVDF, poly(vinylidene fluoride); PVDF-TrFE, poly-(vinylidenefluoride-*co*-trifluro-ethylene); PHB, polyhydroxy-butyrate; HA, hydroxyapatite; BT, barium titanate; LNKN, lithium sodium potassium niobate; LN, lithium

niobate; PZT, lead zirconate titanate; ZO, zinc oxide; BNNT, boron nitride nanotubes; PV, photovoltaic; NGF, neural growth factor; PSS, polystyrene sulfonate; PAA, poly(acrylic acid); BDNF, brain-derived neurotrophic factor; ATP, adenosine triphosphate; PLGA, poly(lactide-*co*-glycolide); GO, graphene oxide; PEG, poly(ethylene glycol); PCL, poly(ε-caprolactone); PPV, poly(p-phenylenevinylene); PAAM, polyacrylamide; NP, nanoparticle; PEI, poly(ethylene imine); TDD, transdermal drug delivery; PTFE, polytetrafluoroethylene; PP, polypropylene; TMC, N- trimethyl chitosan; PVT, photovoltaic therapy; NPVDs, photovoltaic based nanoparticle cells; MOFs, metal organic frameworks; ES, electrical stimulation; SPAN, self-doped sulfonated polyaniline; PU, polyurethane; KNN, potassium sodium niobate; ROS, reactive oxygen species; P3HT-PCBM, poly(3-hexylthiophene)-phenyl-C61-butyric acid methyl ester; PPy-PTh, polypyrrole-thiophene; PXDOP, poly(3,4-alkylenedioxypyrrole); PFM, piezoresponse force microscopy

Graphical abstract



1. Introduction

Wound healing is a coordinated process relying on precise spatiotemporal mechanisms of action. Significant progress has been made to identify specific signals (e.g. small molecules, cytokines, growth factors, RNA interface, genes, cell-based therapies) of therapeutic benefit [1,2]. To this end, there is great interest in applying these mechanisms to enhance and accelerate wound healing and enable tissue repair that otherwise could not occur naturally. However, despite the advances made in the field, wound regeneration continues to be a constant challenge for health-care professionals.

Injuries to healthy tissues are known to give rise to localized electric fields that play a key role in the process of healing of these wounded tissues [3]. Both delivery of therapeutic drugs and electrical stimulation therapies have been identified as essential tools to enhance the process of wound healing [4–6]. Advances in the delivery systems of these therapeutics have been reviewed [7,8], however, establishing control over their release and stimulus is challenging. To this regard, electroactive biomaterials are gaining prominence and are the focus of the current review in the field of therapeutics for drug delivery and tissue regeneration.

2. Electroactive biomaterials and their modes of action

The family of electroactive biomaterials (**Figure 1**) is considered a new generation of smart materials that allow direct delivery of electrical signals by control over the electric potential. They have the advantage that they can be combinatorially active (i.e. stimulatory to the tissues as well as triggering controlled/responsive release of therapeutics). Such systems provide clinicians and scientists with an alternative delivery mechanism in wound care, facilitating in turn the development of new therapeutic approaches for patients.

Electroactive biomaterials have the potential to have their chemical, electrical and physical properties tailored for the specific needs of their application. The family of electroactive biomaterials includes conductive polymers, piezoelectrics, photovoltaic materials, and electrets.

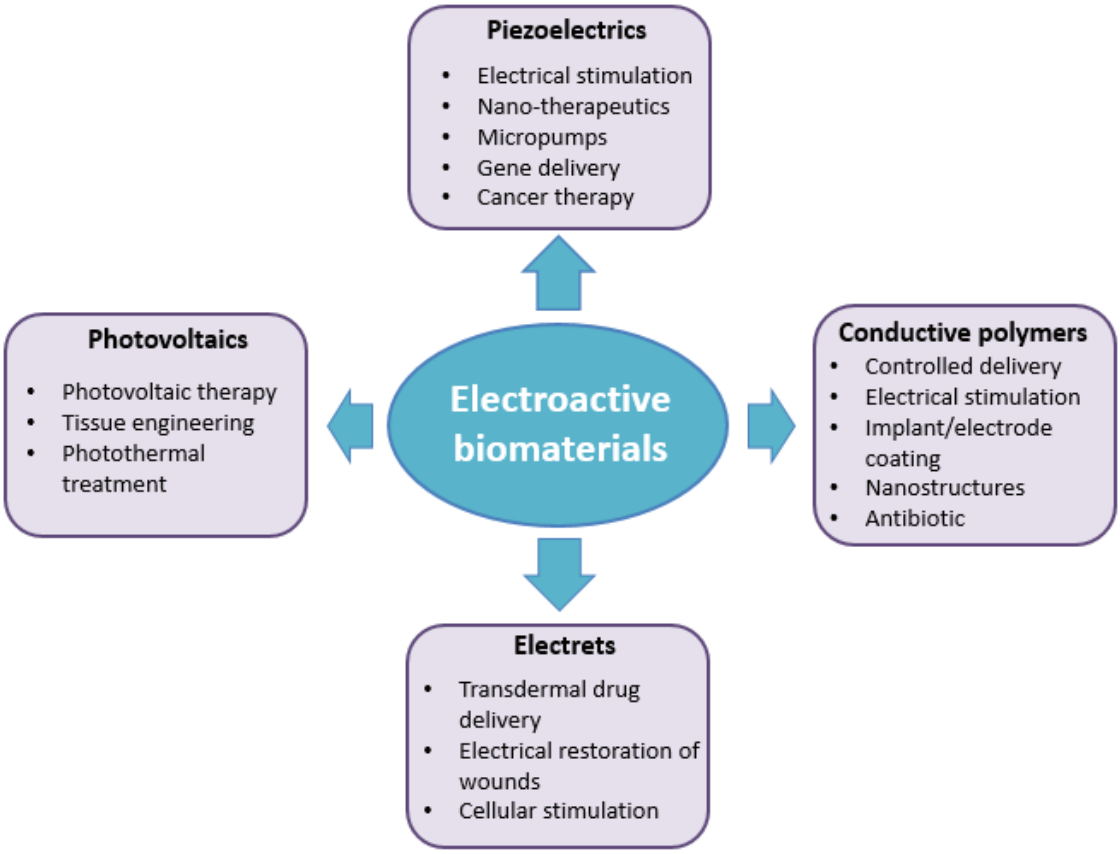


Figure 1 The family of electroactive materials and their applications

2.1 Conductive polymers

Conductive polymers (CP) are organic polymers that offer a compromise between the good electrical, magnetic and optical properties of metals and the ease of processing and mechanical properties associated with polymers [9–12]. Currently there are over 25 conductive polymer systems [9,10]. The most widely researched of these are polypyrrole (PPy), poly(3,4-ethylenedioxythiophene) (PEDOT) and polyaniline (PANI) [9,10].

CPs are electrically conductive due to the ease with which electrons jump within and between their polymer chains [13]. A key factor in this conductivity is the "dopant" [13–15]. Conductive polymers are synthesized in an oxidized state and require a negatively charged (anion) molecule - the dopant - to enter the polymer so that the polymer backbone can be stabilized [16]. This dopant is what introduces a charge carrier into this system by removing or adding electrons from/to the polymer

chain, creating polarons or bipolarons. Polarons and bipolarons are loosely held, localized electrons that are surrounded by a distortion in the crystal lattice. When an electrical potential is applied, the backbone is disrupted by the movement of the dopant molecules in or out of the polymer. This allows electrical charge to be passed through a polymer in the form of the above-mentioned polarons and bipolarons [13–15,17]. Many of the CPs have been shown to be cell friendly, supporting the growth of a large number of cell types and displaying good biocompatibility in animal models [13,18–22]. For example, PPy has been demonstrated to support the growth, adhesion and differentiation of neural [23,24], glial [25], endothelial [26,27] and bone cells [18,28], fibroblasts [29], keratinocytes [29] and mesenchymal stem cells [30]. Similarly, PEDOT has been demonstrated biocompatible with neural [31] and neuroblastoma cells [32], epithelial cells [13], and the L929 [33] and NIH3T3 fibroblasts cell lines [13].

2.2 Piezoelectric materials

Since their discovery in 1880 by the Curie brothers, piezoelectric materials have found applications in different fields such as energy harvesting, biomedical instrumentation, tissue engineering and drug delivery [34–39]. These materials are capable of generating charges (i.e. electrical output) in response to applied mechanical deformations (i.e. direct effect) and also deform in response to applied electric fields (i.e. converse effect) [38]. This effect is attributed to their non-centrosymmetric crystal/chemical structure, which is deformed on application of a force resulting in formation of a net dipole leading to electric polarization [40]. Though these materials are inherently piezoelectric, the dipoles are randomly oriented in the bulk of the material and need to be rearranged to enhance their piezoelectric feature. The procedure used to carry out such rearrangement is termed poling and involves the application of a high electric field at a specific temperature followed by cooling the material under the same electric field [41]. A schematic of the poling procedures and representation of direct and converse piezoelectric effects is shown in **Figure 2**.

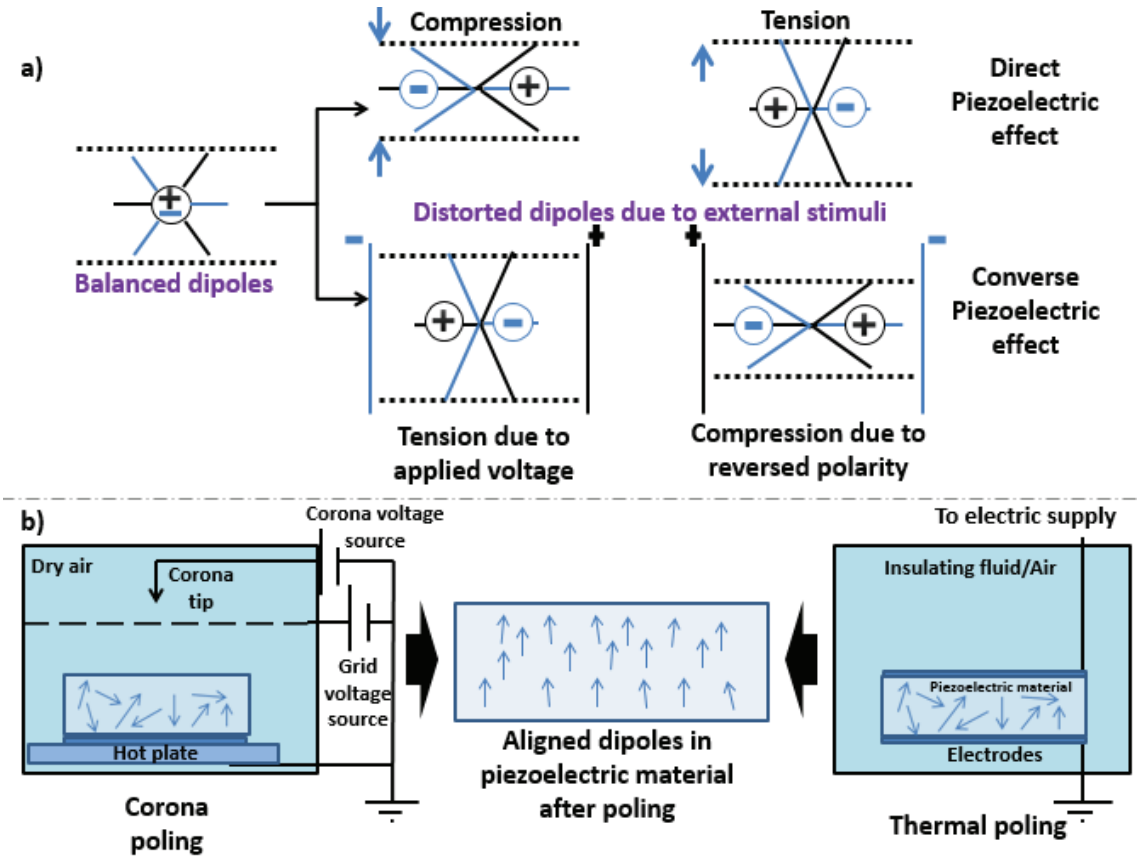


Figure 2 a) Direct and converse piezoelectric effect mechanisms and b) types of poling procedures to maximize piezoelectricity

Piezoelectric materials can be based on synthetic polymers or ceramics, naturally occurring materials or hydrogel systems (a list of piezoelectric materials is shown in **Table 1**). These materials can be fabricated into macro-, micro or nano- level structures and consequently be used for efficient and controlled release of drugs and therapeutic agents. The potential applications of these materials in the field of medicine require considerable attention of the scientific community.

Table 1 Piezoelectric materials and their classifications

Polymers	**Ceramics**	**Others**
Poly($_L$-Lactide) (PLLA)	Hydroxyapatite (HA)	Diphenylalanine
Poly-(vinylidene fluoride) (PVDF)	Barium titanate (BT)	Collagen

Poly-(vinylidene fluoride-*co*-trifluro ethylene) (PVDF-TrFE)	Lithium sodium potassium niobate (LNKN)	Boron nitride nano tubes (BNNTs)
Polyhydroxy-butyrate (PHB)	Lithium niobate (LN)	Silk
	Lead zirconate titanate (PZT)	
	Zinc Oxide (ZO)	

111

112 **2.3 Electrets**

113 Electrets are dielectric materials capable of retaining quasi permanent electrical charge or dipole
114 polarisation which is not destroyed over time [42,43]. The process of fabricating electrets is similar to
115 the poling process of piezoelectric materials by which the material is charged at a constant voltage. A
116 dielectric material is sandwiched between electrodes, heated to softening temperature and a direct
117 current electric field is applied and maintained while the material is cooled to room temperature [44].
118 Based on the type of charges developed on the surface of the electret, they can be classified into two
119 types (i) homocharged and (ii) heterocharged [45]. The different types of electrets and the charges
120 associated with their formation are shown in **Figure 3**.

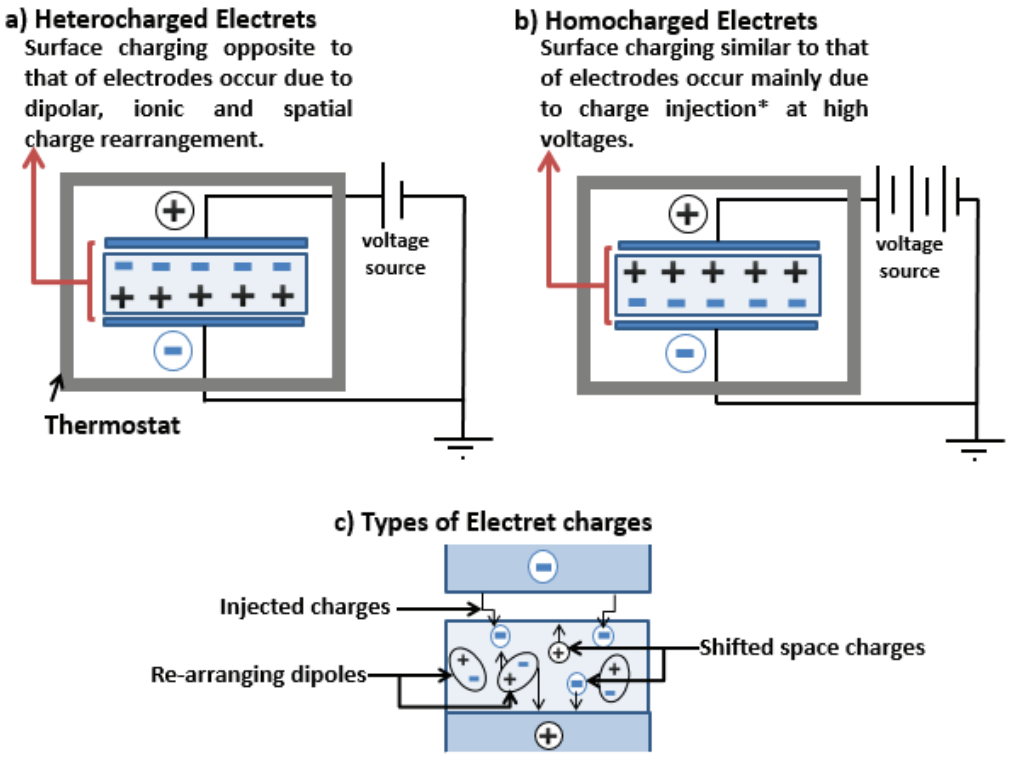


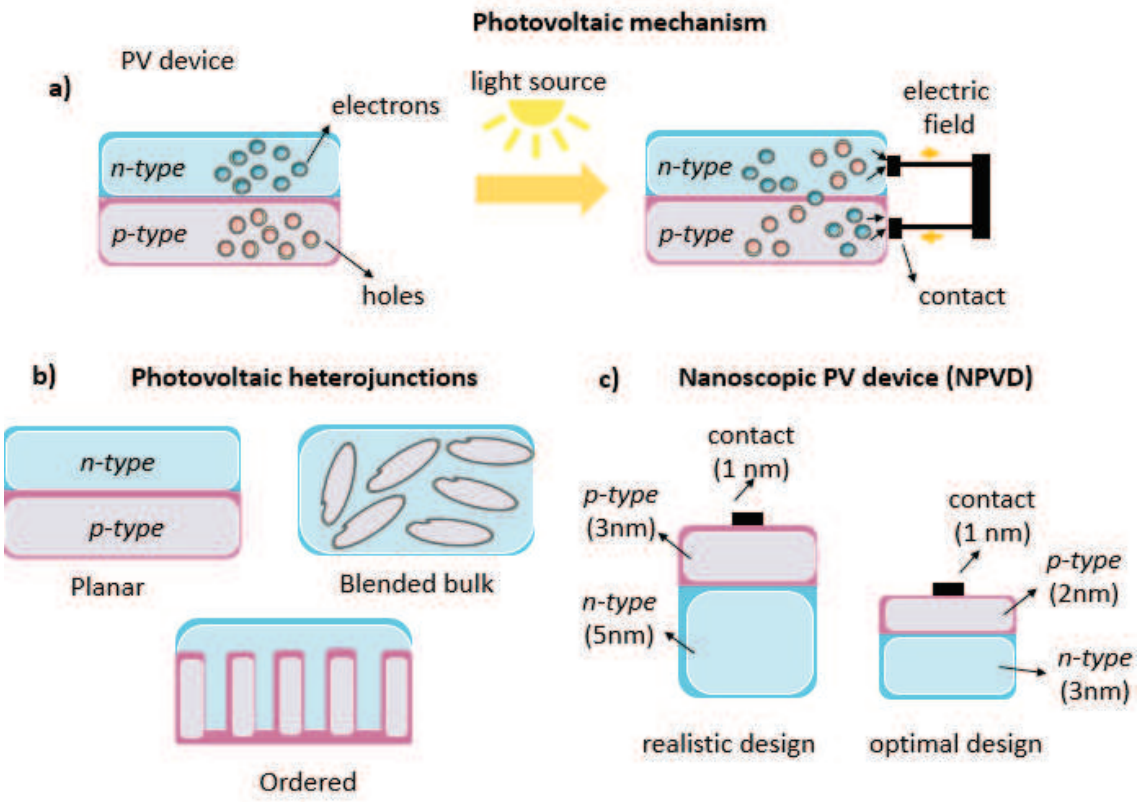
Figure 3 Types of electrets: (a) heterocharged and (b) homocharged (*injected charges are those which get deposited on the material surface from the surrounding electrode); and (c) charge carriers involved during the formation of electrets

2.4 Photovoltaic materials

Photovoltaics (PV) is the process of converting light into electrical power by using semiconductor materials that are able to absorb and trap light while exciting a charge carrier to a higher energy state, creating an electron flow: light absorption creates electron-hole pairs, and electrons and holes respectively migrate to opposite electrodes [46] (**Figure 4a**).

Essentially, a PV device (**Figure 4a**) consists of two regions, an *n-type* dope region and a *p-type* dope region, respectively featuring an excess of electrons and a deficit of electrons (i.e. holes), and the presence of contacts [47,48]. When both components come into contact, the excess of electrons flow from the *n-type* dope region into the *p-type* dope region, creating an electric field in between.

While PV devices can be found in many forms, these can be classified into three main types. The simplest PV device consists of an electron donor and an electron acceptor sandwiched together into a thin film (single or double layer) for the charge carrier to be allowed to diffuse through the junction (**Figure 4b**) [49]. However, the thinner the film the less amount of light it can entrap. The previous shortcoming can be addressed by mixing the electron donor and electron acceptor components into a blend (**Figure 4b**) [50], enhancing carrier diffusion. These PV devices generally consist of composite blends mixing semiconductor nanoparticles with conjugated polymers [51–54], where one functions as an electron donor and the other as an electron acceptor [52]. Blending semiconductor nanoparticles with conjugated polymers combines the easy processability and low cost of the polymer with the high charge mobility of the nanoparticle, which may include spherical, rod-like or branched organic and inorganic particles such as CdSe, ZnO, PbS, fullerene derivatives or single-walled nanotubes [55–57]. The performance of the composite can be enhanced in terms of light absorbance, charge separation or charge transport, which depends on the choice of the conjugated polymer and the processing condition [58,59]. However, the size and shape of the nanoparticle is also key: branched morphologies exhibit higher efficiencies compared to the use of nanorods or quantum dots [50], and small dimensions (i.e. large surface area to volume ratio) improve energy absorption and emission owning to high optical density [52]. An alternative to the PV blend device format is for a conjugated polymer to be inserted into a porous inorganic network as an ordered heterojunction-like structure (**Figure 4b**) [60]. Electron transport is facilitated this way as the interface between the polymer and the inorganic component is mainly governed by the dimension of the nanostructure particle, these interfaces can be chemically controlled to assist charge separation or block charge recombination across the donor-acceptor interface [60].



156

157 **Figure 4** Photovoltaic mechanism: a) conventional photovoltaic cell where electron-hole pairs
158 migrate to opposite electrodes upon photo stimulation and electric current is produced; b) photovoltaic
159 cells depicting the schematics of a planar heterojunction, a blended bulk heterojunction and an
160 ordered heterojunction; c) model of a conceptual nanoscopic photovoltaic device depicting realistic
161 and optimal design dimensions

162 ## 3. Electroactive biomaterials as drug delivery systems

163 ### 3.1 Electrochemically controlled drug delivery based on CPs

164 CPs have been investigated as potential candidates for drug delivery systems since as early as the
165 1980s, when Zinger and Miller demonstrated that glutamate and ferrocyanide can be released from
166 polypyrrole films through the application of an electric potential [61].

167 #### 3.1.1 Drug loading and release mechanisms for CPs

Drug delivery systems based on CPs exploit the polymers' ability to be electrically switched between an oxidized and a reduced state, resulting in the uptake or expulsion of charged molecules from the bulk of the polymer [62–64]. A wide range of solutions have been developed based on this phenomenon for the loading and controlled delivery of both positively and negatively charged and neutral drug compounds [62,65–67]. Amongst others, dexamethasone [68], heparin [69], dopamine [70], naproxen [71], neutrophin-3 [72], and neural growth factor (NGF) [22,31] have all been successfully bound and released from conductive polymers.

Loading of the drug compound can be performed in a number of ways depending on the type of the drug (**Figure 5**): small anionic compounds can be loaded through one-step immobilization (**Figure 5a**), as dopants during the polymer synthesis process [65,73,74]. This is the simplest method; however, if the drug molecule interferes with the polymerization process, the created material will suffer from low conductivity and drug loading capacity, and unfavourable mechanical properties [65].

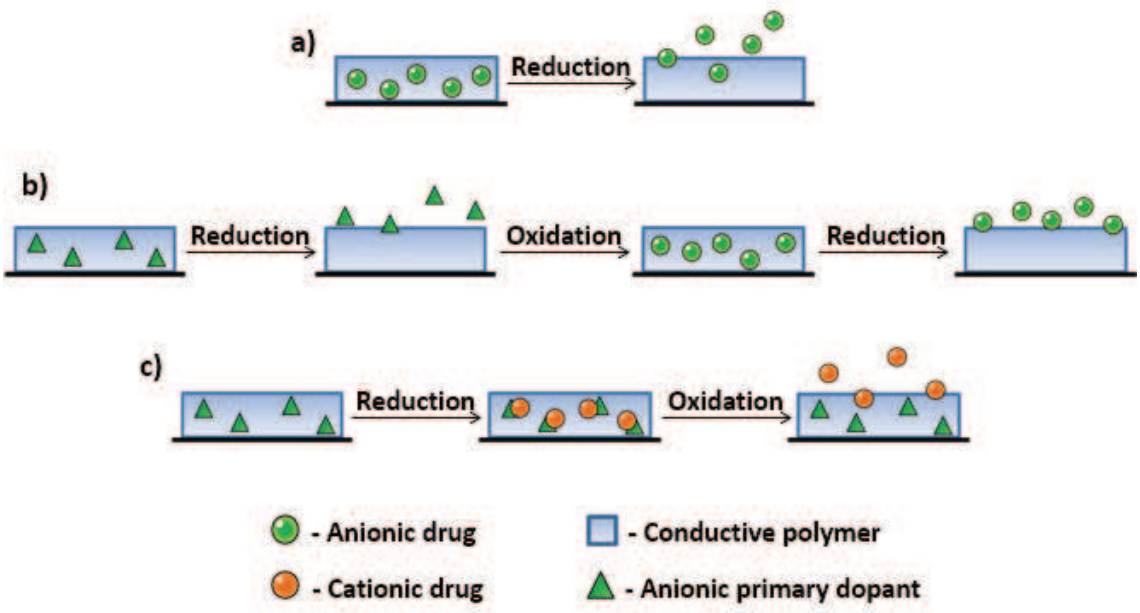


Figure 5 Mechanisms of drug loading and release in CPs: a) one-step loading of anionic drug; b) three-step loading of anionic drug; and c) loading of cationic drug

This limitation of the one-step methods can be overcome through the use of the more elaborate three-step method [11,65,67,74]. The three-step method (**Figure 5b**) separates the synthesis and drug loading processes, allowing both to be carried out with optimal parameters. First, the polymer is synthesized using an ideal anionic "primary" dopant. Following synthesis, a reducing potential is applied flushing out the primary dopant. Afterwards, the desired medicinal compound can be incorporated into the polymer by reversing the potential. A great benefit of this method is its application to the loading of large anionic compounds. However, if the process of removing the dopant and incorporating the drug are inefficient, drug loading capacity will be limited [65].

In a comparison of the one-step and three-step methods, post-synthesis loading has been shown to produce the highest loading for ciprofloxacin, while incorporation during synthesis provided the highest loading for quercetin [74]. This difference was due to quercetin crystallizing on the surface of the polymer when introduced post-synthesis and the subsequent matrix conditioning steps removing it [74]. Cationic drugs require a modified version (**Figure 5c**) of the three-step method [63,67,73–75]. Here, the polymer is synthesized with a large primary anionic dopant that, due to its size, is immobilized inside the polymer matrix during synthesis. Following this, the application of a reducing potential to the polymer results in the positively charged drug entering the material to maintain electroneutrality. This method was successfully applied to the loading and release of dopamine [70] and chlorpromazine [64], using poly(styrene-sulfonate) (PSS) and melanin as the dopant respectively. It has also been adapted to the loading of the neutral drug, *N*-methylphenothiazine, relying on the hydrophobic-hydrophilic interaction between the drug and an anionic "host" molecule, β-cyclodextrins [76].

Anionic drugs can be released with the application of a reducing - negative – potential, while cations can be unbound by either the removal of a negative potential or the application of an oxidizing – positive – potential [67,77,78]. The required voltage, generally speaking, depends on the reduction potential of the polymer [79]. In published studies, reported applied values range between 0.6 and 2 V

[62,63,73,80–82]. A higher potential results in faster release [83–85]. For example, -2 V releases fluorescein from nanoporous PPy films 3-4 times faster than -1.5 V [81]. A similar trend was observed during the co-release of fluorescein and dexamethasone from PPy sponges, where -2 V produced a two-fold release rate compared to -0.5 V [82]. On the other hand, too high potentials can result in the destruction of the bound drug compound through oxidation or hydrolysis, as it was observed in the case of dopamine above -0.6 V [63], and neural growth factor above 3 V [86]. Switching to the opposite polarity can help maintain the drug inside the polymer matrix by counteracting diffusion [83,85,87,88]. However, this does not apply to every case as during the release of the cationic compound acetylcholine from PEDOT:PSS both +1 V and -1 V produced a the same release profile [73].

The method of delivering the potential is also important: different drug release profiles have been observed depending on whether pulsed potential, pulsed current or cyclic voltammetry was applied [66]. In another study, potentiodynamic stimulation generated higher drug release efficiency than potentiostatic stimulation [65]. Cyclic voltammetry has been stated as the most efficient method for stimulation [11], also allowing greater control over release speed through the setting of different scan rates [89]. Beyond the applied electrical potential, stimulation time [86,90]; polymer film roughness, porosity, density and thickness [11,62,66,67,84,91]; the dopant [84,87]; and temperature [83,92] are known to affect and allow greater control over optimising the release profile.

The chemical environment can also have a profound effect. The release of insulin from PPy-gold nanoparticle composites has been observed to be pH-sensitive with the release slowing down at low pH [85]. The co-application of an electric potential further increased this sensitivity [85]. A strange relationship was noted between pH and the effect of the electric potential in the case of safranin release from PPy-poly-(acrylic acid) (PPy-PAA) hydrogel composites. At pH 6.4, a potential of +0.4 V enhanced release, while -0.4 V helped block diffusion. On the other hand, at pH 3.8 the exact opposite was seen with -0.4 V promoting release, and +0.4 V preventing it [93]. In contrast to these

pH dependent responses, the release of aspirin from PPy-montmorillonite composites was insensitive to whether it was performed at pH 3.4, 7.4 or 11.4 [94]. Chemistry alone can be used to propagate the release of the drug compounds. Hydrazine and alkaline medium was able trigger the release of adenosine triphosphate (ATP) from PPy membranes, albeit to a lesser extent compared to an electrical potential [95].

3.1.2 Polypyrrole (PPy) and poly-(3,4-ethylenedioxythiophene) (PEDOT)

PPy and PEDOT are members of the polyheterocycles family of conductive polymers, and have been almost predominantly the CP of choice for drug delivery applications [13,85,96,97]. PPy and PEDOT films have been used, for example, for the release of chlorpromazine [64], dexamethasone [68,79,98], neurotrophin-3 [66,99,100], risperidone [88,101,102], brain-derived neurotrophic factor (BDNF) [103], adenosine triphosphate (ATP) [95], dopamine [63], acetylcholine [73], methotrexate [83], betulin [104], quercetin and ciprofloxacin [74]. However, this section will focus on the more advanced drug delivery solutions that have been developed in recent years based on these two polymers.

For many applications, simple CP films alone do not provide sufficient drug storage capacity [89]. The use of micro- and nanostructures can provide a solution to this by offering greater volume and surface area for drug binding. One such structure was created from PPy nanowires, where the micro- and nanogaps between the wires served as reservoirs for the binding of ATP and dexamethasone [89]. Micro- and nano-tubes consisting of a drug laden inner core of bacterial cellulose [80], PLLA or poly(lactide-*co*-glycolide) (PLGA) [105] and an outer shell of PEDOT have also been fabricated.

Sponge-like structures can be created by polymerising PPy around sacrificial nano- or microbeads that are then later removed. Such nanostructures have been used for the release of rhodamine B [106], dexamethasone [82,107], fluoroscein [81,82], chlorpromazine [92], and risperidone [91]. The nanoporous PPy structure provided a capacity nine times greater compared to conventional PPy films in the case of fluorescein [81], and four times greater in case of risperidone [91]. Brush-like structures were generated by depositing PPy on top of aligned carbon nanotube surfaces for the delivery of

neurotrophin-3, possessing a surface area ten times higher than a film [108]. A similar approach was used for the enhanced binding and release of dexamethasone and penicillin [109]. A petal-like structure was achieved through polymerising PEDOT on top of single-wall carbon nanotubes immobilized on a gold surface [110]. Compared to neat PEDOT this material possessed improved conductivity, charge capacity and drug release rate [110]. Furthermore, it was able to resist three times longer the degradation effects (e.g. delimitation and cracking) of cycling the CP through its redox states during electrical stimulation [110]. Carbon nanotubes have been used in an alternative approach by Luo *et al.* as containers for drug molecules [111]: PPy was electropolymerized on the open ends of dexamethasone loaded carbon nanotubes, providing a seal on the ends of the nanotubes that could be opened with electrical stimulation [111].

Nanocomposites offer an additional solution to improving drug-loading capacity. Graphene oxide (GO) has been successfully combined with PPy to generate a composite material with twice greater dexamethasone binding capacity than PPy alone, a linear release profile up to 400 stimulations, and no passive drug diffusion [112]. GO has been used in combination with PEDOT to deliver dexamethasone in a smart coating for orthopaedic implants [113]. An interesting new approach in CP composites is the use of clay particles, such as palygorskite [114] and montmorillonite [94], that lend their large specific surface area to the composite material.

PPy and PEDOT have been combined with hydrogels, that are themselves important drug delivery tools, made from PAA [93,115], poly(lactic-*co*-glycolic acid)-*co*-poly(ethylene glycol) (PLGA-PEG) [78], alginate [116], and xanthan [117]. These blends combine the high electrical conductivity and electrically and chemically switchable properties of CPs, with the high swelling ability, excellent small molecules diffusivity, and good biocompatibility of hydrogels [93,115].

Ge *et al*. used microfabrication to construct a PPy based microchip with 36 independent electrodes. This novel device is able to supply multiple drugs at the same time or sequentially over multiple days, while offering greater control over doses then simple PPy films [77]. The same authors have also

created a very interesting self-activating system by turning the CP based drug release system into a galvanic cell. Magnesium was coated onto one side of a PPy coated porous cellulose film. Submerging the film into a NaCl solution resulted in the magnesium oxidizing, which in turn resulted in the reduction of the PPy, releasing the bound ATP [118]. This created a flexible, lightweight and partially-biodegradable device that does not require an external power source to operate [118]. Similar solutions have been developed by coating magnesium onto PPy nanowires containing ATP [119], and depositing PEDOT/GO onto biodegradable magnesium substrate [113].

In order to overcome limitations that might arise from limited drug loading capacity, the molecular weight of the medicinal compound, or the drug-dopant interference, a drug binding method based on biotin-streptavidin coupling has been proposed [86,120]. This technique was successfully used for the binding and release of molecules both directly attached to the polymer [86] or coated on the surface of intermediating gold nanoparticles [120].

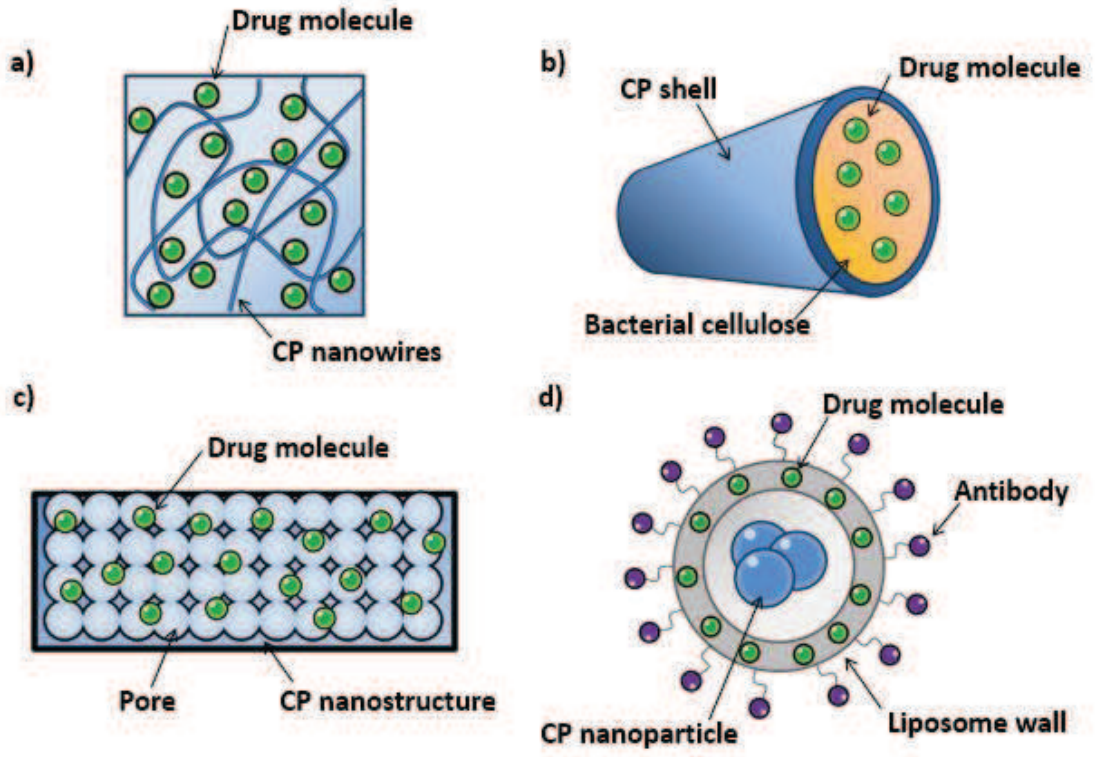


Figure 6 Examples of advanced CP based drug delivery solutions: a) nanowires [89]; b) microtubes [80]; c) nanoporous structures [106]; and d) nanoparticles [121]

Nanoparticles have also been fabricated out of CPs (**Figure 6**). An encapsulation efficiency of 95% was achieved when loading ketoprofen inside PPy-iron oxide nanoparticles [122]. PPy nanoparticles with the capability to release both at acidic and basic pH have been engineered, enabling their use in a wide range of tissue environments, including the pH 1-3 of the stomach and the pH 7-8 of the colon [123]. These PPy nanoparticles have also been immobilized in a calcium alginate hydrogel for the sustained pH dependent release of the anti-inflammatory drug piroxicam [123]. In a recent study, a targeted nanocarrier system was developed for chemotherapy, where rapamycin was bound in a liposome wall formed around PPy nanoparticles. The liposome was coated with Herceptin® (trastuzumab) that binds specifically to the HER2/neu receptor expressed by breast cancer cells, enabling target cell specific cellular uptake. Exposing the target area/cells to an 808 nm laser heated up the particles, releasing rapamycin and triggering apoptosis [121].

A very different drug release mechanism was engineered by Jeon *et al*. [124], instead of the electrostatic binding and release, a delivery system exploiting the mechanical swelling and contraction of PPy was fabricated. PPy pores were polymerized on top of anodized aluminium oxide membranes [124]. The PPy pores could be opened and closed through the application of an electrical potential, releasing on demand the bovine serum albumin contained in a reservoir situated on one side of the membrane [124]. The created device possessed a very fast response time in the range of 10 s, and a capacity only limited by the reservoir behind the aluminium oxide membrane [124].

3.1.3 Other conductive polymers

The field of CP based drug delivery is dominated by PPy and PEDOT. However, there are examples of other CPs being applied, including degradable electroactive copolymers synthesized from oligoaniline and PEG or poly(ε-caprolactone) (PCL) blocks. The resultant materials were found to be degradable *in vitro*, supported the adhesion of human dermal fibroblasts, and successfully delivered

dexamethasone with potential cycling between 0.7 V and − 0.5 V [125]. Oligoaniline has also been combined with oligoalanine to form electroactive supramolecular polymers for the delivery of dexamethasone phosphate [126]. Poly(*N*-methylpyrrolylium) poly(styrenesulfonate) was successfully used as a cation exchanger for the binding and the release of dopamine [70]. The conductive polymer poly(p-phenylenevinylene) (PPV) has been applied in combination with polyacrylamide (PAAM) to create a hydrogel with a tailorable release profile. The presence of PPV in the hydrogel delayed the release of salicylic acid in the first three hours, and this blocking effect could be extended to above fifteen hours with the application of a 0.1 V anodic potential. Release could be triggered with the application of a cathodic potential, the rate increasing with greater electric field strength. The release profile could be further optimised by varying the crosslinking density, and the size of the drug and the pores in the hydrogel [127].

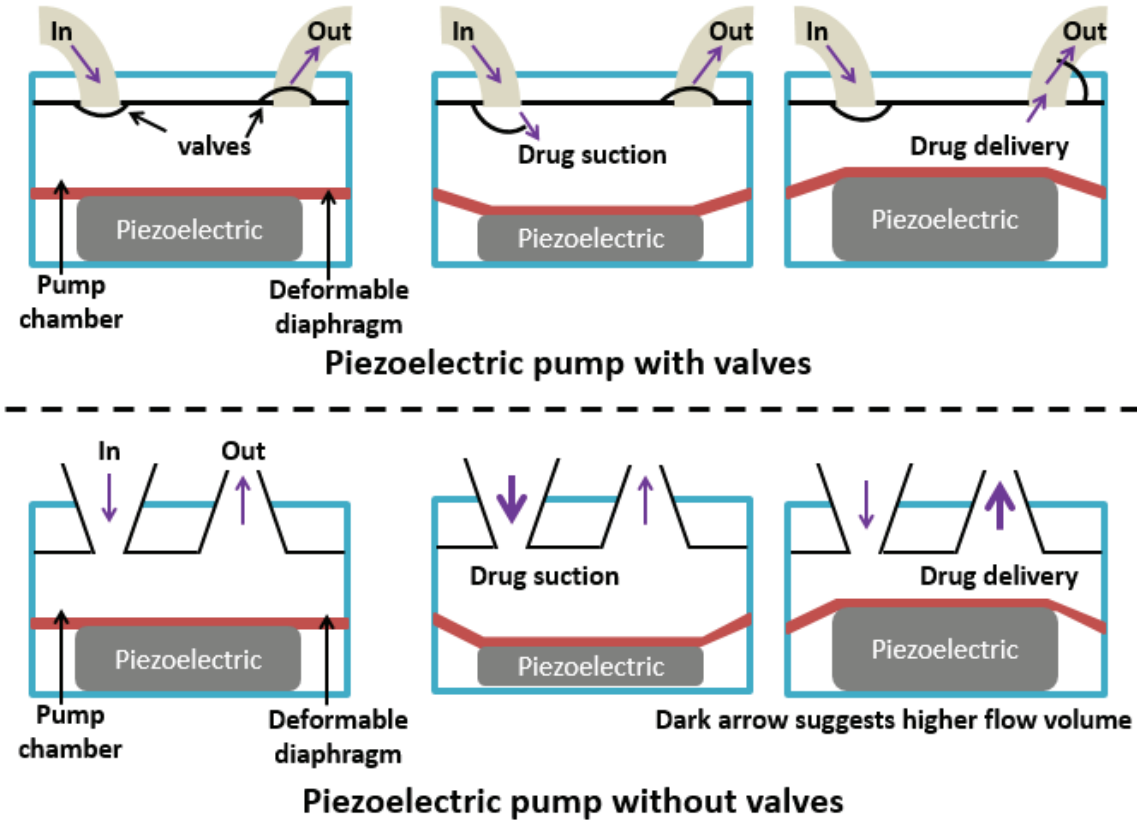
3.2 Piezoelectrically active materials for drug delivery

The piezoelectric principle of some materials has been researched in the field of drug delivery; for instance, in the fabrication of micropumps to treat diseases such as diabetes, with direct effects on tissue healing [128–132], or in the development of hybrid composite scaffolds made out of piezoelectrically active materials [133–135].

3.2.1 Drug release mechanism on piezoelectric based materials

The use of the piezoelectric mechanism for driving micropumps for drug delivery is common due to various advantages such as low power consumption, wide range of frequency operation, a rapid signal response and the ability of piezo actuators to be integrated in microsystems with ease [136].

Micropumps are preferred drug delivery systems as they provide better control, precision, accuracy and reliability than other drug delivery methods such as oral, injectable, nanoparticle based delivery or others [137]. Primarily localized delivery of insulin in diabetic patients has been explored using micropumps alongside some other lesser researched fields [138]. A schematic of the working principle of different types of piezoelectric micropumps for drug delivery is shown in **Figure 7**.



346

347 **Figure 7** Schematic of working principle of piezoelectric micropumps with or without valves, based
348 on deformable piezoelectric based diaphragms that regulate drug suction and delivery

349 PZT based actuators are the most commonly utilized piezomaterials over the past three decades to
350 fabricate micropumps for controlled release of drugs [34,137,139]; piezoelectric micropumps with
351 and without valves have been studied extensively [137,140]. In 2014, Wei *et al*. reported the design
352 and fabrication of a valve-less piezoelectric micropump which was screen printed on a substrate using
353 multiple layers of different materials [141]. These pumps printed on flexible substrates have possible
354 applications in wearable smart fabric devices for drug/bactericide delivery. The absence of valves in
355 the micropumps makes their design and fabrication process simpler and also, they are less prone to
356 clogging and require lower voltages of operation [136,141]. A drive frequency of 3 kHz was used to
357 achieve a maximum flow rate of 38 µL/min. Different designs reported for valve-less pumps have
358 been well optimized for higher delivery rates (i.e. flow rates) and better reliability [136,142].

359 However, successful operation of valve-less micropumps depends on the efficiency of the flow
360 rectification process of the proposed design [140]. The presence of valves in micropumps ensure
361 precise control over the flow rate, direction and stability, and makes them more reliable than valve-
362 less designs [143]. Modifications to different parts of the micropump such as vibrating mechanisms
363 and valve design can be made to improve the performance [143–145]. Wang *et al*. proposed the use of
364 a folding vibrator system in combination with check valves and compressible spaces [143]. A
365 minimum stable flow rate of 160 μL/min was obtained using a low drive voltage. The study clearly
366 suggests that highly efficient micropumps can be fabricated if proper design considerations are made.
367 To ensure successful implantation of these micropumps, it is important to use biocompatible
368 components to design them. However, the non-degradability of these pumps limits their use as
369 invasive procedures may be required for implantation and removal of these pumps after the function
370 has been served.

371 Advances in microfluidics and nanofabrication technologies have enabled the miniaturisation of
372 implantable drug delivery systems [146,147]. Piezoelectric based micropumps could be worn as
373 dermal patches, smart wearables or implanted within the body with a power source to achieve
374 delivery of desired drug profiles. This approach of administering drugs in a controlled manner is
375 encouraging, with some of these implantable pumps commercially available. However, the use of
376 drug-loaded implants/scaffolds is a more promising solution. Through the use of drug-loaded
377 scaffolds, an efficient delivery of drugs can be ensured and the repair process enhanced due to the
378 presence of localized electrical environments set up by the electroactive scaffolds [148,149].
379 However, controlling the adsorption and release behaviour of drugs through external stimuli has been
380 explored [150].

381 Piezoelectric materials have been used to develop hybrid composite scaffolds for the release of drugs
382 and genes [133–135]. In 2010, Ciofani *et al.* reported the use of BTNPs dispersions in glycol-chitosan
383 to form complexes with a widely used chemotherapy drug, doxorubicin, to enhance its delivery to
384 cells and improve treatment efficiency [134]. Similar to this study, Suh *et al.* reported on increased

385 cellular uptake of BTNPs coated with polyethylenimine (PEI) [133]. Both studies highlight the use of
386 BTNPs as vectors without any mentions of the role of the piezoelectric properties and their possible
387 role in altering delivery of genes or drugs. On similar lines, a more recent study published in 2016
388 highlights the use of BNNTs for delivery of fluorescent probes and drugs such as curcumin, a potent
389 anti-inflammatory, anti-microbial and anti-oxidant wound-healing agent [135]. Curcumin was shown
390 to be entrapped within the nanotubes through characterisation by transmission electron microscopy
391 imaging [135]. In another study, He *et al*. reported loading of electrospun fibrous PVDF membranes
392 with antibacterial drug enrofloxacin for treating dermal injuries [151]. The drug release profile
393 observed was similar to that desired for wound healing processes [151]. In this study, it was
394 mentioned that the enrofloxacin was present in large portions on the outer surface of the fibres and
395 diffusion was the main driving mechanism of drug release [151]. However, the contribution of the
396 piezoelectric effect towards drug loading and release was not studied in any of these works and
397 remains to be explored.

398 **3.3 Electret mediated delivery of drugs**

399 Electrets for drug delivery mainly come in the form of patches and are mainly limited to transdermal
400 delivery. They can carry different values of surface potentials depending on the amount of surface
401 charges retained. These can subsequently give rise to electrostatic fields and microcurrents which can
402 assist in the process of wound healing and transdermal drug delivery (i.e. TDD, a process of
403 administrating drugs/therapeutic agents through intact skin) [152,153].

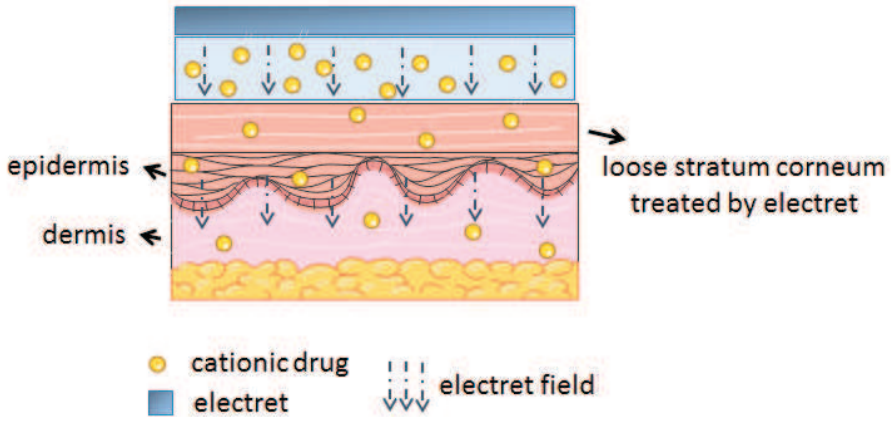


Figure 8 Transdermal drug delivery system based on electrets

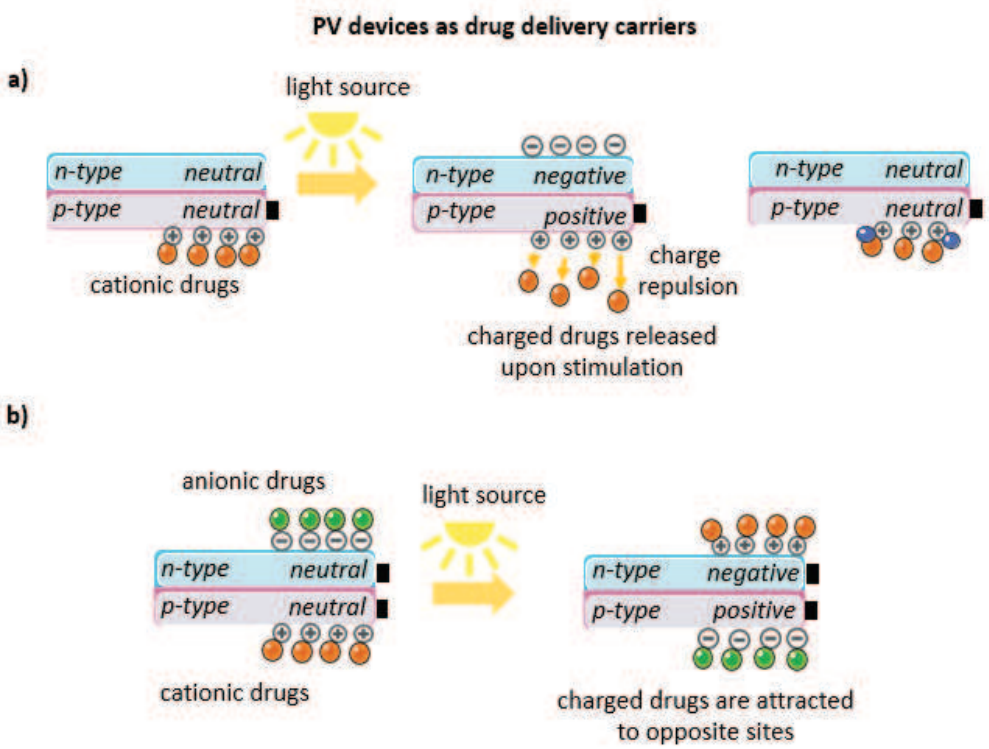
Research reported over the last two decades have shown that the electrical fields generated by electrets based on polytetrafluoroethylene (PTFE) and polypropylene (PP) are capable of altering the permeability of skin and promote transdermal delivery of drugs [154–156] (**Figure 8**). Regulation of the electret state of the skin, arrangement and fluidity of lamellar lipids and structure of proteins in the stratum corneum (the outermost layer of skin considered to be the main barrier for TDD), leading to formation of wide gaps have been shown to be the key mechanisms for improvement of TDD [154,155,157–159]. Cui *et al.* performed several studies using PP electrets prepared by film casting technique, combined with different chemical enhancers (that promote TDD by altering skin structure) for different types of drug formulations [158,160,161]. In one of the studies, it was observed that electrets of various surface potentials alone enhanced the permeation of meloxicam, a low molecular weight drug (< 1 kDa), more than the chemical enhancer on its own [161]. However, in case of cyclosporine A, a drug with higher molecular weight (> 1 kDa), electrets alone of different surface potentials were not able to achieve similar levels of drug permeation as the chemical enhancer [160]. Similar results were obtained in a study by Murthy *et al*. which showed that Teflon electrets were unable to enhance delivery of high molecular weight drugs [162]. To this regard, a novel approach has been suggested by Tu *et al*. to address the issue of delivering high molecular weight drugs [158]. The study shows that using drug loaded *N*- trimethyl chitosan nanoparticles (TMC NPs) in combination

with PP electret films enhances transdermal delivery of protein drugs, thanks in part to the mucoadhesive ability of chitosan to be absorbed across mucosa epithelia. The results obtained in the studies are promising, showing that the skin permeation to protein drugs and nanoparticles is increased with the increase of surface voltage of positively charged electrets, and gradually decreases with an increase of surface voltage of negatively charged electrets. However, there are factors that require optimization for success of such systems. In particular, the nature, sign and magnitude of the surface potential of the electret, the type of drugs and the type of nanoparticles are all equally important to be analysed [158]. Also, it is important to assure that the surface charge of the electrets is not shielded by moisture or other contaminants [162].

3.4 Targeted drug delivery using photovoltaic materials

One of the main goals of drug delivery systems is to minimize the exposure of the drug to healthy tissues while achieving an appropriate therapeutic dosage concentration in the wound site. Photovoltaic materials have recently started to gain attention in therapeutic applications as a way to control the release of specific drugs when the charge intensity or polarity of the material changes upon external light stimulation (i.e. near infrared or laser source, 650 - 900 nm wavelength). This is known as photovoltaic therapy (PVT), where positively and negatively charged drugs can be loaded onto the surface of a PV device (either on *n-type* or *p-type* doped regions) by means of electrical attraction (i.e. negative or positive) and be released to target sites via electrical repulsion upon light initiation (**Figure 9**).

To date, PV devices have not been extensively research for drug delivery applications and scarce examples are found in the literature. The proof of concept dates back to 2013 when Bhuyan *et al.* demonstrated that negatively charged bovine serum albumin and positively charged poly-L-lysine, attached to the positive and negative sides of a PV cell respectively, were released upon external photo stimulation [163].



447

448 **Figure 9** Photovoltaic devices used as drug delivery carriers: a) PV device coated with positively
449 charged drugs, which are released upon stimulation and attracted back again in a retractable-wise
450 manner; b) PV device coated with positively and negatively charged drugs that are attracted to
451 opposite sites upon stimulation of the device instead of being repelled towards the environment

452 As long as the principle of photovoltaics is maintained, PV devices can be manufactured from a wide
453 range of micro/nano mesoporous materials such as silica [164,165], with tuneable pore sizes, shapes
454 and morphologies, which also provide for high drug loading capacity and manipulative surface in
455 terms of cell-material interactions. For instance, micro-size PV cells from silica have already been
456 manufactured, being more effective at dissipating heat when they range below the millimetre size
457 [163]. However, the move is now focused towards developing nanoscale devices in formats other than
458 films that could further facilitate drug delivery. For instance, photovoltaic based nanoparticle cells
459 (NPVDs) have already been envisioned with designs theoretically functional [166], and have been
460 produced from silica, gold and silver materials [167]. However, it is important to target the

sequestration of these NPVDs as drug carriers to the wound site (**Table 2**), and an optimal size of around 6 nm (*n-type* thickness of 3 nm, *p-type* thickness of 2 nm and contact thickness of 2 nm) is required for them to be successfully used as delivery carriers to ensure maximum renal filtration. Based on the current technology, the realistic achievable NPVD size is 9 nm (*n-type* thickness of 5 nm, *p-type* thickness of 3 nm and contact thickness of 1 nm), though, with an 8 nm glomerular pore size [166] (**Figure 4c**). The activation of these NPVDs remains in the near infrared, and any drug can theoretically be transported.

Table 2 Size dimensions of nanoparticles regarding their target site and route of excretion

Target tissue	Size particle	Excretion route
Any	3 – 10 nm	Renal filtration [168]
Liver and brain tissue	10 – 30 nm	Phagocyte system [169]
Lung and inflamed tissues	30 – 80 nm	Phagocyte system [170]
Liver and spleen	> 80 nm	Hepatobiliary excretion [169]

3.4.1 Drug loading and release on photovoltaic based materials

Two hypothetical mechanisms of action have been proposed regarding PVT, mainly drug retractability and contact to *p-type* region. In the drug retractability mechanism [166] (**Figure 9a**), a PV device in neutral state is coated with a positively charged drug on the *p-type* region. Upon stimulation, positive and negative charges form in the *p-type* and *n-type* regions respectively, and the presence of a contact in the *p-type* region allows positive charges to interact with the environment and repel the positively charged drug in the material. When stimulation ceases, both the *p-type* and *n-type* regions return to their neutral state attracting the drug and any other charged molecules from the environment, thus, controlling timing and duration of the drug-environment interactions in a back and forth of neutral and charging cycles and reducing the impact of any side effects. In the contact to *p-type* region mechanism [166], contacts are only applied on the *p-type* region of the device. While contacts can be applied to both the *p-type* and *n-type* regions for higher drug capacity (i.e. positively

charge drugs adsorbed onto the *p-type* and negatively charged drugs adsorbed onto the *n-type* regions), there is a chance that upon stimulation of the device the negatively and positively charged drugs will be attracted to opposite regions upon initial repulsion (**Figure 9b**). This limits drug interaction at the desired site of action, but can be easily solved by removing the contact from the *n-type* region so that negative charges do not interact with the environment. In this sense, higher drug delivery efficacy is achieved at the expense of a reduced drug capacity.

3.4.2 Metal organic frameworks as photovoltaic devices in wound care

Metal organic frameworks (MOFs) are highly porous network materials consisting of metal ions linked together by organic bridging ligands [171,172]. MOFs were first proposed as an alternative new controlled drug delivery system back in 2004 [173] due to their combined high pore volume, regular porosity, and tuneable organic groups within the framework that allow easy modulation of the pore size and makes them more competitive as therapeutic containers [174–178] than conventional pore materials (**Figure 10**). Since then, several studies on the use of MOFs as delivery vehicles of molecular therapeutics (i.e. antimicrobial metal ions [179] or homeostasis regulators such as copper [180]) and gaseous therapeutics (i.e. nitric oxide [181]) for skin wound treatment have emerged in the form of hydrogel systems [182–184].

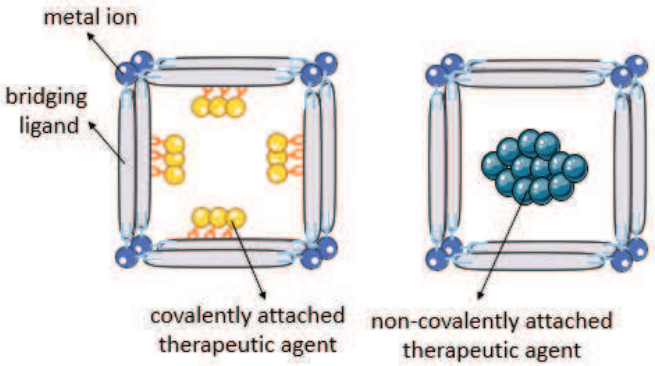


Figure 10 Schematic representation of a metal organic framework (MOF) structure used as a delivery carrier

Although MOFs are mainly non-conductive, the use of structural doping or short inorganic and conjugated organic bridging ligands in their structures can extend their potential to be used as PV devices [185–187]. PV-based MOF systems have been thoroughly reviewed by Kaur *et al.* [188]. In this sense, there is growing interest in combining the capabilities of MOFs with the PV effect for these devices to be used as therapeutic delivery carriers to promote and enhance skin regeneration.

4. The stimulatory response of electroactive materials in wound healing

Electrical stimulation (ES) alone has been shown beneficial for the treatment of wounds and injuries. ES has been shown to aid the re-epithelisation of skin and corneal wounds; to enhance angiogenesis; and to promote the migration of fibroblasts, keratynocytes and epithelial cells [189–195]. ES's ability to induce re-innervation [196,197] and increase skin blood flow [198] aids in the healing of wounds. ES can show significant antibacterial effects, for example, it has been demonstrated to reduce the number of methicillin-resistant *Staphylococcus aureus* colonies by over 87% both *in vitro* and *in vivo* [199]. Furthermore, ES has been successfully used in the treatment of diabetic ulcers [200]; and nerve damage in sciatic nerve [201] and spinal cord injury models [202]; and as an osteoinductive tool in treating normal and non-union fractures, osteoporosis and osteoarthrosis [203–207]. ES's ability to manage pain is also an important consideration [208,209]. Transcutaneous ES has been shown as to be a non-invasive, drug-free alternative in managing acute and chronic pain [208], in one example reducing pain scores by 38% and drug consumption by 25% [209].

4.1 Stimulatory response of CPs in tissue repair

The use of CPs in the treatment of injuries ranges from conduits [210] and injectable particles [211] for the repair of nerve damage, to tissue engineered solutions [212] and biosensing devices [213]. Most of the wound healing techniques developed from CPs utilize their antibacterial properties [214–218]. Wound covering fabrics produced from PPy and PANI have been shown to decimate populations of *E. coli*, *E. agglomerans*, *B. subtilis* and *S. aureus* [214,217,218]. The antibacterial effect of CPs have been attributed to the excessive positive charge and oxidizing potential of the

polycationic backbone of the polymer disrupting the cell wall and interfering with bacterial respiration; and to the electron donor–acceptor character of CPs hindering bacterial adhesion and blocking biofilm formation [214,216,217]. The effect has also been demonstrated to be a result of the polymer itself, and not due to the oxidising agent or dopant used during the synthesis of the CP [216]. Their already strong bactericidal effect has been enhanced through the binding and release of silver nanoparticles [215] and the antibacterial drug ciprofloxacin hydrochloride [87].

When used synergistically, ES and CPs have been shown to activate dermal fibroblasts and promote the expression of $TGF\beta_1$ and other key factors that drive cell proliferation, differentiation, inflammation response, keratinocyte migration and extra-cellular matrix production [219]. Human dermal fibroblasts cultured on PPy-PDLLA composite membranes displayed enhanced proliferation when stimulated with a direct current [220]. Comparably, ES delivered through nanofibres of PANI blended with PLLA-*co*-PCL was observed to increase the growth and adhesion of NIH-3T3 fibroblasts [221]. Stimulating human skin fibroblasts on PPy/PLLA membranes resulted in greater viability and mitochondrial activity [222]. A tenfold increase in the secretion of interleukin-6 and interleukin-8, two cytokines important for wound repair and the growth of new blood vessels, was reported when exposing skin fibroblasts on conductive PPy and degradable PLLA composite scaffolds to an electrical stimulus [223]. The delivery of ES through conductive polymers can be useful for the formation of new blood vessels: human umbilical vein endothelial cells stimulated with 200-400 mV/cm on PANI-coated PCL fibres exhibited highly enhanced viability and adhesion [224]. Subjecting PC12 nerve cells to ES through PPy scaffolds resulted in the formation of greater numbers of longer neurites [225,226]. Nerve stem cells displayed a similar behaviour, extending more neurites when stimulated on a PLLA/PANI scaffold [226], and enhanced proliferation and neurite outgrowth on PANI-PCL/gelatin substrates [227]. ES and conductive scaffolds have been combined with stem cell based therapies: the pre-stimulation of human neural progenitor cells on PPy scaffolds before transplantation improved functional outcomes in rat stroke models [228]. Bone formation was successfully promoted by stimulating rat bone marrow stromal cells on PPy films; resulting in the up-

regulation of osteogenic markers, accelerated cell differentiation, and improved calcium deposition and matrix mineralization [229]. The delivery of 200 μA of direct current for 4 hours for 21 days increased the calcium deposition by 100% in human adipose-derived mesenchymal stem cells cultured on PPy-PCL substrates [230]. Similarly, marrow stromal cells and MC3T3-E1 pre-osteoblast cells displayed significantly increased mineralisation when stimulated on self-doped sulfonated polyaniline (SPAN)-based electrodes [231].

4.2 The piezoelectric mechanism in tissue regeneration

As previously stated, ES therapy has been well established as an important cue for enhancing the process of wound healing in different tissues [232,233] by governing cellular behaviour and tissue response. Piezoelectric materials in the form of scaffolds and NPs (**Figure 11**) have been used to administer this cue efficiently to cells with great therapeutic potential in treating cancer, bone injures and neural disorders [37,40,234–239].

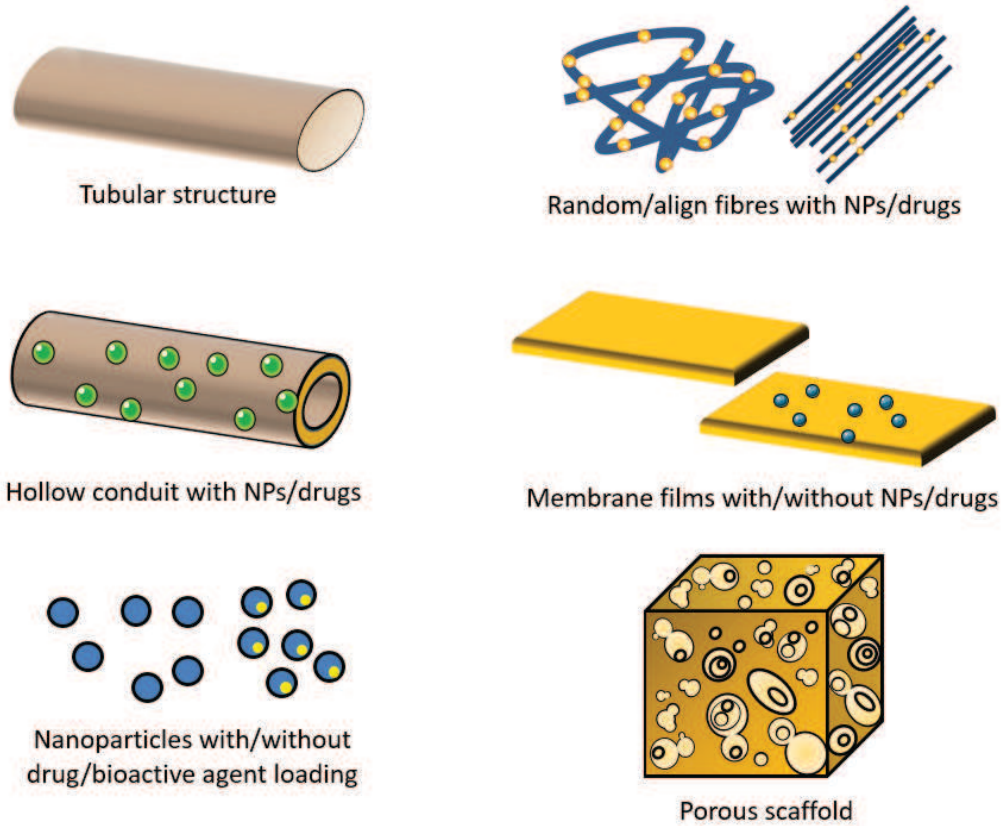


Figure 11 Examples of different piezoelectric based scaffolds

Piezoelectric polymers as nerve guidance channels were reported by Aebischer *et al.* in the late 20th century [240–242]. Compelling *in vivo* results obtained by use of PVDF and its copolymers in these studies affirmed the role of electrical charges in the process of nerve repair. However, research in the following years was more focussed on deciphering the mechanisms through which electrical stimulation influences nerve cell behaviour [243,244]. The field has gathered growing interest of the scientific community in the last few years. To this regard, BN, ZO and BT piezoelectric nanomaterials that have been fabricated in various forms including: nanotubes, nanowires and nanospheres, providing greater surface area to volume ratio for better cell-material interactions [245,246]. BNNTs and BTNPs have shown promising results for wireless neuronal stimulation. For instance, Ciofani *et al*. used BNNTs and BTNPs in two different studies using different neuronal like cell lines [237,247]. The piezoelectric nanomaterials stimulated by ultrasound generated potentials in the range of 0.07 to 0.19 mV [247] that contributed to greater neurite sprouts by a 30-fold increase compared to the controls after treatment [237]. Other than piezoelectric nanoparticle systems, scaffolds based on piezoelectric materials have been explored for nerve regeneration [238,247–252]. In a series of studies by Lee *et al.*, electrospun piezoelectric membranes of PVDF-TrFE were fabricated and different cell lines were tested for neuroregenration capability [250,253,254]. The effect of fibre alignment and piezoelectricity on neurite extension of dorsal root ganglion neurons was assessed, and it was reported that cell growth and neurite extension was well-supported by annealed and aligned fibres that also exhibited the greatest piezoelectric effect [250]. These results were confirmed by another study which reported that PVDF electrospun scaffolds with controlled alignment and physical properties were best suited for survival and differentiation of monkey neural stem cells [252]. Both *in vivo* and *in vitro* results obtained were supportive of the use of piezoelectric conduits for repairing nerve injuries [250,253,254]. Unlike these studies in which the initiation of the piezoelectric mechanism of the scaffold relies on the cellular interactions and natural animal movements, several studies have reported on externally simulating the effect using ultrasound or vibrating waves [248,249,255].

591 Piezoelectric electrospun PVDF and BTNPs nanocomposite membranes with and without external
592 mechanical stimulation have also been studied in recent years for nerve tissue engineering
593 applications [251,256].

594 Similar studies conducted by Ciofani *et al*. with BNNTs and BTNPs enhanced gene expression and
595 cytokine production by stimulating osteoblasts, myoblasts and fibroblasts in comparison to controls
596 [235,236,239,257]. However, such non-invasive techniques using piezoelectric nanoparticles to
597 deliver the electrical therapy to wounds and injuries is relatively new and requires extensive research
598 before clinical applications are approved [238].

599 Piezoelectric scaffolds have been used as wound patches for dermal injuries to electrically stimulate
600 the injury site ensuring enhanced recovery through improved cellular response. The presence of piezo
601 receptors on cells and their role in controlling cell behaviour to enhance wound healing corroborates
602 the use of piezoelectrics to stimulate cell response [258,259]. The piezo receptors on cells are
603 activated when cells undergo mechanical deformation in response to an injury or otherwise, this
604 deformation activates ionic channels consequently leading to generation of electrical signals which
605 assist in intracellular signalling and hold great physiological importance [258,259]. A study by Ying
606 *et al*. focused on exploiting the piezoelectric property of PVDF electrospun scaffolds blended with
607 polyurethane (PU) for treatment of skin wounds [260]. These were deformed in a controlled manner,
608 and enhanced migration (to the scratched area of scaffolds in a wound healing assay) and adhesion of
609 fibroblasts were observed when compared to non-deformed samples [260]. A more recent study
610 published in 2017 by Bhang *et al*. reported ZO based piezoelectric dermal patches [261]. The study
611 included *in vitro* and *in vivo* results supporting the promotion of wound healing through generation of
612 optimum levels of electric potentials ranging from 300-900 mV. These electric potentials enhanced
613 dermal fibroblast activity and lead to the upregulation of biochemical factors such as CD68 protein
614 and vascular endothelial growth factor contributing towards improved wound healing [261]. Tan *et al*.
615 observed that potassium sodium niobate (KNN) based piezo ceramics show surface selective
616 antibacterial activity [262]. They observed that reactive oxygen species (ROS) were formed around

617 the piezoelectric ceramic surfaces as a result of microelectrolytic activity. The formation of ROS
618 around the cathode surface was higher and led to significant antibacterial activity, while the ROS
619 levels generated remaining safe for mammalian cells. This study suggests that inherently antibacterial
620 scaffolds can also be manufactured using piezoelectric materials.

621 The most prominent use of piezoelectric materials as scaffolds has been found in the field of bone
622 tissue engineering [36,37]. Use of piezoelectric materials for bone repair application ensures that the
623 electrical stimulation therapy is delivered to the injury area effectively. Piezoelectric materials are
624 capable of restoring the electrical microenvironment around the injury site and can generate electrical
625 signals which can alter cellular behaviour [263,264]. Piezoelectric polymers such as PVDF, PVDF-
626 TrFE, PLLA, PHB alongside piezoelectric ceramics including BT, LN, LNKN, HA have been
627 assessed for their osteogenic capability [36,37,148]. In particular, the last two years have seen a rise in
628 the number of publications in this area and the promising results obtained point towards a clinical
629 solution to the problem of orthopaedic regeneration [148,234,264–269].

630 Control over the amount of electrical stimulation delivered by nanoparticles or scaffolds has been
631 established by controlling the uptake of NPs by cells (specific amount of NPs), or a material with
632 optimized piezoelectric characteristics to generate physiological levels of potentials in response to
633 deformation. To mechanically stimulate the piezoelectric materials *in vitro* and consequently study the
634 effect of piezo characteristics on drug release, different strategies such as deformable cell culture
635 plates or ultrasound should be utilized, while in the case of scaffolds implanted *in vivo*, the same can
636 achieved through the natural movement of the animal. It must be noted that different stimulation
637 mechanisms such as ultrasound, bending and others are capable of inducing different responses and
638 the choice of methodology should depend on the type of application desired.

639 **4.3 Electrets as exogenous stimulators for wound healing**

640 Other than the use of electrets as transdermal delivery of drugs, electrets have been found useful as
641 exogenous electrical stimulators in terms of wound healing in several tissues such as bone and skin

[270]. The first studies on the use of electrets for healing of dermal wounds dates back to the 1990s [152]. In an *in vivo* study conducted in pigs, it was found that the treatment of skin wounds using PTFE electrets enhanced the growth of epithelial cells and accelerated the process of wound healing [152]. Though the results obtained in this study were compelling, there has not been considerable amount of research for fabricating electret based wound dressings. On the other hand, HA based electrets have gathered significant attention in the past decade, not only for skin but also for bone tissue engineering [270–273]. Nakamura *et al.* fabricated wound dressings based on silk fibroin and HA electrets and tested their dermal healing capability *in vitro* and *in vivo* [274,275]. It was observed that cellular migration and angiogenesis was promoted by the presence of charged HA in wound dressings. Chitosan and HA based electret membranes have also been reported for bone healing applications [272,276]. While chitosan electrets show stable surface charges [277,278], HA electrets have exhibited accelerated bone bonding rate and osteogenic gene expression *in vivo* [279–281]. In this regard, Qu *et al.* showed that heat treated chitosan electrets showed superior charge storage stability, with *in vivo* studies exhibiting their enhanced osteogenic potential as guided bone regeneration membranes [276]. In a similar study by the same group, the relatively poor mechanical properties of chitosan was enhanced with negatively charged HA into a composite electret membrane [272]. Their results showed that electret composite membranes based on chitosan and HA could promote osteoblast proliferation and differentiation *in vitro,* with potential clinical applications as a new strategy for such electret based scaffolds. The nerve healing potential of electrically charged electrets have also been reported on poled PVDF [241,282], PTFE [283] and PLGA [284] polymers in the form of film conduit scaffolds, suggesting the potential of electret guides prepared by electrical poling for peripheral nerve regeneration.

4.4 Photovoltaic mediated tissue response

Strategies are emerging for the use of photovoltaic-based materials as carriers of electrical stimuli for tissue regeneration. For instance, in 2015 Lorach *et al*. demonstrated that subretinal array implants with 70 μm-wide photovoltaic pixels were able to provide highly localized stimulation to retinal

neurons in rats, and that the electrical receptive fields recorded were similar in size to the natural visual receptive ones [285]. This opens up the possibility to using photovoltaic arrays as functional restoration wireless devices that can safely elicit and modulate cellular responses, not only on the retina [286–288] but on other tissues as well [289]. A similar strategy can be envisioned to facilitate wound healing rates [290,291], which may serve as a promising modality for controlling and treating various skin diseases and disorders. To this regard, the usefulness of delivering specific electrical signals for enhanced wound healing is demonstrated by its ability to induce re-epithelization of skin wounds by enhancing angiogenesis, blocking edema formation or promoting migration and proliferation of various skin cells (i.e. fibroblasts, keratinocytes and epithelial cells) [189–191]. Photovoltaic based materials such as poly(3-hexylthiophene)-phenyl-C61-butyric acid methyl ester (P3HT-PCBM) have also been proposed as optical modulators of cellular activity based on their photothermal effect upon light stimulation [292]. Light absorption generates different photo-excited states in the material that release thermal energy into the living cells of the environment, and such photoexcitation could be useful into developing new platforms for cell control by light to promote wound healing [293–295]. To this regard, electrospun photovoltaic based P3HT/PCL fibres were shown to significantly increased proliferation, extracellular matrix secretion and favour cell morphology of fibroblasts into the characteristic spindle shape upon light stimulation *in vitro* using white light-emitting diodes within the range of visible light (390–750 nm) [296].

5. Future perspectives on the use of electroactive biomaterials in drug delivery and tissue regeneration

Future CP-based drug delivery systems will see the use of biodegradable variants of CPs [125,126] that degrade at the end of their useful lifetime and clear from the patient's body without the need for removal surgery. Such polymers have already been developed by combining polypyrrole-thiophene (PPy–PTh) [297] or quaterthiophene [298] with degradable ester linkages. New CP materials will be created to become more resilient to the structural damage and conductivity loss caused by repeated redox switching. A good example of one such promising material is poly(3,4-alkylenedioxypyrrole)

694 (PXDOP) [299]. Novel approaches based on the co-delivery of multiple medicinal compounds,
695 injectable CP microcapsules, or micro- and nano-porous structures are currently of great interest and
696 will see wider application [14,300,301]. Also of great interest are CP based drug delivery systems that
697 are self-regulating, i.e. release drug compounds in response to changes in mechanical, biological
698 chemical and/or electrical conditions in their vicinity, without the need for an external power source,
699 and will likely be developed in the future [14,67].

700 The area of piezoelectric polymers and ceramics for tissue engineering applications has been
701 researched extensively in the last decade [37], and they have shown great potential for use in the field
702 of controlled therapeutics. The capabilities of these materials for delivery of electric cues and essential
703 drugs to the damaged wound have been studied independently. However, the correlation between the
704 two processes and the mechanism through which the release of drugs can be affected due to the
705 piezoelectric characteristics (varying surface charge and potential of the material) remains to be
706 explored. While significant progress has been made towards improving wound healing, the current
707 research in the area is focused on the use of synthetic polymers or ceramics, and there is recent
708 interest in developing piezoelectric hydrogels and controlled (bio)degradable piezoelectrics [302–
709 304]. There is a need for developing strategies for loading piezoelectric materials with different
710 hydrophobic and hydrophilic drugs and studying their release kinetics *in vitro* and *in vivo*. The
711 challenge is to fabricate a smart bio-active scaffold with combined capability. A drug-loaded
712 piezoelectric scaffold with tuneable release of drug or composites based on piezomaterials might be
713 utilized for this purpose. Emerging strategies are focused on developing bioreactors to mimic *in vivo*
714 conditions and explore the mechanical stimulation of the material to provide suitable electric cues and
715 drug profile release before these therapies can be translated from the bench to the market. A new
716 generation of bioreactors is needed to achieve a deep knowledge of the transduction effects of these
717 materials on specific cells. Indeed, piezoelectric characteristics of different biological systems and
718 biomaterials have been studied using piezoresponse force microscopy (PFM) [305,306], a technique
719 to study the material characteristics at the nanoscale and obtain a better understanding of the

mechanisms by which the physiological processes are affected [307]. Nevertheless, as discussed in this review, piezoelectric materials have independently been used for delivery of drugs or electrical stimulation of cells and tissues, and amalgamating these two approaches is promising.

There is limited literature on the use of electrets for dermal, bone and neural healing applications, and considerable amount of research is still required to confirm their usage for TDD or wound dressings. Though these materials have been found useful for TDD, there has been little mention of how the release behaviour of specific drugs can be controlled. Some electrets also possess piezo properties [308], however, their combined role on release behaviour of drugs is still to be explored. Combining their capability for TDD and altering cellular behaviour is a promising area of research. Electrets also present unique capability of being used for fabrication of smart electronic skins [309], and while the typical format is in the form of films, there is significant research scope for developing novel electret hydrogel dressings. However, the ability to permanently store charges on these other formats might pose challenging.

PV-based devices present significant challenge in preparing assemblies of particles that result in continuous but separate conduction paths for electrons and holes [310], and further formulation optimization is required to improve efficiency of light entrapment in these devices. For instance, surface plasmon resonance, metal-particle scattering and surface structuring techniques have been studied as new alternatives to enhance light trapping in PV devices [311–313]. On the other hand, most PV systems to date come in the format of films [54], which is useful for wound dressings. PV systems in the form of gels and hydrogels have been developed as well [314]. However, these systems should also be developed towards other formats such as porous sponges, fibres, rods or spherical structures [50,315] for the purpose of facilitating drug delivery at the wound site. To this regard, Labastide *et al.* have envisioned organizing *n-type* and *p-type* moieties into separate spherical nanoparticles and arranging them into stable superlattices whose structure is defined by the nanoparticle radii [310]. Further research on PV-based MOFs should be carried out; existing systems

745 have proven poor performances and their capability as photovoltaic based delivery carriers for wound
746 healing has not been tested yet. Extensive research towards attaching and releasing drugs or other
747 therapeutics from PV cells in the most efficient way is needed both *in vitro* and *in vivo* clinical
748 applications before this technology can be translated from the bench to the market. Another issue to
749 bear in mind is degradability and cytotoxicity of the existing PV materials. In this sense, surface
750 modification is a factor to take into account for enhanced delivery efficiency, and pharmacokinetics of
751 the therapeutic loaded PV based device is an important step that demands full investigation to
752 estimate their actual performance. Although important improvements need to be taken care of before
753 clinical applications are a reality, there might be a bright future in their application as delivery
754 systems for wound treatment.

755 ## 6. Conclusions

756 Controlled delivery of drugs and electrical stimulation are promising approaches for enhanced wound
757 healing of damaged tissues, which are well demonstrated by conductive polymers, electrets,
758 piezoelectric and photovoltaic based materials. The capability of conductive polymers and
759 piezoelectrics as multi-tasking scaffolds is well supported by the encouraging results presented, while
760 electrets and photovoltaics are still new to the field of research. Electroactive biomaterials have been
761 found useful for treating injuries to tissues such as skin, bone and nerve. However, clinical translation
762 for wound healing is achievable after thorough attempts are made to overcome the limitations
763 presented by individual systems. There is a need to amalgamate different electroactive systems, such
764 as piezoelectrics and CPs to eliminate the need of an external stimulation device to attain desired
765 outcomes.

766 The field of electroactive biomaterials for release of therapeutic agents is growing. There are
767 challenges and limitations in the translation of these new therapeutic approaches that remain to be
768 answered, such as safety, cost, and efficacy of treatment and degradability of the material. It is safe to
769 predict that as our understanding of electroactive materials improves along with technological

advancements in scaffold fabrication, therapeutic encapsulation and drug release, the near future will see electroactive based techniques become a standard practice for wound regeneration.

Competing interests

The authors declare no potential conflicts of interests with respect to the research, authorship and/or publication of this article.

Funding sources and acknowledgments

BT is grateful to the Commonwealth Scholarship Commission (UK) for PhD funding; AM acknowledges the EPSRC DTP and The University of Manchester for PhD funding (EP/N509565/1, studentship 1786315); RB acknowledges the EPSRC for fellowship support (EP/P016898/1). The views contained within are those of the authors and do not represent the views of funding organizations.

References

[1] B. Behm, P. Babilas, M. Landthaler, S. Schreml, Cytokines, chemokines and growth factors in wound healing, J. Eur. Acad. Dermatol. Venereol. JEADV. 26 (2012) 812–820. doi:10.1111/j.1468-3083.2011.04415.x.

[2] H. Brem, M. Tomic-Canic, Cellular and molecular basis of wound healing in diabetes, J. Clin. Invest. 117 (2007) 1219–1222. doi:10.1172/JCI32169.

[3] B. Reid, M. Zhao, The electrical response to injury: molecular mechanisms and wound healing, Adv. Wound Care. 3 (2014) 184–201. doi:10.1089/wound.2013.0442.

[4] G. Thakral, J. LaFontaine, B. Najafi, T.K. Talal, P. Kim, L.A. Lavery, Electrical stimulation to accelerate wound healing, Diabet. Foot Ankle. 4 (2013). doi:10.3402/dfa.v4i0.22081.

[5] R.R. Isseroff, S.E. Dahle, Electrical stimulation therapy and wound healing: Where are we now?, Adv. Wound Care. 1 (2012) 238–243. doi:10.1089/wound.2011.0351.

[6] L.C. Kloth, Electrical stimulation technologies for wound healing, Adv. Wound Care. 3 (2014) 81–90. doi:10.1089/wound.2013.0459.

[7] J.S. Boateng, K.H. Matthews, H.N.E. Stevens, G.M. Eccleston, Wound healing dressings and drug delivery systems: a review, J. Pharm. Sci. 97 (2008) 2892–2923. doi:10.1002/jps.21210.

[8] P. Koria, Delivery of growth factors for tissue regeneration and wound healing, BioDrugs Clin. Immunother. Biopharm. Gene Ther. 26 (2012) 163–175. doi:10.2165/11631850-000000000-00000.

[9] R. Balint, N.J. Cassidy, S.H. Cartmell, Conductive polymers: Towards a smart biomaterial for tissue engineering, Acta Biomater. 10 (2014) 2341–2353. doi:10.1016/j.actbio.2014.02.015.

[10] D.. Ateh, H.. Navsaria, P. Vadgama, Polypyrrole-based conducting polymers and interactions with biological tissues, J. R. Soc. Interface. 3 (2006) 741–752. doi:10.1098/rsif.2006.0141.

[11] D. Svirskis, J. Travas-Sejdic, A. Rodgers, S. Garg, Electrochemically controlled drug delivery based on intrinsically conducting polymers, J. Control. Release Off. J. Control. Release Soc. 146 (2010) 6–15. doi:10.1016/j.jconrel.2010.03.023.

[12] B. Guo, L. Glavas, A.-C. Albertsson, Biodegradable and electrically conducting polymers for biomedical applications, Prog. Polym. Sci. 38 (2013) 1263–1286. doi:10.1016/j.progpolymsci.2013.06.003.

[13] L. Ghasemi-Mobarakeh, M.P. Prabhakaran, M. Morshed, M.H. Nasr-Esfahani, H. Baharvand, S. Kiani, S.S. Al-Deyab, S. Ramakrishna, Application of conductive polymers, scaffolds and electrical stimulation for nerve tissue engineering, J. Tissue Eng. Regen. Med. 5 (2011) e17-35. doi:10.1002/term.383.

[14] R. Ravichandran, S. Sundarrajan, J.R. Venugopal, S. Mukherjee, S. Ramakrishna, Applications of conducting polymers and their issues in biomedical engineering, J. R. Soc. Interface. 7 Suppl 5 (2010) S559-579. doi:10.1098/rsif.2010.0120.focus.

[15] X. Liu, K.J. Gilmore, S.E. Moulton, G.G. Wallace, Electrical stimulation promotes nerve cell differentiation on polypyrrole/poly (2-methoxy-5 aniline sulfonic acid) composites, J. Neural Eng. 6 (2009) 065002. doi:10.1088/1741-2560/6/6/065002.

[16] G. Wallace, G. Spinks, Conducting polymers – bridging the bionic interface, Soft Matter. 3 (2007) 665–671. doi:10.1039/B618204F.

[17] J.L. Bredas, G.B. Street, Polarons, bipolarons, and solitons in conducting polymers, Acc. Chem. Res. 18 (1985) 309–315. doi:10.1021/ar00118a005.

[18] B. Lakard, L. Ploux, K. Anselme, F. Lallemand, S. Lakard, M. Nardin, J.Y. Hihn, Effect of ultrasounds on the electrochemical synthesis of polypyrrole, application to the adhesion and growth of biological cells, Bioelectrochemistry. 75 (2009) 148–157. doi:10.1016/j.bioelechem.2009.03.010.

[19] J.-W. Lee, F. Serna, J. Nickels, C.E. Schmidt, Carboxylic acid-functionalized conductive polypyrrole as a bioactive platform for cell adhesion, Biomacromolecules. 7 (2006) 1692–1695. doi:10.1021/bm060220q.

[20] P.R. Bidez, S. Li, A.G. MacDiarmid, E.C. Venancio, Y. Wei, P.I. Lelkes, Polyaniline, an electroactive polymer, supports adhesion and proliferation of cardiac myoblasts, J. Biomater. Sci. Polym. Ed. 17 (2006) 199–212. doi:10.1163/156856206774879180.
[21] X. Cui, V.A. Lee, Y. Raphael, J.A. Wiler, J.F. Hetke, D.J. Anderson, D.C. Martin, Surface modification of neural recording electrodes with conducting polymer/biomolecule blends, J. Biomed. Mater. Res. 56 (2001) 261–272.
[22] B. Garner, A.J. Hodgson, G.G. Wallace, P.A. Underwood, Human endothelial cell attachment to and growth on polypyrrole-heparin is vitronectin dependent, J. Mater. Sci. Mater. Med. 10 (1999) 19–27.
[23] Z. Zhang, M. Rouabhia, Z. Wang, C. Roberge, G. Shi, P. Roche, J. Li, L.H. Dao, Electrically conductive biodegradable polymer composite for nerve regeneration: electricity-stimulated neurite outgrowth and axon regeneration, Artif. Organs. 31 (2007) 13–22. doi:10.1111/j.1525-1594.2007.00335.x.
[24] P.M. George, A.W. Lyckman, D.A. LaVan, A. Hegde, Y. Leung, R. Avasare, C. Testa, P.M. Alexander, R. Langer, M. Sur, Fabrication and biocompatibility of polypyrrole implants suitable for neural prosthetics, Biomaterials. 26 (2005) 3511–3519. doi:10.1016/j.biomaterials.2004.09.037.
[25] X. Wang, X. Gu, C. Yuan, S. Chen, P. Zhang, T. Zhang, J. Yao, F. Chen, G. Chen, Evaluation of biocompatibility of polypyrrole in vitro and in vivo, J. Biomed. Mater. Res. A. 68 (2004) 411–422. doi:10.1002/jbm.a.20065.
[26] J.H. Collier, J.P. Camp, T.W. Hudson, C.E. Schmidt, Synthesis and characterization of polypyrrole-hyaluronic acid composite biomaterials for tissue engineering applications, J. Biomed. Mater. Res. 50 (2000) 574–584.
[27] Z. Zhang, R. Roy, F.J. Dugré, D. Tessier, L.H. Dao, In vitro biocompatibility study of electrically conductive polypyrrole-coated polyester fabrics, J. Biomed. Mater. Res. 57 (2001) 63–71.
[28] Z. Wang, C. Roberge, Y. Wan, L.H. Dao, R. Guidoin, Z. Zhang, A biodegradable electrical bioconductor made of polypyrrole nanoparticle/poly(D,L-lactide) composite: A preliminary in vitro biostability study, J. Biomed. Mater. Res. A. 66A (2003) 738–746. doi:10.1002/jbm.a.10037.
[29] D.D. Ateh, P. Vadgama, H.A. Navsaria, Culture of human keratinocytes on polypyrrole-based conducting polymers, Tissue Eng. 12 (2006) 645–655. doi:10.1089/ten.2006.12.645.
[30] H. Castano, E.A. O'Rear, P.S. McFetridge, V.I. Sikavitsas, Polypyrrole thin films formed by admicellar polymerization support the osteogenic differentiation of mesenchymal stem cells, Macromol. Biosci. 4 (2004) 785–794. doi:10.1002/mabi.200300123.
[31] D.-H. Kim, S.M. Richardson-Burns, J.L. Hendricks, C. Sequera, D.C. Martin, Effect of immobilized nerve growth factor on conductive polymers: electrical properties and cellular response, Adv. Funct. Mater. 17 (2007) 79–86. doi:10.1002/adfm.200500594.
[32] M.H. Bolin, K. Svennersten, X. Wang, I.S. Chronakis, A. Richter-Dahlfors, E.W.H. Jager, M. Berggren, Nano-fiber scaffold electrodes based on PEDOT for cell stimulation, Sens. Actuators B Chem. 142 (2009) 451–456. doi:10.1016/j.snb.2009.04.062.
[33] V. Karagkiozaki, P.G. Karagiannidis, M. Gioti, P. Kavatzikidou, D. Georgiou, E. Georgaraki, S. Logothetidis, Bioelectronics meets nanomedicine for cardiovascular implants: PEDOT-based nanocoatings for tissue regeneration, Biochim. Biophys. Acta BBA - Gen. Subj. 1830 (2013) 4294–4304. doi:10.1016/j.bbagen.2012.12.019.
[34] E.A. Tetteh, M.A. Boatemaa, E.O. Martinson, A review of various actuation methods in micropumps for drug delivery appliactions, Proc. 11th Int. Conf. Electron. Comput. Comput. ICECCO 2014. (2014). doi:10.1109/ICECCO.2014.6997540.
[35] K.S. Ramadan, D. Sameoto, S. Evoy, A review of piezoelectric polymers as functional materials for electromechanical transducers, Smart Mater. Struct. 23 (2014) 033001. doi:10.1088/0964-1726/23/3/033001.

882 [36] C. Ribeiro, V. Sencadas, D.M. Correia, S. Lanceros-Mendez, Piezoelectric polymers as
883 biomaterials for tissue engineering applications, Colloids Surf B Biointerfaces. 136 (2015) 46–
884 55. doi:10.1016/j.colsurfb.2015.08.043.
885 [37] A.H. Rajabi, M. Jaffe, T.L. Arinzeh, Piezoelectric materials for tissue regeneration: A review,
886 Acta Biomater. 24 (2015) 12–23. doi:10.1016/j.actbio.2015.07.010.
887 [38] W.S. Jung, M.J. Lee, S.H. Baek, I.K. Jung, S.J. Yoon, C.Y. Kang, Structural approaches for
888 enhancing output power of piezoelectric polyvinylidene fluoride generator, Nano Energy. 22
889 (2016) 514–523. doi:10.1016/j.nanoen.2016.02.043.
890 [39] J. Curie, P. Curie, Development by pressure of polar electricity in hemihedral crystals with
891 inclined faces, Bull Soc Min Fr. 3 (1880) 90.
892 [40] A. Marino, G.G. Genchi, E. Sinibaldi, G. Ciofani, Piezoelectric effects of materials on
893 biointerfaces, ACS Appl. Mater. Interfaces. (2017). doi:10.1021/acsami.7b04323.
894 [41] K.S. Ramadan, D. Sameoto, S. Evoy, A review of piezoelectric polymers as functional
895 materials for electromechanical transducers, Smart Mater. Struct. 23 (2014) 033001.
896 doi:10.1088/0964-1726/23/3/033001.
897 [42] G.M. Sessler, Physical principles of electrets, in: G.M. Sessler (Ed.), Electrets, Springer Berlin
898 Heidelberg, Berlin, Heidelberg, 1987: pp. 13–80. doi:10.1007/3540173358_10.
899 [43] M. Eguchi, XX. On the permanent electret, Philos. Mag. Ser. 6. 49 (1925) 178–192.
900 doi:10.1080/14786442508634594.
901 [44] P.K.C. Pillai, E.L. Shriver, Electrets and their applications in contamination studies, NASA
902 Tech. Rep. (1975).
903 [45] V.N. Kestelman, L.S. Pinchuk, V.A. Goldade, Electret effect and electric technologies, in:
904 Electrets Eng. Fundam. Appl., Springer US, Boston, MA, 2000: pp. 1–45. doi:10.1007/978-1-
905 4615-4455-5_1.
906 [46] J.J.M. Halls, C.A. Walsh, N.C. Greenham, E.A. Marseglia, R.H. Friend, S.C. Moratti, A.B.
907 Holmes, Efficient photodiodes from interpenetrating polymer networks, Nature. 376 (1995)
908 498–500. doi:10.1038/376498a0.
909 [47] F. Priolo, T. Gregorkiewicz, M. Galli, T.F. Krauss, Silicon nanostructures for photonics and
910 photovoltaics, Nat. Nanotechnol. 9 (2014) 19–32. doi:10.1038/nnano.2013.271.
911 [48] A. Moliton, J.-M. Nunzi, How to model the behaviour of organic photovoltaic cells, Polym.
912 Int. 55 (2006) 583–600. doi:10.1002/pi.2038.
913 [49] Z. Tang, W. Tress, O. Inganäs, Light trapping in thin film organic solar cells, Mater. Today. 17
914 (2014) 389–396. doi:10.1016/j.mattod.2014.05.008.
915 [50] B. Sun, E. Marx, N.C. Greenham, Photovoltaic devices using blends of branched CdSe
916 nanoparticles and conjugated polymers, Nano Lett. 3 (2003) 961–963. doi:10.1021/nl0342895.
917 [51] S. Dayal, N. Kopidakis, D.C. Olson, D.S. Ginley, G. Rumbles, Photovoltaic devices with a low
918 band gap polymer and CdSe nanostructures exceeding 3% efficiency, Nano Lett. 10 (2010)
919 239–242. doi:10.1021/nl903406s.
920 [52] N.C. Greenham, X. Peng, A.P. Alivisatos, Charge separation and transport in conjugated-
921 polymer/semiconductor-nanocrystal composites studied by photoluminescence quenching and
922 photoconductivity, Phys. Rev. B. 54 (1996) 17628–17637. doi:10.1103/PhysRevB.54.17628.
923 [53] G. Grancini, M. Biasiucci, R. Mastria, F. Scotognella, F. Tassone, D. Polli, G. Gigli, G.
924 Lanzani, Dynamic microscopy study of ultrafast charge transfer in a hybrid
925 P3HT/hyperbranched CdSe nanoparticle blend for photovoltaics, J. Phys. Chem. Lett. 3 (2012)
926 517–523. doi:10.1021/jz3000382.
927 [54] S. Günes, N. Marjanovic, J.M. Nedeljkovic, N.S. Sariciftci, Photovoltaic characterization of
928 hybrid solar cells using surface modified TiO 2 nanoparticles and poly(3-hexyl)thiophene,
929 Nanotechnology. 19 (2008) 424009. doi:10.1088/0957-4484/19/42/424009.
930 [55] B.R. Saunders, M.L. Turner, Nanoparticle–polymer photovoltaic cells, Adv. Colloid Interface
931 Sci. 138 (2008) 1–23. doi:10.1016/j.cis.2007.09.001.
932 [56] W.U. Huynh, J.J. Dittmer, A.P. Alivisatos, Hybrid nanorod-polymer solar cells, Science. 295
933 (2002) 2425–2427. doi:10.1126/science.1069156.

[57] A. Ghezelbash, B. Koo, B.A. Korgel, Self-Assembled Stripe Patterns of CdS Nanorods, Nano Lett. 6 (2006) 1832–1836. doi:10.1021/nl061035l.
[58] D. Ciprari, K. Jacob, R. Tannenbaum, Characterization of Polymer nanocomposite interphase and its impact on mechanical properties, Macromolecules. 39 (2006) 6565–6573. doi:10.1021/ma0602270.
[59] P. Ravirajan, A.M. Peiró, M.K. Nazeeruddin, M. Graetzel, D.D.C. Bradley, J.R. Durrant, J. Nelson, Hybrid polymer/zinc oxide photovoltaic devices with vertically oriented ZnO nanorods and an amphiphilic molecular interface layer, J. Phys. Chem. B. 110 (2006) 7635–7639. doi:10.1021/jp0571372.
[60] J. Bouclé, H.J. Snaith, N.C. Greenham, Simple approach to hybrid polymer/porous metal oxide solar cells from solution-processed ZnO nanocrystals, J. Phys. Chem. C. 114 (2010) 3664–3674. doi:10.1021/jp909376f.
[61] B. Zinger, L.L. Miller, Timed release of chemicals from polypyrrole films, J. Am. Chem. Soc. 106 (1984) 6861–6863. doi:10.1021/ja00334a076.
[62] E. Shamaeli, N. Alizadeh, Kinetic studies of electrochemically controlled release of salicylate from nanostructure conducting molecularly imprinted polymer, Electrochimica Acta. 114 (2013) 409–415. doi:10.1016/j.electacta.2013.10.119.
[63] L. Sui, X.J. Song, J. Ren, W.J. Cai, L.H. Ju, Y. Wang, L.Y. Wang, M. Chen, In vitro and in vivo evaluation of poly(3,4-ethylenedioxythiophene)/poly(styrene sulfonate)/dopamine-coated electrodes for dopamine delivery, J. Biomed. Mater. Res. A. 102 (2014) 1681–1696. doi:10.1002/jbm.a.34837.
[64] M. Hepel, F. Mahdavi, Application of the electrochemical quartz crystal microbalance for electrochemically controlled binding and release of chlorpromazine from conductive polymer matrix, Microchem. J. 56 (1997) 54–64. doi:10.1006/mchj.1996.1436.
[65] K. Krukiewicz, B. Bednarczyk-Cwynar, R. Turczyn, J.K. Zak, EQCM verification of the concept of drug immobilization and release from conducting polymer matrix, Electrochimica Acta. 212 (2016) 694–700. doi:10.1016/j.electacta.2016.07.055.
[66] B.C. Thompson, S.E. Moulton, J. Ding, R. Richardson, A. Cameron, S. O'Leary, G.G. Wallace, G.M. Clark, Optimising the incorporation and release of a neurotrophic factor using conducting polypyrrole, J. Control. Release Off. J. Control. Release Soc. 116 (2006) 285–294. doi:10.1016/j.jconrel.2006.09.004.
[67] D. Uppalapati, B.J. Boyd, S. Garg, J. Travas-Sejdic, D. Svirskis, Conducting polymers with defined micro- or nanostructures for drug delivery, Biomaterials. 111 (2016) 149–162. doi:10.1016/j.biomaterials.2016.09.021.
[68] R. Wadhwa, C.F. Lagenaur, X.T. Cui, Electrochemically controlled release of dexamethasone from conducting polymer polypyrrole coated electrode, J. Controlled Release. 110 (2006) 531–541. doi:10.1016/j.jconrel.2005.10.027.
[69] Y. Li, K.G. Neoh, E.T. Kang, Controlled release of heparin from polypyrrole-poly(vinyl alcohol) assembly by electrical stimulation, J. Biomed. Mater. Res. A. 73 (2005) 171–181. doi:10.1002/jbm.a.30286.
[70] L.L. Miller, X.Q. Zhou, Poly(N-methylpyrrolylium) poly(styrenesulfonate) - a conductive, electrically switchable cation exchanger that cathodically binds and anodically releases dopamine, Macromolecules. 20 (1987) 1594–1597. doi:10.1021/ma00173a027.
[71] K. Kontturi, P. Pentti, G. Sundholm, Polypyrrole as a model membrane for drug delivery, J. Electroanal. Chem. 453 (1998) 231–238. doi:10.1016/S0022-0728(98)00246-0.
[72] R.L. Williams, P.J. Doherty, A preliminary assessment of poly(pyrrole) in nerve guide studies, J. Mater. Sci. Mater. Med. 5 (1994) 429–433. doi:10.1007/BF00058978.
[73] Susanne Löffler, Silke Seyock, Rolf Nybom, Gunilla B. Jacobson, Agneta Richter-Dahlfors, Electrochemically triggered release of acetylcholine from scCO2 impregnated conductive polymer films evokes intracellular Ca2+ signaling in neurotypic SH-SY5Y cells, J. Controlled Release. 243 (2016) 283–290.

[74] K. Krukiewicz, A. Stokfisz, J.K. Zak, Two approaches to the model drug immobilization into conjugated polymer matrix, Mater. Sci. Eng. C. 54 (2015) 176–181. doi:10.1016/j.msec.2015.05.017.
[75] C. Arbizzani, M. Mastragostino, L. Nevi, L. Rambelli, Polypyrrole: A drug-eluting membrane for coronary stents, Electrochimica Acta. 52 (2007) 3274–3279. doi:10.1016/j.electacta.2006.10.003.
[76] G. Bidan, C. Lopez, F. Mendes-Viegas, E. Vieil, A. Gadelle, Incorporation of sulphonated cyclodextrins into polypyrrole: an approach for the electro-controlled delivering of neutral drugs, Biosens. Bioelectron. 10 (1995) 219–229. doi:10.1016/0956-5663(95)96808-C.
[77] D. Ge, X. Tian, R. Qi, S. Huang, J. Mu, S. Hong, S. Ye, X. Zhang, D. Li, W. Shi, A polypyrrole-based microchip for controlled drug release, Electrochimica Acta. 55 (2009) 271–275. doi:10.1016/j.electacta.2009.08.049.
[78] J. Ge, E. Neofytou, T.J. Cahill, R.E. Beygui, R.N. Zare, Drug release from electric-field-responsive nanoparticles, ACS Nano. 6 (2012) 227–233. doi:10.1021/nn203430m.
[79] B. Massoumi, A. Entezami, Electrochemically controlled binding and release of dexamethasone from conducting polymer bilayer films, J. Bioact. Compat. Polym. 17 (2002) 51–62. doi:10.1177/088391150201700181 3.
[80] C. Chen, X. Chen, H. Zhang, Q. Zhang, L. Wang, C. Li, B. Dai, J. Yang, J. Liu, D. Sun, Electrically-responsive core-shell hybrid microfibers for controlled drug release and cell culture, Acta Biomater. 55 (2017) 434–442. doi:10.1016/j.actbio.2017.04.005.
[81] X. Luo, X.T. Cui, Electrochemically controlled release based on nanoporous conducting polymers, Electrochem. Commun. 11 (2009) 402–404. doi:10.1016/j.elecom.2008.11.052.
[82] X. Luo, X.T. Cui, Sponge-like nanostructured conducting polymers for electrically controlled drug release, Electrochem. Commun. 11 (2009) 1956. doi:10.1016/j.elecom.2009.08.027.
[83] N. Alizadeh, E. Shamaeli, Electrochemically controlled release of anticancer drug methotrexate using nanostructured polypyrrole modified with cetylpyridinium: Release kinetics investigation, Electrochimica Acta. 130 (2014) 488–496. doi:10.1016/j.electacta.2014.03.055.
[84] S. Carquigny, B. Lakard, S. Lakard, V. Moutarlier, J.-Y. Hihn, L. Viau, Investigation of pharmaceutically active ionic liquids as electrolyte for the electrosynthesis of polypyrrole and active component in controlled drug delivery, Electrochimica Acta. 211 (2016) 950–961. doi:10.1016/j.electacta.2016.06.080.
[85] E. Shamaeli, N. Alizadeh, Functionalized gold nanoparticle-polypyrrole nanobiocomposite with high effective surface area for electrochemical/pH dual stimuli-responsive smart release of insulin, Colloids Surf. B Biointerfaces. 126 (2015) 502–509. doi:10.1016/j.colsurfb.2015.01.003.
[86] P.M. George, D.A. LaVan, J.A. Burdick, C.-Y. Chen, E. Liang, R. Langer, Electrically controlled drug delivery from biotin-doped conductive polypyrrole, Adv. Mater. 18 (2006) 577–581. doi:10.1002/adma.200501242.
[87] D. Esrafilzadeh, J.M. Razal, S.E. Moulton, E.M. Stewart, G.G. Wallace, Multifunctional conducting fibres with electrically controlled release of ciprofloxacin, J. Controlled Release. 169 (2013) 313–320. doi:10.1016/j.jconrel.2013.01.022.
[88] D. Svirskis, B.E. Wright, J. Travas-Sejdic, A. Rodgers, S. Garg, Development of a controlled release system for risperidone using polypyrrole: mechanistic studies, Electroanalysis. 22 (2010) 439–444. doi:10.1002/elan.200900401.
[89] S. Jiang, Y. Sun, X. Cui, X. Huang, Y. He, S. Ji, W. Shi, D. Ge, Enhanced drug loading capacity of polypyrrole nanowire network for controlled drug release, Synth. Met. 163 (2013) 19–23. doi:10.1016/j.synthmet.2012.12.010.
[90] A. Pourjavadi, M. Doroudian, Synthesis and characterization of semi-conductive nanocomposite based on hydrolyzed collagen and in vitro electrically controlled drug release study, Polymer. 76 (2015) 287–294. doi:10.1016/j.polymer.2015.06.050.

[91] M. Sharma, G.I.N. Waterhouse, S.W.C. Loader, S. Garg, D. Svirskis, High surface area polypyrrole scaffolds for tunable drug delivery, Int. J. Pharm. 443 (2013) 163–168. doi:10.1016/j.ijpharm.2013.01.006.
[92] E. Shamaeli, N. Alizadeh, Nanostructured biocompatible thermal/electrical stimuli-responsive biopolymer-doped polypyrrole for controlled release of chlorpromazine: kinetics studies, Int. J. Pharm. 472 (2014) 327–338. doi:10.1016/j.ijpharm.2014.06.036.
[93] S.H. Takahashi, L.M. Lira, S.I.C. de Torresi, Zero-order release profiles from a multistimuli responsive electro-conductive hydrogel, J. Biomater. Nanobiotechnology. 03 (2012) 262. doi:10.4236/jbnb.2012.322032.
[94] R. Wang, Y. Peng, M. Zhou, D. Shou, Smart montmorillonite-polypyrrole scaffolds for electro-responsive drug release, Appl. Clay Sci. 134 (2016) 50–54. doi:10.1016/j.clay.2016.05.004.
[95] J.-M. Pernaut, J.R. Reynolds, Use of conducting electroactive polymers for drug delivery and sensing of bioactive molecules. A Redox chemistry approach, J. Phys. Chem. B. 104 (2000) 4080–4090. doi:10.1021/jp994274o.
[96] D.D. Zhou, X.T. Cui, A. Hines, R.J. Greenberg, Conducting polymers in neural stimulation applications, in: D. Zhou, E. Greenbaum (Eds.), Implant. Neural Prostheses 2, Springer New York, 2009: pp. 217–252. doi:10.1007/978-0-387-98120-8_8.
[97] G. NK, Gomez N, Schmidt CE, Conducting engineering, Prog Polym Sci. 32 (2007) 876–921.
[98] C. Boehler, C. Kleber, N. Martini, Y. Xie, I. Dryg, T. Stieglitz, U.G. Hofmann, M. Asplund, Actively controlled release of Dexamethasone from neural microelectrodes in a chronic in vivo study, Biomaterials. 129 (2017) 176–187. doi:10.1016/j.biomaterials.2017.03.019.
[99] R.T. Richardson, B. Thompson, S. Moulton, C. Newbold, M.G. Lum, A. Cameron, G. Wallace, R. Kapsa, G. Clark, S. O'Leary, The effect of polypyrrole with incorporated neurotrophin-3 on the promotion of neurite outgrowth from auditory neurons, Biomaterials. 28 (2007) 513–523. doi:10.1016/j.biomaterials.2006.09.008.
[100] R.T. Richardson, A.K. Wise, B.C. Thompson, B.O. Flynn, P.J. Atkinson, N.J. Fretwell, J.B. Fallon, G.G. Wallace, R.K. Shepherd, G.M. Clark, S.J. O'Leary, Polypyrrole-coated electrodes for the delivery of charge and neurotrophins to cochlear neurons, Biomaterials. 30 (2009) 2614–2624. doi:10.1016/j.biomaterials.2009.01.015.
[101] Darren Svirskis, Jadranka Travas- Sejdic, Anthony Rodgers, Sanjay Garg, Polypyrrole film as a drug delivery system for the controlled release of risperidone, AIP Conf. Proc. 1151 (2009).
[102] D. Svirskis, B.E. Wright, J. Travas-Sejdic, A. Rodgers, S. Garg, Evaluation of physical properties and performance over time of an actuating polypyrrole based drug delivery system, Sens. Actuators B Chem. 151 (2010) 97–102. doi:10.1016/j.snb.2010.09.042.
[103] B.C. Thompson, R.T. Richardson, S.E. Moulton, A.J. Evans, S. O'Leary, G.M. Clark, G.G. Wallace, Conducting polymers, dual neurotrophins and pulsed electrical stimulation--dramatic effects on neurite outgrowth, J. Control. Release Off. J. Control. Release Soc. 141 (2010) 161–167. doi:10.1016/j.jconrel.2009.09.016.
[104] K. Krukiewicz, M. Cichy, P. Ruszkowski, R. Turczyn, T. Jarosz, J.K. Zak, M. Lapkowski, B. Bednarczyk-Cwynar, Betulin-loaded PEDOT films for regional chemotherapy, Mater. Sci. Eng. C Mater. Biol. Appl. 73 (2017) 611–615. doi:10.1016/j.msec.2016.12.115.
[105] M.R. Abidian, D.-H. Kim, D.C. Martin, Conducting-polymer nanotubes for controlled drug release, Adv. Mater. 18 (2006) 405–409. doi:10.1002/adma.200501726.
[106] J. Pokki, O. Ergeneman, K. M. Sivaraman, B. Özkale, M. A. Zeeshan, T. Lühmann, B. J. Nelson, S. Pané, Electroplated porous polypyrrole nanostructures patterned by colloidal lithography for drug -delivery applications, Nanoscale. 4 (2012) 3083–3088. doi:10.1039/C2NR30192J.
[107] A. Seyfoddin, A. Chan, W.-T. Chen, I.D. Rupenthal, G.I.N. Waterhouse, D. Svirskis, Electro-responsive macroporous polypyrrole scaffolds for triggered dexamethasone delivery, Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Pharm. Verfahrenstechnik EV. 94 (2015) 419–426. doi:10.1016/j.ejpb.2015.06.018.

[108] B.C. Thompson, J. Chen, S.E. Moulton, G.G. Wallace, Nanostructured aligned CNT platforms enhance the controlled release of a neurotrophic protein from polypyrrole, Nanoscale. 2 (2010) 499–501. doi:10.1039/B9NR00259F.
[109] S. Sirivisoot, R. Pareta, T.J. Webster, Electrically controlled drug release from nanostructured polypyrrole coated on titanium, Nanotechnology. 22 (2011) 085101. doi:10.1088/0957-4484/22/8/085101.
[110] Y. Xiao, X. Ye, L. He, J. Che, New carbon nanotube–conducting polymer composite electrodes for drug delivery applications, Polym. Int. 61 (2012) 190–196. doi:10.1002/pi.3168.
[111] X. Luo, C. Matranga, S. Tan, N. Alba, X.T. Cui, Carbon nanotube nanoreservior for controlled release of anti-inflammatory dexamethasone, Biomaterials. 32 (2011) 6316–6323. doi:10.1016/j.biomaterials.2011.05.020.
[112] C.L. Weaver, J.M. LaRosa, X. Luo, X.T. Cui, Electrically controlled drug delivery from graphene oxide nanocomposite films, ACS Nano. 8 (2014) 1834–1843. doi:10.1021/nn406223e.
[113] K. Catt, H. Li, V. Hoang, R. Beard, X.T. Cui, Self-powered therapeutic release from conducting polymer/graphene oxide films on magnesium, Nanomedicine Nanotechnol. Biol. Med. 0 (2017). doi:10.1016/j.nano.2017.02.021.
[114] Y. Kong, H. Ge, J. Xiong, S. Zuo, Y. Wei, C. Yao, L. Deng, Palygorskite polypyrrole nanocomposite: A new platform for electrically tunable drug delivery, Appl. Clay Sci. 99 (2014) 119–124. doi:10.1016/j.clay.2014.06.020.
[115] P. Chansai, A. Sirivat, S. Niamlang, D. Chotpattananont, K. Viravaidya-Pasuwat, Controlled transdermal iontophoresis of sulfosalicylic acid from polypyrrole/poly(acrylic acid) hydrogel, Int. J. Pharm. 381 (2009) 25–33. doi:10.1016/j.ijpharm.2009.07.019.
[116] J.A. Chikar, J.L. Hendricks, S.M. Richardson-Burns, Y. Raphael, B.E. Pfingst, D.C. Martin, The use of a dual PEDOT and RGD-functionalized alginate hydrogel coating to provide sustained drug delivery and improved cochlear implant function, Biomaterials. 33 (2012) 1982–1990. doi:10.1016/j.biomaterials.2011.11.052.
[117] V.B. Bueno, S.H. Takahashi, L.H. Catalani, S.I.C. de Torresi, D.F.S. Petri, Biocompatible xanthan/polypyrrole scaffolds for tissue engineering, Mater. Sci. Eng. C Mater. Biol. Appl. 52 (2015) 121–128. doi:10.1016/j.msec.2015.03.023.
[118] D. Ge, X. Ru, S. Hong, S. Jiang, J. Tu, J. Wang, A. Zhang, S. Ji, V. Linkov, B. Ren, W. Shi, Coating metals on cellulose–polypyrrole composites: A new route to self-powered drug delivery system, Electrochem. Commun. 12 (2010) 1367–1370. doi:10.1016/j.elecom.2010.07.022.
[119] X. Ru, W. Shi, X. Huang, X. Cui, B. Ren, D. Ge, Synthesis of polypyrrole nanowire network with high adenosine triphosphate release efficiency, Electrochimica Acta. 56 (2011) 9887–9892. doi:10.1016/j.electacta.2011.08.063.
[120] Y. Cho, R.B. Borgens, Biotin-doped porous polypyrrole films for electrically controlled nanoparticle release, Langmuir ACS J. Surf. Colloids. 27 (2011) 6316–6322. doi:10.1021/la200160q.
[121] H.T. Nguyen, T.H. Tran, R.K. Thapa, C.D. Phung, B.S. Shin, J.-H. Jeong, H.-G. Choi, C.S. Yong, J.O. Kim, Targeted co-delivery of polypyrrole and rapamycin by trastuzumab-conjugated liposomes for combined chemo-photothermal therapy, Int. J. Pharm. 527 (2017) 61–71. doi:10.1016/j.ijpharm.2017.05.034.
[122] M.F. Attia, N. Anton, I.U. Khan, C.A. Serra, N. Messaddeq, A. Jakhmola, R. Vecchione, T. Vandamme, One-step synthesis of iron oxide polypyrrole nanoparticles encapsulating ketoprofen as model of hydrophobic drug, Int. J. Pharm. 508 (2016) 61–70. doi:10.1016/j.ijpharm.2016.04.073.
[123] D. Samanta, J.L. Meiser, R.N. Zare, Polypyrrole nanoparticles for tunable, pH-sensitive and sustained drug release, Nanoscale. 7 (2015) 9497–9504. doi:10.1039/c5nr02196k.
[124] G. Jeon, S.Y. Yang, J. Byun, J.K. Kim, Electrically actuatable smart nanoporous membrane for pulsatile drug release, Nano Lett. 11 (2011) 1284–1288. doi:10.1021/nl104329y.

[125] J.G. Hardy, D.J. Mouser, N. Arroyo-Currás, S. Geissler, J.K. Chow, L. Nguy, J.M. Kim, C.E. Schmidt, Biodegradable electroactive polymers for electrochemically-triggered drug delivery, J. Mater. Chem. B. 2 (2014) 6809–6822. doi:10.1039/C4TB00355A.
[126] J. G. Hardy, M. N. Amend, S. Geissler, V. M. Lynch, C. E. Schmidt, Peptide-directed assembly of functional supramolecular polymers for biomedical applications: electroactive molecular tongue-twisters (oligoalanine–oligoaniline–oligoalanine) for electrochemically enhanced drug delivery, J. Mater. Chem. B. 3 (2015) 5005–5009. doi:10.1039/C5TB00106D.
[127] S. Niamlang, A. Sirivat, Electrically controlled release of salicylic acid from poly(p-phenylene vinylene)/polyacrylamide hydrogels, Int. J. Pharm. 371 (2009) 126–133. doi:10.1016/j.ijpharm.2008.12.032.
[128] G. Liu, C. Shen, Z. Yang, X. Cai, H. Zhang, A disposable piezoelectric micropump with high performance for closed-loop insulin therapy system, Sens. Actuators Phys. 163 (2010) 291–296. doi:10.1016/j.sna.2010.06.030.
[129] D.H. Abdelkader, M.A. Osamn, S.A. Elgizawy, A.M. Faheem, P.A. McCarron, The Role of Insulin in Wound Healing Process : Mechanism of Action and Pharmaceutical Applications, J. Anal. Pharm. Res. 2 (2016) 1–6. doi:10.15406/japlr.2016.02.00007.
[130] D. Dumont-Fillon, H. Tahriou, C. Conan, E. Chappel, Insulin micropump with embedded pressure sensors for failure detection and delivery of accurate monitoring, Micromachines. 5 (2014) 1161–1172. doi:10.3390/mi5041161.
[131] M. Hrynyk, R.J. Neufeld, Insulin and wound healing, Burns. 40 (2014) 1433–1446. doi:10.1016/j.burns.2014.03.020.
[132] G. Gainza, S. Villullas, J.L. Pedraz, R.M. Hernandez, M. Igartua, Advances in drug delivery systems (DDSs) to release growth factors for wound healing and skin regeneration, Nanomedicine Nanotechnol. Biol. Med. 11 (2015) 1551–1573. doi:10.1016/j.nano.2015.03.002.
[133] C. Dempsey, I. Lee, K.R. Cowan, J. Suh, Coating barium titanate nanoparticles with polyethylenimine improves cellular uptake and allows for coupled imaging and gene delivery, Colloids Surf. B Biointerfaces. 112 (2013) 108–112. doi:10.1016/j.colsurfb.2013.07.045.
[134] G. Ciofani, S. Danti, D. D'Alessandro, S. Moscato, M. Petrini, A. Menciassi, Barium titanate nanoparticles: Highly cytocompatible dispersions in glycol-chitosan and doxorubicin complexes for cancer therapy, Nanoscale Res. Lett. 5 (2010) 1093–1101. doi:10.1007/s11671-010-9607-0.
[135] J. Niskanen, I. Zhang, Y. Xue, D. Golberg, D. Maysinger, F.M. Winnik, Boron nitride nanotubes as vehicles for intracellular delivery of fluorescent drugs and probes., Nanomed. 11 (2016) 447–463. doi:10.2217/nnm.15.214.
[136] S. Aggarwal, B. Eladi, P. Amitava, Experimental characterization of piezoelectrically actuated micromachined silicon valveless micropump, Microfluid. Nanofluidics. 21 (2017) 1–11. doi:10.1007/s10404-016-1837-8.
[137] A. Nisar, N. Afzulpurkar, B. Mahaisavariya, A. Tuantranont, MEMS-based micropumps in drug delivery and biomedical applications, 130 (2008) 917–942. doi:10.1016/j.snb.2007.10.064.
[138] A. Mahnama, A. Nourbakhsh, G. Ghorbaniasl, A survey on the applications of implantable micropump systems in drug delivery., Curr. Drug Deliv. 11 (2014) 123–31.
[139] A. Cobo, R. Sheybani, E. Meng, MEMS: Enabled Drug Delivery Systems, Adv. Healthc. Mater. 4 (2015) 969–982. doi:10.1002/adhm.201400772.
[140] P.B. Eladi, D. Chatterjee, A. DasGupta, Design and Development of a Piezoelectrically Actuated Micropump for Drug Delivery Application, in: K.J. Vinoy, G.K. Ananthasuresh, R. Pratap, S.B. Krupanidhi (Eds.), Micro Smart Devices Syst., Springer India, New Delhi, 2014: pp. 127–141. doi:10.1007/978-81-322-1913-2_8.
[141] J. Ni, F. Huang, B. Wang, Y. Wei, R. Torah, K. Yang, S. Beeby, J. Tudor, A novel fabrication process to realize a valveless micropump on a flexible substrate, (n.d.). doi:10.1088/0964-1726/23/2/025034.

[142] S. Yang, X. He, S. Yuan, J. Zhu, Z. Deng, Sensors and Actuators A : Physical A valveless piezoelectric micropump with a Coanda jet element, Sens. Actuators Phys. 230 (2015) 74–82. doi:10.1016/j.sna.2015.04.016.
[143] X.Y. Wang, Y.T. Ma, G.Y. Yan, Z.H. Feng, A compact and high fl ow-rate piezoelectric micropump with a folded vibrator, (n.d.). doi:10.1088/0964-1726/23/11/115005.
[144] K. Junwu, Y. Zhigang, P. Taijiang, C. Guangming, W. Boda, Design and test of a high-performance piezoelectric micropump for drug delivery, 121 (2005) 156–161. doi:10.1016/j.sna.2004.12.002.
[145] P. Cazorla, O. Fuchs, M. Cochet, S. Maubert, G. Le, Y. Fouillet, E. Defay, Sensors and Actuators A : Physical A low voltage silicon micro-pump based on piezoelectric thin films, Sens. Actuators Phys. 250 (2016) 35–39. doi:10.1016/j.sna.2016.09.012.
[146] E. Meng, T. Hoang, Micro- and nano-fabricated implantable drug-delivery systems., Ther. Deliv. 3 (2012) 1457–67. doi:10.4155/tde.12.132.
[147] R. Riahi, A. Tamayol, S. Ali, M. Shaegh, A.M. Ghaemmaghami, M.R. Dokmeci, A. Khademhosseini, Microfluidics for advanced drug delivery systems, Curr. Opin. Chem. Eng. 7 (2015) 101–112. doi:10.1016/j.coche.2014.12.001.
[148] P. Vaněk, Z. Kolská, T. Luxbacher, J.A.L. García, M. Lehocký, M. Vandrovcová, L. Bačáková, J. Petzelt, Electrical activity of ferroelectric biomaterials and its effects on the adhesion, growth and enzymatic activity of human osteoblast-like cells, J. Phys. Appl. Phys. 49 (2016) 175403. doi:10.1088/0022-3727/49/17/175403.
[149] X. Zhang, C. Zhang, Y. Lin, P. Hu, Y. Shen, K. Wang, S. Meng, Y. Chai, X. Dai, X. Liu, Y. Liu, X. Mo, C. Cao, S. Li, X. Deng, L. Chen, Nanocomposite membranes enhance bone regeneration through restoring physiological electric microenvironment, ACS Nano. 10 (2016) 7279–7286. doi:10.1021/acsnano.6b02247.
[150] D. Farmanzadeh, S. Ghazanfary, BNNTs under the influence of external electric field as potential new drug delivery vehicle of Glu, Lys, Gly and ser amino acids: A first-principles study, Appl. Surf. Sci. 320 (2014) 391–399. doi:10.1016/j.apsusc.2014.09.061.
[151] T. He, J. Wang, P. Huang, B. Zeng, H. Li, Q. Cao, S. Zhang, Z. Luo, D.Y.B. Deng, H. Zhang, W. Zhou, Electrospinning polyvinylidene fluoride fibrous membranes containing anti-bacterial drugs used as wound dressing, Colloids Surf. B Biointerfaces. 130 (2015) 278–286. doi:10.1016/j.colsurfb.2015.04.026.
[152] J. Jiang, Z. Wang, L. Ha, M. Zhang, L. Cui, Z. Xia, Study on healing effect of PTFE electrets on pig wound, (1996) 4–8.
[153] J. Jiang, Y.Y. Liang, L.L. Cui, X.M. Hou, Y. Tang, X.T. Ye, Y.J. Yang, M.H. Song, Influence of porous PTFE/LDPE/PP composite electret in skin ultrastructure, J. Phys. Conf. Ser. 142 (2008) 012050. doi:10.1088/1742-6596/142/1/012050.
[154] J. Jiang, Y.Y. Liang, L.L. Cui, X.M. Hou, Y. Tang, X.T. Ye, Y.J. Yang, M.H. Song, Influence of porous PTFE/LDPE/PP composite electret in skin ultrastructure, J. Phys. Conf. Ser. 142 (2008) 012050. doi:10.1088/1742-6596/142/1/012050.
[155] L. Cui, Y. Liang, F. Dong, L. Ma, Y. Tu, H. Liu, J. Jiang, Structure of rat skin after application of electret characterized by DSC, J Phys Conf Ser. 301 (2011). doi:10.1088/1742-6596/301/1/012027.
[156] J. Jiang, Y. Liang, D. Fajie, M. Lin, L. Hongyue, L. Cui, Studies of penetration of electrostatic field of electret through skin and its stability, Proc. - Int. Symp. Electrets. (2011) 51–52. doi:10.1109/ISE.2011.6084977.
[157] J. Jiang, Y. Liang, D. Fajie, M. Lin, L. Hongyue, L. Cui, Studies of penetration of electrostatic field of electret through skin and its stability, Proc. - Int. Symp. Electrets. (2011) 51–52. doi:10.1109/ISE.2011.6084977.
[158] Y. Tu, X. Wang, Y. Lu, H. Zhang, Y. Yu, Y. Chen, J. Liu, Z. Sun, L. Cui, J. Gao, Y. Zhong, Promotion of the transdermal delivery of protein drugs by N-trimethyl chitosan nanoparticles combined with polypropylene electret, Int. J. Nanomedicine. 11 (2016) 5549–5561. doi:10.2147/IJN.S109552.

[159] J. Jiang, Y. Liang, F. Dong, H. Liu, Y. Tu, L. Cui, Study of electret effect of rat skin by thermally stimulated discharge analysis, J. Electrost. 70 (2012) 258–263. doi:10.1016/j.elstat.2012.03.007.
[160] L. Cui, H. Liu, Enhanced transdermal delivery of cyclosporine A by PP electret and ethyl oleate, 19 (2012) 1191–1194.
[161] L.L. Cui, X.M. Hou, J. Jiang, G.D. Li, Y.Y. Liang, X. Xin, Comparative enhancing effects of electret with chemical enhancers on transdermal delivery of meloxicam in vitro, J. Phys. Conf. Ser. 142 (2008) 012015. doi:10.1088/1742-6596/142/1/012015.
[162] N.S. Narasimha Sathyanarayana Murthy, V.A. Boguda, K. Payasada, Electret enhances transdermal drug permeation., Biol. Pharm. Bull. 31 (2008) 99–102. doi:10.1248/bpb.31.99.
[163] M. Bhuyan, S. Ambure, D. Reyna, J. Rodriguez-Devora, T. Xu, Targeted drug delivery system using photovoltaic devices, Int. J. Drug Deliv. 4 (2013) 398–406.
[164] A. Yildirim, E. Ozgur, M. Bayindir, Impact of mesoporous silica nanoparticle surface functionality on hemolytic activity, thrombogenicity and non-specific protein adsorption, J. Mater. Chem. B. 1 (2013) 1909–1920. doi:10.1039/C3TB20139B.
[165] Q. Cai, W.Y. Zou, Z.S. Luo, Q.X. Wen, W.Q. Pang, F.Z. Cui, Rectifying and photovoltaic effects observed in mesoporous MCM-41 silica film on silicon, Mater. Lett. 58 (2004) 1–4. doi:10.1016/S0167-577X(03)00393-8.
[166] J.V.N. Batchu, A.U. Ebong, Photovoltaic therapy: Conceptual nanoscopic photovoltaic device for transporting chemotherapeutic drugs, in: 2013 High Capacity Opt. Netw. EmergingEnabling Technol., 2013: pp. 72–77. doi:10.1109/HONET.2013.6729760.
[167] S. Chowdhury, F. Yusof, W.W.A.W. Salim, N. Sulaiman, M.O. Faruck, An overview of drug delivery vehicles for cancer treatment: Nanocarriers and nanoparticles including photovoltaic nanoparticles, J. Photochem. Photobiol. B. 164 (2016) 151–159. doi:10.1016/j.jphotobiol.2016.09.013.
[168] H.S. Choi, W. Liu, P. Misra, E. Tanaka, J.P. Zimmer, B.I. Ipe, M.G. Bawendi, J.V. Frangioni, Renal clearance of nanoparticles, Nat. Biotechnol. 25 (2007) 1165–1170. doi:10.1038/nbt1340.
[169] J.S. Souris, C.-H. Lee, S.-H. Cheng, C.-T. Chen, C.-S. Yang, J.A. Ho, C.-Y. Mou, L.-W. Lo, Surface charge-mediated rapid hepatobiliary excretion of mesoporous silica nanoparticles, Biomaterials. 31 (2010) 5564–5574. doi:10.1016/j.biomaterials.2010.03.048.
[170] F. Alexis, E. Pridgen, L.K. Molnar, O.C. Farokhzad, Factors affecting the clearance and biodistribution of polymeric nanoparticles, Mol. Pharm. 5 (2008) 505–515. doi:10.1021/mp800051m.
[171] R.L. Martin, M. Haranczyk, Optimization-based design of metal-organic framework materials, J. Chem. Theory Comput. 9 (2013) 2816–2825. doi:10.1021/ct400255c.
[172] H.-C. Zhou, J.R. Long, O.M. Yaghi, Introduction to metal–organic frameworks, Chem. Rev. 112 (2012) 673–674. doi:10.1021/cr300014x.
[173] P. Horcajada, C. Serre, M. Vallet-Regí, M. Sebban, F. Taulelle, G. Férey, Metal–organic frameworks as efficient materials for drug delivery, Angew. Chem. Int. Ed. 45 (2006) 5974–5978. doi:10.1002/anie.200601878.
[174] P. Horcajada, C. Serre, G. Maurin, N.A. Ramsahye, F. Balas, M. Vallet-Regí, M. Sebban, F. Taulelle, G. Férey, Flexible porous metal-organic frameworks for a controlled drug delivery, J. Am. Chem. Soc. 130 (2008) 6774–6780. doi:10.1021/ja710973k.
[175] P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrie, T. Baati, J.F. Eubank, D. Heurtaux, P. Clayette, C. Kreuz, J.-S. Chang, Y.K. Hwang, V. Marsaud, P.-N. Bories, L. Cynober, S. Gil, G. Férey, P. Couvreur, R. Gref, Porous metal-organic-framework nanoscale carriers as a potential platform for drug delivery and imaging, Nat. Mater. 9 (2010) 172–178. doi:10.1038/nmat2608.
[176] C.-Y. Sun, C. Qin, X.-L. Wang, Z.-M. Su, Metal-organic frameworks as potential drug delivery systems, Expert Opin. Drug Deliv. 10 (2013) 89–101. doi:10.1517/17425247.2013.741583.
[177] J. Rocca, D. Liu, W. Lin, Nanoscale metal–organic frameworks for biomedical imaging and drug delivery, Acc. Chem. Res. 44 (2011) 957–968. doi:10.1021/ar200028a.

[178] B. Xiao, P.S. Wheatley, X. Zhao, A.J. Fletcher, S. Fox, A.G. Rossi, I.L. Megson, S. Bordiga, L. Regli, K.M. Thomas, R.E. Morris, High-capacity hydrogen and nitric oxide adsorption and storage in a metal−organic framework, J. Am. Chem. Soc. 129 (2007) 1203–1209. doi:10.1021/ja066098k.
[179] C. Rigo, L. Ferroni, I. Tocco, M. Roman, I. Munivrana, C. Gardin, W.R.L. Cairns, V. Vindigni, B. Azzena, C. Barbante, B. Zavan, Active silver nanoparticles for wound healing, Int. J. Mol. Sci. 14 (2013) 4817–4840. doi:10.3390/ijms14034817.
[180] A.P. Kornblatt, V.G. Nicoletti, A. Travaglia, The neglected role of copper ions in wound healing, J. Inorg. Biochem. 161 (2016) 1–8. doi:10.1016/j.jinorgbio.2016.02.012.
[181] J. Luo, A.F. Chen, Nitric oxide: a newly discovered function on wound healing, Acta Pharmacol. Sin. 26 (2005) 259–264. doi:10.1111/j.1745-7254.2005.00058.x.
[182] J. Xiao, S. Chen, J. Yi, H.F. Zhang, G.A. Ameer, A cooperative copper metal–organic framework-hydrogel system improves wound healing in diabetes, Adv. Funct. Mater. 27 (2017) n/a-n/a. doi:10.1002/adfm.201604872.
[183] N.J. Hinks, A.C. McKinlay, B. Xiao, P.S. Wheatley, R.E. Morris, Metal organic frameworks as NO delivery materials for biological applications, Microporous Mesoporous Mater. 129 (2010) 330–334. doi:10.1016/j.micromeso.2009.04.031.
[184] P.S. Wheatley, A.C. McKinlay, R.E. Morris, A comparison of zeolites and metal organic frameworks as storage and delivery vehicles for biologically active nitric oxide, Stud. Surf. Sci. Catal. 174 (2008) 441–446. doi:10.1016/S0167-2991(08)80236-4.
[185] C.H. Hendon, D. Tiana, A. Walsh, Conductive metal–organic frameworks and networks: fact or fantasy?, Phys. Chem. Chem. Phys. 14 (2012) 13120–13132. doi:10.1039/C2CP41099K.
[186] D.Y. Lee, C.Y. Shin, S.J. Yoon, H.Y. Lee, W. Lee, N.K. Shrestha, J.K. Lee, S.-H. Han, Enhanced photovoltaic performance of Cu-based metal-organic frameworks sensitized solar cell by addition of carbon nanotubes, Sci. Rep. 4 (2014) srep03930. doi:10.1038/srep03930.
[187] D.Y. Lee, D.V. Shinde, S.J. Yoon, K.N. Cho, W. Lee, N.K. Shrestha, S.-H. Han, Cu-based metal–organic frameworks for photovoltaic application, J. Phys. Chem. C. 118 (2014) 16328–16334. doi:10.1021/jp4079663.
[188] R. Kaur, K.-H. Kim, A. K. Paul, A. Deep, Recent advances in the photovoltaic applications of coordination polymers and metal organic frameworks, J. Mater. Chem. A. 4 (2016) 3991–4002. doi:10.1039/C5TA09668E.
[189] R. Huo, Q. Ma, J.J. Wu, K. Chin-Nuke, Y. Jing, J. Chen, M.E. Miyar, S.C. Davis, J. Li, Noninvasive electromagnetic fields on keratinocyte growth and migration, J. Surg. Res. 162 (2010) 299–307. doi:10.1016/j.jss.2009.02.016.
[190] B. Farboud, R. Nuccitelli, I.R. Schwab, R.R. Isseroff, DC electric fields induce rapid directional migration in cultured human corneal epithelial cells, Exp. Eye Res. 70 (2000) 667–673. doi:10.1006/exer.2000.0830.
[191] B. Song, M. Zhao, J. V. Forrester, C.D. McCaig, Electrical cues regulate the orientation and frequency of cell division and the rate of wound healing in vivo, Proc. Natl. Acad. Sci. 99 (2002) 13577–13582. doi:10.1073/pnas.202235299.
[192] P.E. Houghton, K.E. Campbell, C.H. Fraser, C. Harris, D.H. Keast, P.J. Potter, K.C. Hayes, M.G. Woodbury, Electrical stimulation therapy increases rate of healing of pressure ulcers in community-dwelling people with spinal cord injury, Arch. Phys. Med. Rehabil. 91 (2010) 669–678. doi:10.1016/j.apmr.2009.12.026.
[193] P. Ferroni, M. Roselli, F. Guadagni, F. Martini, S. Mariotti, E. Marchitelli, C. Cipriani, Biological effects of a software-controlled voltage pulse generator (PhyBack PBK-2C) on the release of vascular endothelial growth factor (VEGF), Vivo Athens Greece. 19 (2005) 949–958.
[194] M. Bayat, Z. Asgari-Moghadam, M. Maroufi, F.-S. Rezaie, M. Bayat, M. Rakhshan, Experimental wound healing using microamperage electrical stimulation in rabbits, J. Rehabil. Res. Dev. 43 (2006) 219–226.

[195] A. Jerčinović, M. Hinsenkamp, B. Scarceriaux, F. Willaert, C. de Graef, M. Heenen, D. Goldshmidt, Effects of direct constant current (DC) on keratinocytes in vitro, Bioelectrochem. Bioenerg. 39 (1996) 209–214. doi:10.1016/0302-4598(95)01900-6.
[196] E. Emmerson, Efficient healing takes some nerve: electrical stimulation enhances innervation in cutaneous human wounds, J. Invest. Dermatol. 137 (2017) 543–545. doi:10.1016/j.jid.2016.10.018.
[197] A. Sebastian, S.W. Volk, P. Halai, J. Colthurst, R. Paus, A. Bayat, Enhanced neurogenic biomarker expression and reinnervation in human acute skin wounds treated by electrical stimulation, J. Invest. Dermatol. 137 (2017) 737–747. doi:10.1016/j.jid.2016.09.038.
[198] C.-S. Huang, Y.-H. Sun, Y.-T. Wang, Y.-H. Pan, S.-F. Wang, Y.-F. Tsai, Asymmetrical responses of skin blood flow in ischemic hindlimbs to electrical stimulation of the unilateral forelimb, Microvasc. Res. 113 (2017) 71–77. doi:10.1016/j.mvr.2017.05.008.
[199] M.T. Ehrensberger, M.E. Tobias, S.R. Nodzo, L.A. Hansen, N.R. Luke-Marshall, R.F. Cole, L.M. Wild, A.A. Campagnari, Cathodic voltage-controlled electrical stimulation of titanium implants as treatment for methicillin-resistant Staphylococcus aureus periprosthetic infections, Biomaterials. 41 (2015) 97–105. doi:10.1016/j.biomaterials.2014.11.013.
[200] M.R. Asadi, G. Torkaman, M. Hedayati, M.R. Mohajeri-Tehrani, M. Ahmadi, R.F. Gohardani, Angiogenic effects of low-intensity cathodal direct current on ischemic diabetic foot ulcers: A randomized controlled trial, Diabetes Res. Clin. Pract. 127 (2017) 147–155. doi:10.1016/j.diabres.2017.03.012.
[201] A.C. Mendonça, C.H. Barbieri, N. Mazzer, Directly applied low intensity direct electric current enhances peripheral nerve regeneration in rats, J. Neurosci. Methods. 129 (2003) 183–190.
[202] D. Becker, D.S. Gary, E.S. Rosenzweig, W.M. Grill, J.W. McDonald, Functional electrical stimulation helps replenish progenitor cells in the injured spinal cord of adult rats, Exp. Neurol. 222 (2010) 211–218. doi:10.1016/j.expneurol.2009.12.029.
[203] C.T. Brighton, W. Wang, R. Seldes, G. Zhang, S.R. Pollack, Signal transduction in electrically stimulated bone cells, J. Bone Joint Surg. Am. 83–A (2001) 1514–1523.
[204] I.S. Kim, J.K. Song, Y.M. Song, T.H. Cho, T.H. Lee, S.S. Lim, S.J. Kim, S.J. Hwang, Novel effect of biphasic electric current on in vitro osteogenesis and cytokine production in human mesenchymal stromal cells, Tissue Eng. Part A. 15 (2009) 2411–2422. doi:10.1089/ten.tea.2008.0554.
[205] G. Thamsborg, A. Florescu, P. Oturai, E. Fallentin, K. Tritsaris, S. Dissing, Treatment of knee osteoarthritis with pulsed electromagnetic fields: a randomized, double-blind, placebo-controlled study, Osteoarthritis Cartilage. 13 (2005) 575–581. doi:10.1016/j.joca.2005.02.012.
[206] J.A. Spadaro, R.O. Becker, Function of implanted cathodes in electrode-induced bone growth, Med. Biol. Eng. Comput. 17 (1979) 769–775. doi:10.1007/BF02441560.
[207] J.M. Toth, H.B. Seim, J.D. Schwardt, W.B. Humphrey, J.A. Wallskog, A.S. Turner, Direct current electrical stimulation increases the fusion rate of spinal fusion cages, Spine. 25 (2000) 2580–2587.
[208] R. Babygirija, M. Sood, P. Kannampalli, J.N. Sengupta, A. Miranda, Percutaneous electrical nerve field stimulation modulates central pain pathways and attenuates post-inflammatory visceral and somatic hyperalgesia in rats, Neuroscience. 356 (2017) 11–21. doi:10.1016/j.neuroscience.2017.05.012.
[209] S.A. Mahure, A.S. Rokito, Y.W. Kwon, Transcutaneous electrical nerve stimulation for postoperative pain relief after arthroscopic rotator cuff repair: a prospective double-blinded randomized trial, J. Shoulder Elbow Surg. 26 (2017) 1508–1513. doi:10.1016/j.jse.2017.05.030.
[210] H. Xu, J.M. Holzwarth, Y. Yan, P. Xu, H. Zheng, Y. Yin, S. Li, P.X. Ma, Conductive PPY/PDLLA conduit for peripheral nerve regeneration, Biomaterials. 35 (2014) 225–235. doi:10.1016/j.biomaterials.2013.10.002.
[211] R. Mondragon-Lozano, C. Ríos, E. Roldan-Valadez, G.J. Cruz, M.G. Olayo, R. Olayo, H. Salgado-Ceballos, J. Morales, M. Mendez-Armenta, L. Alvarez-Mejia, O. Fabela, A. Morales-

Guadarrama, S. Sánchez-Torres, A. Diaz-Ruiz, Delayed injection of polypyrrole doped with iodine particle suspension after spinal cord injury in rats improves functional recovery and decreased tissue damage evaluated by 3.0 Tesla in vivo magnetic resonance imaging, Spine J. 17 (2017) 562–573. doi:10.1016/j.spinee.2016.02.012.

[212] M. Dodel, N. Hemmati Nejad, S.H. Bahrami, M. Soleimani, L. Mohammadi Amirabad, H. Hanaee-Ahvaz, A. Atashi, Electrical stimulation of somatic human stem cells mediated by composite containing conductive nanofibers for ligament regeneration, Biol. J. Int. Assoc. Biol. Stand. 46 (2017) 99–107. doi:10.1016/j.biologicals.2017.01.007.

[213] A.L.P.S. Bailey, A.M. Pisanelli, K.C. Persaud, Development of conducting polymer sensor arrays for wound monitoring, Sens. Actuators B Chem. 131 (2008) 5–9. doi:10.1016/j.snb.2007.12.035.

[214] B. Bideau, J. Bras, S. Saini, C. Daneault, E. Loranger, Mechanical and antibacterial properties of a nanocellulose-polypyrrole multilayer composite, Mater. Sci. Eng. C Mater. Biol. Appl. 69 (2016) 977–984. doi:10.1016/j.msec.2016.08.005.

[215] N.A. Chowdhury, A.M. Al-Jumaily, Regenerated cellulose/polypyrrole/silver nanoparticles/ionic liquid composite films for potential wound healing applications, Wound Med. 14 (2016) 16–18. doi:10.1016/j.wndm.2016.07.001.

[216] A. Varesano, A. Aluigi, L. Florio, R. Fabris, Multifunctional cotton fabrics, Synth. Met. 159 (2009) 1082–1089. doi:10.1016/j.synthmet.2009.01.036.

[217] R. Kumar, M. Oves, T. Almeelbi, N.H. Al-Makishah, M.A. Barakat, Hybrid chitosan/polyaniline-polypyrrole biomaterial for enhanced adsorption and antimicrobial activity, J. Colloid Interface Sci. 490 (2017) 488–496. doi:10.1016/j.jcis.2016.11.082.

[218] N. Maráková, P. Humpolíček, V. Kašpárková, Z. Capáková, L. Martinková, P. Bober, M. Trchová, J. Stejskal, Antimicrobial activity and cytotoxicity of cotton fabric coated with conducting polymers, polyaniline or polypyrrole, and with deposited silver nanoparticles, Appl. Surf. Sci. 396 (2017) 169–176. doi:10.1016/j.apsusc.2016.11.024.

[219] Y. Wang, M. Rouabhia, Z. Zhang, Pulsed electrical stimulation benefits wound healing by activating skin fibroblasts through the TGFβ1/ERK/NF-κB axis, Biochim. Biophys. Acta. 1860 (2016) 1551–1559. doi:10.1016/j.bbagen.2016.03.023.

[220] G. Shi, M. Rouabhia, Z. Wang, L.H. Dao, Z. Zhang, A novel electrically conductive and biodegradable composite made of polypyrrole nanoparticles and polylactide, Biomaterials. 25 (2004) 2477–2488.

[221] S.I. Jeong, I.D. Jun, M.J. Choi, Y.C. Nho, Y.M. Lee, H. Shin, Development of electroactive and elastic nanofibers that contain polyaniline and poly(L-lactide-co-epsilon-caprolactone) for the control of cell adhesion, Macromol. Biosci. 8 (2008) 627–637. doi:10.1002/mabi.200800005.

[222] G. Shi, M. Rouabhia, S. Meng, Z. Zhang, Electrical stimulation enhances viability of human cutaneous fibroblasts on conductive biodegradable substrates, J. Biomed. Mater. Res. A. 84 (2008) 1026–1037. doi:10.1002/jbm.a.31337.

[223] G. Shi, Z. Zhang, M. Rouabhia, The regulation of cell functions electrically using biodegradable polypyrrole–polylactide conductors, Biomaterials. 29 (2008) 3792–3798. doi:10.1016/j.biomaterials.2008.06.010.

[224] Y. Li, X. Li, R. Zhao, C. Wang, F. Qiu, B. Sun, H. Ji, J. Qiu, C. Wang, Enhanced adhesion and proliferation of human umbilical vein endothelial cells on conductive PANI-PCL fiber scaffold by electrical stimulation, Mater. Sci. Eng. C. 72 (2017) 106–112. doi:10.1016/j.msec.2016.11.052.

[225] N. Gomez, C.E. Schmidt, Nerve growth factor-immobilized polypyrrole: bioactive electrically conducting polymer for enhanced neurite extension, J. Biomed. Mater. Res. A. 81 (2007) 135–149. doi:10.1002/jbm.a.31047.

[226] J.Y. Lee, C.A. Bashur, A.S. Goldstein, C.E. Schmidt, Polypyrrole-coated electrospun PLGA nanofibers for neural tissue applications, Biomaterials. 30 (2009) 4325–4335. doi:10.1016/j.biomaterials.2009.04.042.

[227] L. Ghasemi-Mobarakeh, M.P. Prabhakaran, M. Morshed, M.H. Nasr-Esfahani, S. Ramakrishna, Electrical stimulation of nerve cells Using conductive nanofibrous scaffolds for nerve tissue engineering, Tissue Eng. Part A. 15 (2009) 3605–3619. doi:10.1089/ten.tea.2008.0689.
[228] P.M. George, T.M. Bliss, T. Hua, A. Lee, B. Oh, A. Levinson, S. Mehta, G. Sun, G.K. Steinberg, Electrical preconditioning of stem cells with a conductive polymer scaffold enhances stroke recovery, Biomaterials. 142 (2017) 31–40. doi:10.1016/j.biomaterials.2017.07.020.
[229] W.-W. Hu, Y.-T. Hsu, Y.-C. Cheng, C. Li, R.-C. Ruaan, C.-C. Chien, C.-A. Chung, C.-W. Tsao, Electrical stimulation to promote osteogenesis using conductive polypyrrole films, Mater. Sci. Eng. C Mater. Biol. Appl. 37 (2014) 28–36. doi:10.1016/j.msec.2013.12.019.
[230] J. Zhang, M. Li, E.-T. Kang, K.G. Neoh, Electrical stimulation of adipose-derived mesenchymal stem cells in conductive scaffolds and the roles of voltage-gated ion channels, Acta Biomater. 32 (2016) 46–56. doi:10.1016/j.actbio.2015.12.024.
[231] Y. Min, Y. Liu, Y. Poojari, J.-C. Wu, B.E. Hildreth III, T.J. Rosol, A.J. Epstein, Self-doped polyaniline-based interdigitated electrodes for electrical stimulation of osteoblast cell lines, Synth. Met. 198 (2014) 308–313. doi:10.1016/j.synthmet.2014.10.035.
[232] E. Wang, M. Zhao, Regulation of tissue repair and regeneration by electric fields, Chin. J. Traumatol. Zhonghua Chuang Shang Za Zhi. 13 (2010) 55–61.
[233] M. Zhao, Electrical fields in wound healing-An overriding signal that directs cell migration, Semin. Cell Dev. Biol. 20 (2009) 674–682. doi:10.1016/j.semcdb.2008.12.009.
[234] G.G. Genchi, E. Sinibaldi, L. Ceseracciu, M. Labardi, A. Marino, S. Marras, G. De Simoni, V. Mattoli, G. Ciofani, Ultrasound-activated piezoelectric P(VDF-TrFE)/boron nitride nanotube composite films promote differentiation of human SaOS-2 osteoblast-like cells, Nanomedicine Nanotechnol. Biol. Med. (2017) 1–12. doi:10.1016/j.nano.2017.05.006.
[235] S. Danti, G. Ciofani, S. Moscato, D. D'Alessandro, E. Ciabatti, C. Nesti, R. Brescia, G. Bertoni, A. Pietrabissa, M. Lisanti, M. Petrini, V. Mattoli, S. Berrettini, Boron nitride nanotubes and primary human osteoblasts: *in vitro* compatibility and biological interactions under low frequency ultrasound stimulation, Nanotechnology. 24 (2013) 465102. doi:10.1088/0957-4484/24/46/465102.
[236] L. Ricotti, T. Fujie, H. Vazão, G. Ciofani, R. Marotta, R. Brescia, C. Filippeschi, I. Corradini, M. Matteoli, V. Mattoli, L. Ferreira, A. Menciassi, Boron nitride nanotube-mediated stimulation of cell co-culture on micro-engineered hydrogels, PLoS ONE. 8 (2013). doi:10.1371/journal.pone.0071707.
[237] G. Ciofani, S. Danti, D. D'Alessandro, L. Ricotti, S. Moscato, G. Bertoni, A. Falqui, S. Berrettini, M. Petrini, V. Mattoli, A. Menciassi, Enhancement of neurite outgrowth in neuronal-like cells following boron nitride nanotube-mediated stimulation, ACS Nano. 4 (2010) 6267–6277. doi:10.1021/nn101985a.
[238] A. Marino, G.G. Genchi, V. Mattoli, G. Ciofani, Piezoelectric nanotransducers: The future of neural stimulation, Nano Today. 14 (2016) 9–12. doi:10.1016/j.nantod.2016.12.005.
[239] L. Ricotti, R.P. Das Neves, G. Ciofani, C. Canale, S. Nitti, V. Mattoli, B. Mazzolai, L. Ferreira, A. Menciassi, Boron nitride nanotube-mediated stimulation modulates F/G-actin ratio and mechanical properties of human dermal fibroblasts, J. Nanoparticle Res. 16 (2014). doi:10.1007/s11051-014-2247-z.
[240] E.G. Fine, R.F. Valentini, R. Bellamkonda, P. Aebischer, Improved nerve regeneration through piezoelectric vinylidenefluoride-trifluoroethylene copolymer guidance channels, Biomaterials. 12 (1991) 775–780. doi:10.1016/0142-9612(91)90029-A.
[241] P. Aebischer, R.F. Valentini, P. Dario, C. Domenici, V. Guénard, S.R. Winn, P.M. Galletti, Piezoelectric nerve guidance channels enhance peripheral nerve regeneration., ASAIO Trans. 33 (1987) 456–8.
[242] P. Aebischer, R.F. Valentini, P. Dario, C. Domenici, P.M. Galletti, Piezoelectric guidance channels enhance regeneration in the mouse sciatic nerve after axotomy, Brain Res. 436 (1987) 165–168. doi:10.1016/0006-8993(87)91570-8.

[243] T. Gordon, O.A.R. Sulaiman, A. Ladak, Chapter 24 Electrical Stimulation for Improving Nerve Regeneration: Where do we Stand?, 1st ed., Elsevier Inc., 2009. doi:10.1016/S0074-7742(09)87024-4.
[244] M.P. Willand, M.-A. Nguyen, G.H. Borschel, T. Gordon, Electrical Stimulation to Promote Peripheral Nerve Regeneration., Neurorehabil. Neural Repair. (2015) 1545968315604399-. doi:10.1177/1545968315604399.
[245] L. Vannozzi, C. Filippeschi, S. Sartini, V. Piazza, P. Pingue, C. La Motta, A. Menciassi, Nanostructured ultra-thin patches for ultrasound- modulated delivery of anti-restenotic drug, (2016) 69–92.
[246] G. Ciofani, A. Menciassi, eds., Piezoelectric Nanomaterials for Biomedical Applications, Springer Berlin Heidelberg, Berlin, Heidelberg, 2012. doi:10.1007/978-3-642-28044-3.
[247] A. Marino, S. Arai, Y. Hou, E. Sinibaldi, M. Pellegrino, Y. Chang, B. Mazzolai, V. Mattoli, M. Suzuki, G. Ciofani, Piezoelectric Nanoparticle-Assisted Wireless Neuronal Stimulation, ACS Nano. 9 (2015) 7678–7689. doi:10.1021/acsnano.5b03162.
[248] N. Royo-Gascon, M. Wininger, J.I. Scheinbeim, B.L. Firestein, W. Craelius, Piezoelectric substrates promote neurite growth in rat spinal cord neurons, Ann. Biomed. Eng. 41 (2013) 112–122. doi:10.1007/s10439-012-0628-y.
[249] M. Hoop, X.-Z. Chen, A. Ferrari, F. Mushtaq, G. Ghazaryan, T. Tervoort, D. Poulikakos, B. Nelson, S. Pan?, Ultrasound-mediated piezoelectric differentiation of neuron-like PC12 cells on PVDF membranes, Sci. Rep. 7 (2017) 4028. doi:10.1038/s41598-017-03992-3.
[250] Y.S. Lee, G. Collins, T. Livingston Arinzeh, Neurite extension of primary neurons on electrospun piezoelectric scaffolds, Acta Biomater. 7 (2011) 3877–3886. doi:10.1016/j.actbio.2011.07.013.
[251] C. Mota, M. Labardi, L. Trombi, L. Astolfi, M. D'Acunto, D. Puppi, G. Gallone, F. Chiellini, S. Berrettini, L. Bruschini, S. Danti, Design, fabrication and characterization of composite piezoelectric ultrafine fibers for cochlear stimulation, Mater. Des. 122 (2017) 206–219. doi:10.1016/j.matdes.2017.03.013.
[252] L.C. Lins, F. Wianny, S. Livi, C. Dehay, J. Duchet-Rumeau, J.F. G??rard, Effect of polyvinylidene fluoride electrospun fiber orientation on neural stem cell differentiation, J. Biomed. Mater. Res. - Part B Appl. Biomater. (2016) 1–18. doi:10.1002/jbm.b.33778.
[253] Y.S. Lee, S. Wu, T.L. Arinzeh, M.B. Bunge, Enhanced noradrenergic axon regeneration into schwann cell-filled PVDF-TrFE conduits after complete spinal cord transection, Biotechnol. Bioeng. 114 (2017) 444–456. doi:10.1002/bit.26088.
[254] Y.-S. Lee, T.L. Arinzeh, The Influence of Piezoelectric Scaffolds on Neural Differentiation of Human Neural Stem/Progenitor Cells, Tissue Eng. Part A. 18 (2012) 2063–2072. doi:10.1089/ten.TEA.2011.0540.
[255] G.G. Genchi, L. Ceseracciu, A. Marino, M. Labardi, S. Marras, F. Pignatelli, L. Bruschini, V. Mattoli, G. Ciofani, P(VDF-TrFE)/BaTiO3 Nanoparticle Composite Films Mediate Piezoelectric Stimulation and Promote Differentiation of SH-SY5Y Neuroblastoma Cells, Adv. Healthc. Mater. 5 (2016) 1808–1820. doi:10.1002/adhm.201600245.
[256] A.S. Motamedi, H. Mirzadeh, F. Hajiesmaeilbaigi, S. Bagheri-Khoulenjani, M.A. Shokrgozar, Piezoelectric electrospun nanocomposite comprising Au NPs/PVDF for nerve tissue engineering, J. Biomed. Mater. Res. - Part A. (2017) 1984–1993. doi:10.1002/jbm.a.36050.
[257] S. Danti, G. Ciofani, G. Pertici, S. Moscato, D. D'Alessandro, E. Ciabatti, F. Chiellini, M. D'Acunto, V. Mattoli, S. Berrettini, Boron nitride nanotube-functionalised myoblast/microfibre constructs: a nanotech-assisted tissue-engineered platform for muscle stimulation, J. Tissue Eng. Regen. Med. 9 (2015) 847–851. doi:10.1002/term.1878.
[258] B.M. Gaub, D.J. M??ller, Mechanical Stimulation of Piezo1 Receptors Depends on Extracellular Matrix Proteins and Directionality of Force, Nano Lett. 17 (2017) 2064–2072. doi:10.1021/acs.nanolett.7b00177.
[259] E. Piddini, Epithelial Homeostasis: A Piezo of the Puzzle, Curr. Biol. 27 (2017) R232–R234. doi:10.1016/j.cub.2017.02.002.

[260] H.F. Guo, Z.S. Li, S.W. Dong, W.J. Chen, L. Deng, Y.F. Wang, D.J. Ying, Piezoelectric PU/PVDF electrospun scaffolds for wound healing applications, Colloids Surf. B Biointerfaces. 96 (2012) 29–36. doi:10.1016/j.colsurfb.2012.03.014.
[261] S.H. Bhang, W.S. Jang, J. Han, J.K. Yoon, W.G. La, E. Lee, Y.S. Kim, J.Y. Shin, T.J. Lee, H.K. Baik, B.S. Kim, Zinc Oxide Nanorod-Based Piezoelectric Dermal Patch for Wound Healing, Adv. Funct. Mater. 27 (2017). doi:10.1002/adfm.201603497.
[262] G. Tan, S. Wang, Y. Zhu, L. Zhou, P. Yu, X. Wang, T. He, J. Chen, C. Mao, C. Ning, L. Industry, S. Life, U. States, Surface-Selective Preferential Production of Reactive Oxygen Species on Piezoelectric Ceramics for Bacterial Killing., 8 (2016) 24306–24309. doi:10.1021/acsami.6b07440.
[263] R. Balint, N.J. Cassidy, S.H. Cartmell, Electrical Stimulation: A Novel Tool for Tissue Engineering, Tissue Eng. Part B-Rev. 19 (2013) 48–57. doi:10.1089/ten.TEB.2012.0183.
[264] X. Zhang, C. Zhang, Y. Lin, P. Hu, Y. Shen, K. Wang, S. Meng, Y. Chai, X. Dai, X. Liu, Y. Liu, X. Mo, C. Cao, S. Li, X. Deng, L. Chen, Nanocomposite membranes enhance bone regeneration through restoring physiological electric microenvironment, ACS Nano. 10 (2016) 7279–7286. doi:10.1021/acsnano.6b02247.
[265] H. Shokrollahi, F. Salimi, A. Doostmohammadi, The fabrication and characterization of barium titanate/akermanite nano-bio-ceramic with a suitable piezoelectric coefficient for bone defect recovery, J. Mech. Behav. Biomed. Mater. 74 (2017) 365–370. doi:10.1016/j.jmbbm.2017.06.024.
[266] T.G.M. Bonadio, V.F. Freitas, T.T. Tominaga, R.Y. Miyahara, J.M. Rosso, L.F. Cótica, M.L. Baesso, W.R. Weinand, I.A. Santos, R. Guo, A.S. Bhalla, Polyvinylidene fluoride/hydroxyapatite/β-tricalcium phosphate multifunctional biocomposite: Potentialities for bone tissue engineering, Curr. Appl. Phys. 17 (2017) 767–773. doi:10.1016/j.cap.2017.02.022.
[267] C. Ribeiro, D.M. Correia, I. Rodrigues, L. Guardão, S. Guimarães, R. Soares, S. Lanceros-Méndez, In-vivo demonstration of the suitability of piezoelectric stimuli for bone reparation, Mater. Lett. (2017). doi:10.1016/j.matlet.2017.07.099.
[268] W. Chen, Z. Yu, J. Pang, P. Yu, G. Tan, C. Ning, Fabrication of biocompatible potassium sodium niobate piezoelectric ceramic as an electroactive implant, Materials. 10 (2017) 18–21. doi:10.3390/ma10040345.
[269] B. Liu, L. Chen, C. Shao, F. Zhang, K. Zhou, J. Cao, D. Zhang, Improved osteoblasts growth on osteomimetic hydroxyapatite/BaTiO3 composites with aligned lamellar porous structure, Mater. Sci. Eng. C. 61 (2016) 8–14. doi:10.1016/j.msec.2015.12.009.
[270] M. Nakamura, A study on tissue regeneration of the functionalized bioceramics, Nippon Seramikkusu Kyokai Gakujutsu RonbunshiJournal Ceram. Soc. Jpn. 122 (2014) 755–761. doi:10.2109/jcersj2.122.755.
[271] F.R. Baxter, C.R. Bowen, I.G. Turner, A.C.E. Dent, Electrically active bioceramics: A review of interfacial responses, Ann. Biomed. Eng. 38 (2010) 2079–2092. doi:10.1007/s10439-010-9977-6.
[272] Y. Qu, D. Ao, P. Wang, Y. Wang, X. Kong, Y. Man, Chitosan/nano-hydroxyapatite composite electret membranes enhance cell proliferation and osteoblastic expression in vitro, J. Bioact. Compat. Polym. 29 (2014) 3–14. doi:10.1177/0883911513513094.
[273] M. Nakamura, A. Nagai, T. Hentunen, J. Salonen, Y. Sekijima, T. Okura, K. Hashimoto, Y. Toda, H. Monma, K. Yamashita, Surface electric fields increase osteoblast adhesion through improved wettability on hydroxyapatite electret, ACS Appl. Mater. Interfaces. 1 (2009) 2181–2189. doi:10.1021/am900341v.
[274] M. Nakamura, T. Soya, R. Hiratai, A. Nagai, K. Hashimoto, I. Morita, K. Yamashita, Endothelial cell migration and morphogenesis on silk fibroin scaffolds containing hydroxyapatite electret, J. Biomed. Mater. Res. - Part A. 100 A (2012) 969–977. doi:10.1002/jbm.a.34046.
[275] R. Okabayashi, M. Nakamura, T. Okabayashi, Y. Tanaka, A. Nagai, K. Yamashita, Efficacy of polarized hydroxyapatite and silk fibroin composite dressing gel on epidermal recovery from

full-thickness skin wounds, J. Biomed. Mater. Res. - Part B Appl. Biomater. 90 B (2009) 641–646. doi:10.1002/jbm.b.31329.
[276] Y. Qu, Y. Wang, X. Kong, J. Li, Y. Zuo, Q. Zou, P. Gong, Y. Man, Heat-treated membranes with bioelectricity promote bone regeneration, J. Biomater. Sci. Polym. Ed. 25 (2014) 211–223. doi:10.1080/09205063.2013.849903.
[277] Yanying Wang, Yili Qu, Ping Gong, Ping Wang, Yi Man, Jidong Li, Preparation and in vitro evaluation of chitosan bioelectret membranes for guided bone regeneration, J. Bioact. Compat. Polym. 25 (2010) 622–633. doi:10.1177/0883911510382765.
[278] Y. Wang, R. Shi, P. Gong, J. Li, J. Li, D. Ao, P. Wang, Y. Yang, Y. Man, Y. Qu, Bioelectric effect of a chitosan bioelectret membrane on bone regeneration in rabbit cranial defects, J. Bioact. Compat. Polym. 27 (2012) 122–132. doi:10.1177/0883911512436773.
[279] T. Kizuki, M. Ohgaki, M. Katsura, S. Nakamura, K. Hashimoto, Y. Toda, S. Udagawa, K. Yamashita, Effect of bone-like layer growth from culture medium on adherence of osteoblast-like cells, Biomaterials. 24 (2003) 941–947.
[280] S. Nakamura, T. Kobayashi, M. Nakamura, K. Yamashita, Enhanced in vivo responses of osteoblasts in electrostatically activated zones by hydroxyapatite electrets, J. Mater. Sci. Mater. Med. 20 (2009) 99–103. doi:10.1007/s10856-008-3546-7.
[281] S. Itoh, S. Nakamura, T. Kobayashi, K. Shinomiya, K. Yamashita, S. Itoh, Effect of electrical polarization of hydroxyapatite ceramics on new bone formation, Calcif. Tissue Int. 78 (2006) 133–142. doi:10.1007/s00223-005-0213-6.
[282] R.F. Valentini, T.G. Vargo, J.A. Gardella, P. Aebischer, Electrically charged polymeric substrates enhance nerve fibre outgrowth in vitro, Biomaterials. 13 (1992) 183–190.
[283] R.F. Valentini, A.M. Sabatini, P. Dario, P. Aebischer, Polymer electret guidance channels enhance peripheral nerve regeneration in mice, Brain Res. 480 (1989) 300–304.
[284] D.J. Bryan, J.B. Tang, S.A. Doherty, D.D. Hile, D.J. Trantolo, D.L. Wise, I.C. Summerhayes, Enhanced peripheral nerve regeneration through a poled bioresorbable poly(lactic-co-glycolic acid) guidance channel, J. Neural Eng. 1 (2004) 91. doi:10.1088/1741-2560/1/2/004.
[285] H. Lorach, G. Goetz, R. Smith, X. Lei, Y. Mandel, T. Kamins, K. Mathieson, P. Huie, J. Harris, A. Sher, D. Palanker, Photovoltaic restoration of sight with high visual acuity, Nat. Med. 21 (2015) 476–482. doi:10.1038/nm.3851.
[286] Y. Mandel, G. Goetz, D. Lavinsky, P. Huie, K. Mathieson, L. Wang, T. Kamins, L. Galambos, R. Manivanh, J. Harris, D. Palanker, Cortical responses elicited by photovoltaic subretinal prostheses exhibit similarities to visually evoked potentials, Nat. Commun. 4 (2013) ncomms2980. doi:10.1038/ncomms2980.
[287] L. Wang, K. Mathieson, T.I. Kamins, J.D. Loudin, L. Galambos, G. Goetz, A. Sher, Y. Mandel, P. Huie, D. Lavinsky, J.S. Harris, D. V. Palanker, Photovoltaic retinal prosthesis: implant fabrication and performance, J. Neural Eng. 9 (2012) 046014. doi:10.1088/1741-2560/9/4/046014.
[288] K. Mathieson, J. Loudin, G. Goetz, P. Huie, L. Wang, T.I. Kamins, L. Galambos, R. Smith, J.S. Harris, A. Sher, D. Palanker, Photovoltaic retinal prosthesis with high pixel density, Nat. Photonics. 6 (2012) 391–397. doi:10.1038/nphoton.2012.104.
[289] Y.-S. Hsiao, Y.-H. Liao, H.-L. Chen, P. Chen, F.-C. Chen, Organic photovoltaics and bioelectrodes providing electrical stimulation for PC12 cell differentiation and neurite outgrowth, ACS Appl. Mater. Interfaces. 8 (2016) 9275–9284. doi:10.1021/acsami.6b00916.
[290] G. Torkaman, Electrical stimulation of wound healing: A Review of animal experimental evidence, Adv. Wound Care. 3 (2014) 202–218. doi:10.1089/wound.2012.0409.
[291] S. Ud-Din, A. Bayat, Electrical stimulation and cutaneous wound healing: A review of clinical evidence, Healthcare. 2 (2014) 445–467. doi:10.3390/healthcare2040445.
[292] N. Martino, P. Feyen, M. Porro, C. Bossio, E. Zucchetti, D. Ghezzi, F. Benfenati, G. Lanzani, M.R. Antognazza, Photothermal cellular stimulation in functional bio-polymer interfaces, Sci. Rep. 5 (2015) srep08911. doi:10.1038/srep08911.

[293] J.-L. Wu, F.-C. Chen, M.-K. Chuang, K.-S. Tan, Near-infrared laser-driven polymer photovoltaic devices and their biomedical applications, Energy Environ. Sci. 4 (2011) 3374–3378. doi:10.1039/C1EE01723C.
[294] S.N. Leite, T.A.M. de Andrade, D. dos S. Masson-Meyers, M.N. Leite, C.S. Enwemeka, M.A.C. Frade, Phototherapy promotes healing of cutaneous wounds in undernourished rats, An. Bras. Dermatol. 89 (2014) 899–904. doi:10.1590/abd1806-4841.20143356.
[295] A.L. Whinfield, I. Aitkenhead, The light revival: Does phototherapy promote wound healing? A review, The Foot. 19 (2009) 117–124. doi:10.1016/j.foot.2009.01.004.
[296] G. Jin, M. P. Prabhakaran, D. Kai, M. Kotaki, S. Ramakrishna, Electrospun photosensitive nanofibers: potential for photocurrent therapy in skin regeneration, Photochem. Photobiol. Sci. 12 (2013) 124–134. doi:10.1039/C2PP25070E.
[297] T.J. Rivers, T.W. Hudson, C.E. Schmidt, Synthesis of a novel, biodegradable electrically conducting polymer for biomedical applications, Adv. Funct. Mater. 12 (2002) 33–37. doi:10.1002/1616-3028(20020101)12:1<33::AID-ADFM33>3.0.CO;2-E.
[298] N.K.E. Guimard, J.L. Sessler, C.E. Schmidt, Towards a biocompatible, biodegradable copolymer incorporating electroactive oligothiophene units, Macromolecules. 42 (2009) 502–511. doi:10.1021/ma8019859.
[299] C.A. Thomas, K. Zong, P. Schottland, J.R. Reynolds, Poly(3,4-alkylenedioxypyrrole)s as highly stable aqueous-compatible conducting polymers with biomedical implications, Adv. Mater. 12 (2000) 222–225. doi:10.1002/(SICI)1521-4095(200002)12:3<222::AID-ADMA222>3.0.CO;2-D.
[300] S. Sankoh, M.Y. Vagin, A.N. Sekretaryova, P. Thavarungkul, P. Kanatharana, W.C. Mak, Colloid electrochemistry of conducting polymer: towards potential-induced in-situ drug release, Electrochimica Acta. 228 (2017) 407–412. doi:10.1016/j.electacta.2017.01.028.
[301] S. Szunerits, F. Teodorescu, R. Boukherroub, Electrochemically triggered release of drugs, Eur. Polym. J. 83 (2016) 467–477. doi:10.1016/j.eurpolymj.2016.03.001.
[302] M. Shahid, A.P. Deshpande, C.L. Rao, Electro-mechanical properties of hydrogel composites with micro- and nano-cellulose fillers, Smart Mater. Struct. 24 (2015) 095013. doi:10.1088/0964-1726/24/9/095013.
[303] V. Nguyen, R. Zhu, K. Jenkins, R. Yang, Self-assembly of diphenylalanine peptide with controlled polarization for power generation, Nat. Commun. 7 (2016) ncomms13566. doi:10.1038/ncomms13566.
[304] K.N. Kim, J. Chun, S.A. Chae, C.W. Ahn, I.W. Kim, S.-W. Kim, Z.L. Wang, J.M. Baik, Silk fibroin-based biodegradable piezoelectric composite nanogenerators using lead-free ferroelectric nanoparticles, Nano Energy. 14 (2015) 87–94. doi:10.1016/j.nanoen.2015.01.004.
[305] K. Ryan, J. Beirne, G. Redmond, J.I. Kilpatrick, J. Guyonnet, N. Buchete, A.L. Kholkin, B.J. Rodriguez, Nanoscale Piezoelectric Properties of Self-Assembled Fmoc − FF Peptide Fibrous Networks, (2015). doi:10.1021/acsami.5b01251.
[306] M.H. SHAMOS, L.S. LAVINE, Piezoelectricity as a Fundamental Property of Biological Tissues, Nature. 213 (1967) 267–269. doi:10.1038/213267a0.
[307] D. Denning, J. Guyonnet, B.J. Rodriguez, Applications of piezoresponse force microscopy in materials research: from inorganic ferroelectrics to biopiezoelectrics and beyond, Int. Mater. Rev. 61 (2016) 46–70. doi:10.1179/1743280415Y.0000000013.
[308] X. Guo, Y.Y. Liang, H.Y. Liu, L.L. Cui, J. Jiang, Study on the electrostatic and piezoelectric properties of positive polypropylene electret cyclosporine A patch, J. Phys. Conf. Ser. 418 (2013) 012148. doi:10.1088/1742-6596/418/1/012148.
[309] X. Wang, L. Dong, H. Zhang, R. Yu, C. Pan, Z.L. Wang, Recent progress in electronic skin, Adv. Sci. 2 (2015) 1–21. doi:10.1002/advs.201500169.
[310] J.A. Labastide, M. Baghgar, I. Dujovne, Y. Yang, A.D. Dinsmore, B. G. Sumpter, D. Venkataraman, M.D. Barnes, Polymer nanoparticle superlattices for organic photovoltaic applications, J. Phys. Chem. Lett. 2 (2011) 3085–3091. doi:10.1021/jz2012275.
[311] P.H. Wang, M. Millard, A.G. Brolo, Optimizing plasmonic silicon photovoltaics with Ag and Au nanoparticle mixtures, J. Phys. Chem. C. 118 (2014) 5889–5895. doi:10.1021/jp409351v.

[312] K.R. Catchpole, A. Polman, Plasmonic solar cells, Opt. Express. 16 (2008) 21793–21800. doi:10.1364/OE.16.021793.
[313] I. Hwang, D. Choi, S. Lee, J.H. Seo, K.-H. Kim, I. Yoon, K. Seo, Enhancement of light absorption in photovoltaic devices using textured polydimethylsiloxane stickers, ACS Appl. Mater. Interfaces. 9 (2017) 21276–21282. doi:10.1021/acsami.7b04525.
[314] H.-J. Koo, S. Tai Chang, J. M. Slocik, R. R. Naik, O. D. Velev, Aqueous soft matter based photovoltaic devices, J. Mater. Chem. 21 (2011) 72–79. doi:10.1039/C0JM01820A.
[315] A.G. Kanaras, C. Sönnichsen, H. Liu, A.P. Alivisatos, Controlled Synthesis of Hyperbranched Inorganic Nanocrystals with Rich Three-Dimensional Structures, Nano Lett. 5 (2005) 2164–2167. doi:10.1021/nl0518728.

Figure 1

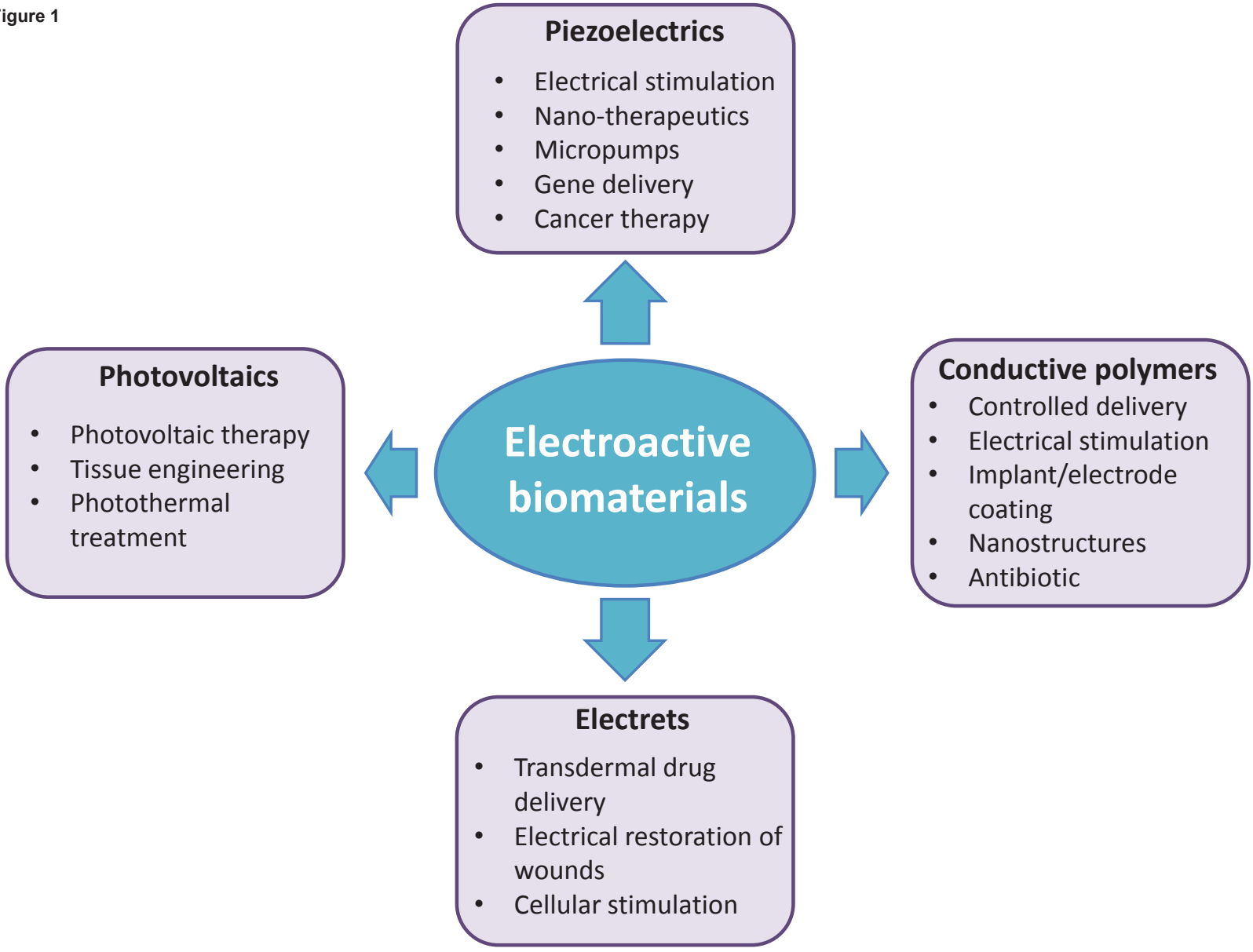

Piezoelectrics
Electrical stimulation
Nano-therapeutics
Micropumps
Gene delivery
Cancer therapy
Photovoltaics
Photovoltaic therapy
Tissue engineering
Photothermal treatment
Electroactive biomaterials
Conductive polymers
Controlled delivery
Electrical stimulation
Implant/electrode coating
Nanostructures
Antibiotic
Electrets
Transdermal drug delivery
Electrical restoration of wounds
Cellular stimulation

Figure 2

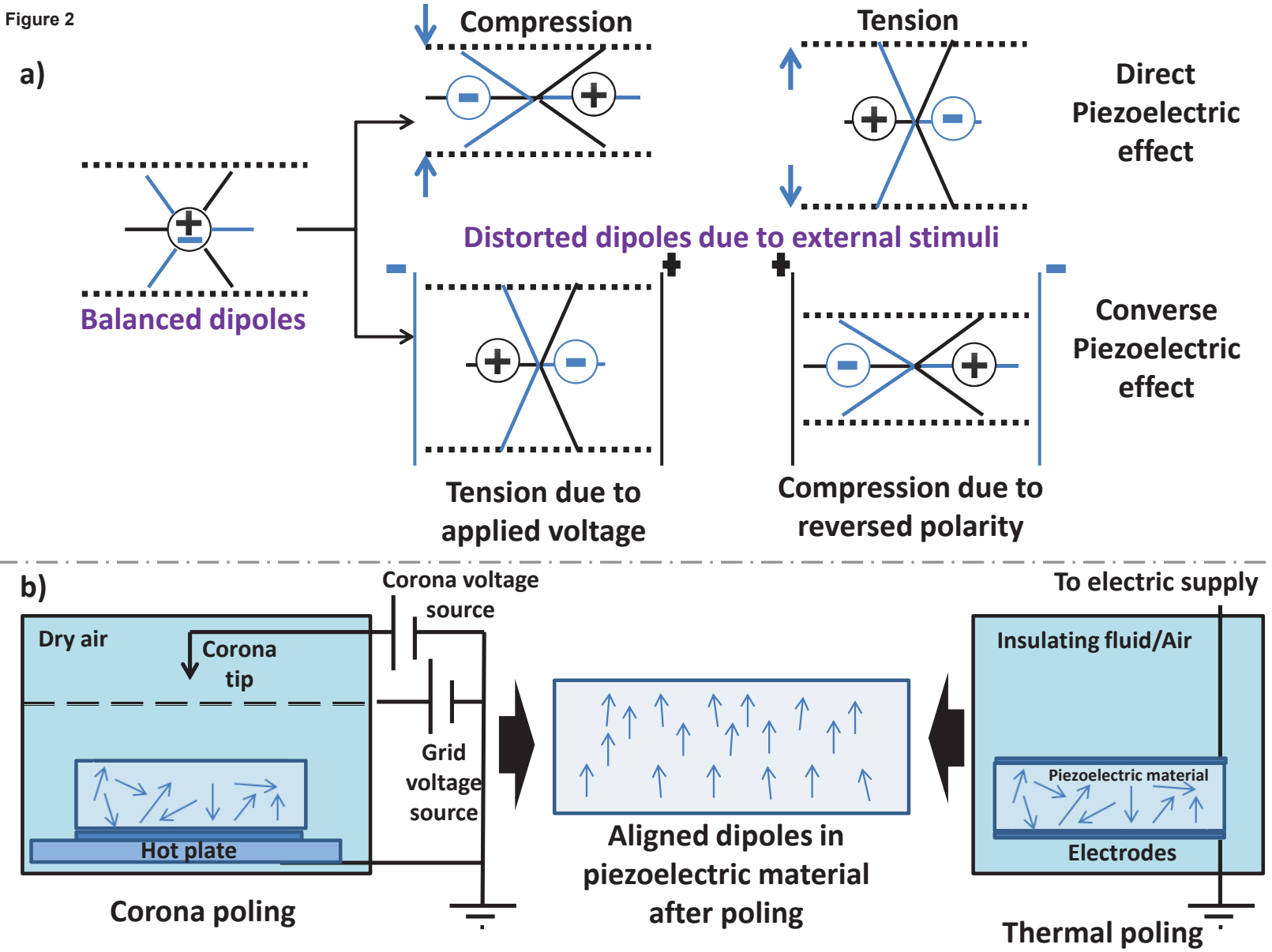

a)
Compression
Tension
Direct Piezoelectric effect
Balanced dipoles
Distorted dipoles due to external stimuli
Converse Piezoelectric effect
Tension due to applied voltage
Compression due to reversed polarity
b)
Corona voltage source
To electric supply
Dry air
Corona tip
Insulating fluid/Air
Grid voltage source
Piezoelectric material
Hot plate
Electrodes
Aligned dipoles in piezoelectric material after poling
Corona poling
Thermal poling

Figure 3

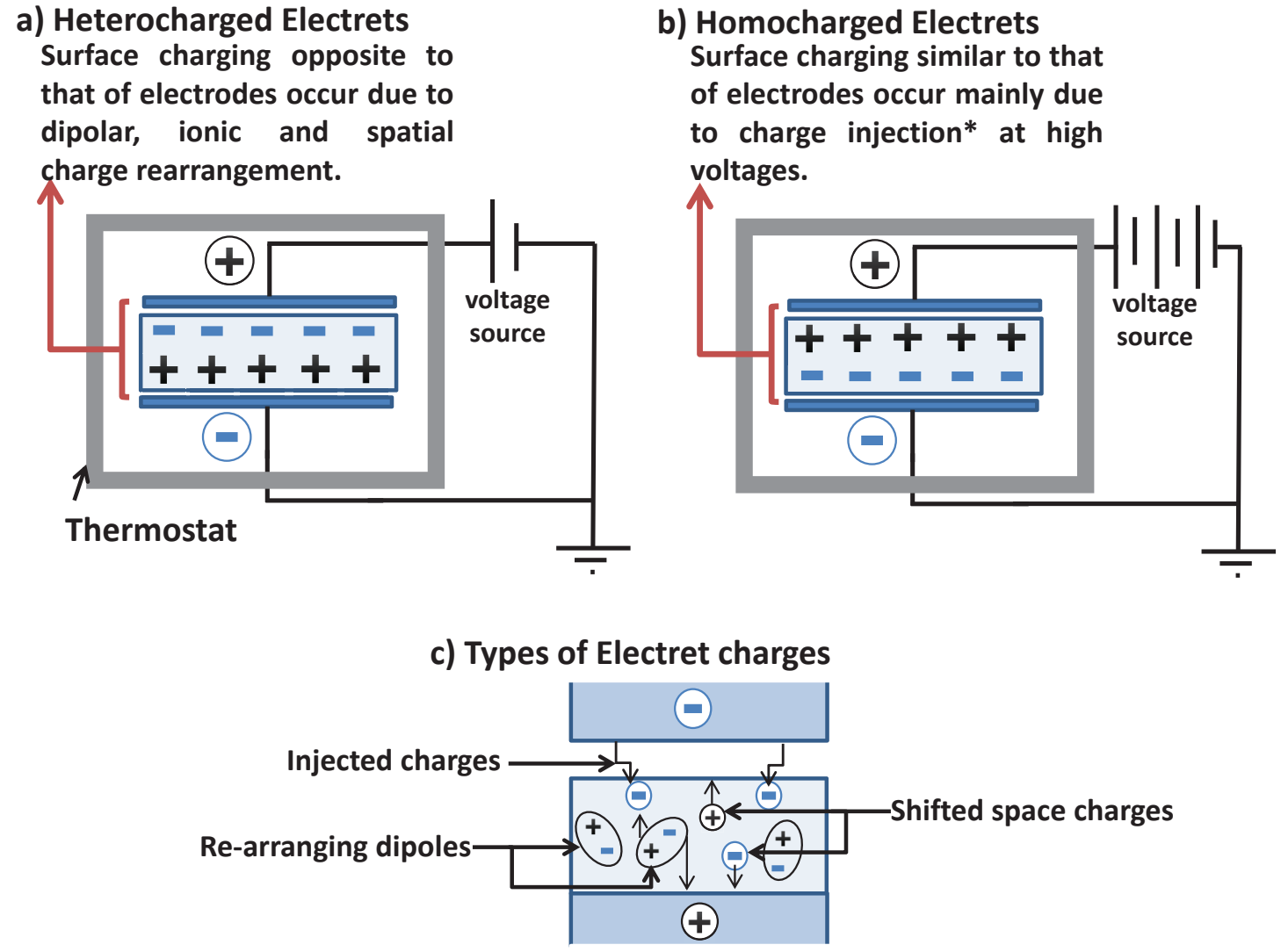

a) Heterocharged Electrets
Surface charging opposite to that of electrodes occur due to dipolar, ionic and spatial charge rearrangement.
voltage source
Thermostat
b) Homocharged Electrets
Surface charging similar to that of electrodes occur mainly due to charge injection* at high voltages.
voltage source
c) Types of Electret charges
Injected charges
Re-arranging dipoles
Shifted space charges

Figure 4

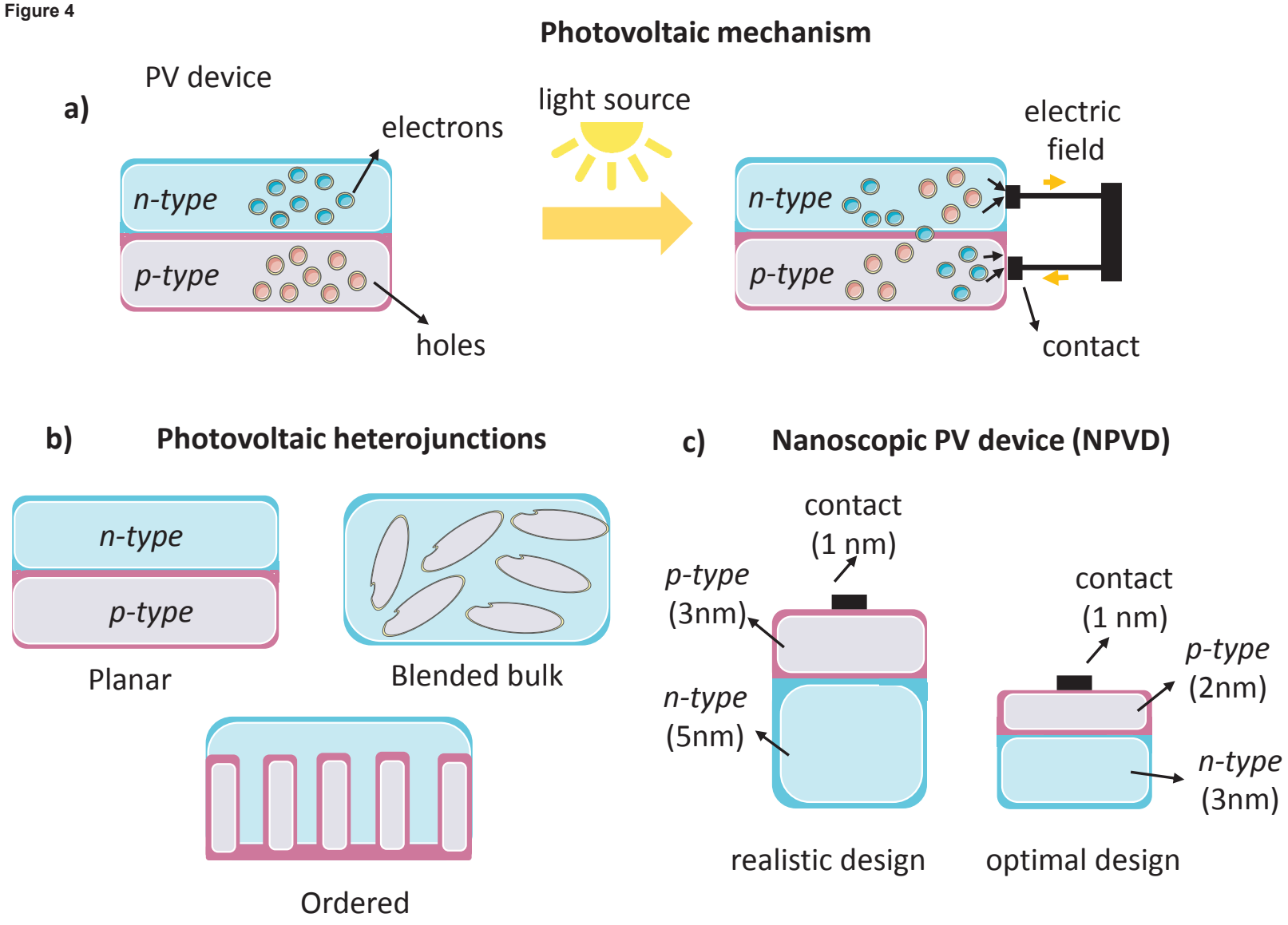

Photovoltaic mechanism
a)
PV device
electrons
n-type
p-type
holes
light source
electric
field
n-type
p-type
contact
b)
Photovoltaic heterojunctions
n-type
p-type
Planar
Blended bulk
Ordered
c)
Nanoscopic PV device (NPVD)
contact
(1 nm)
p-type
(3nm)
n-type
(5nm)
realistic design
contact
(1 nm)
p-type
(2nm)
n-type
(3nm)
optimal design

Figure 5

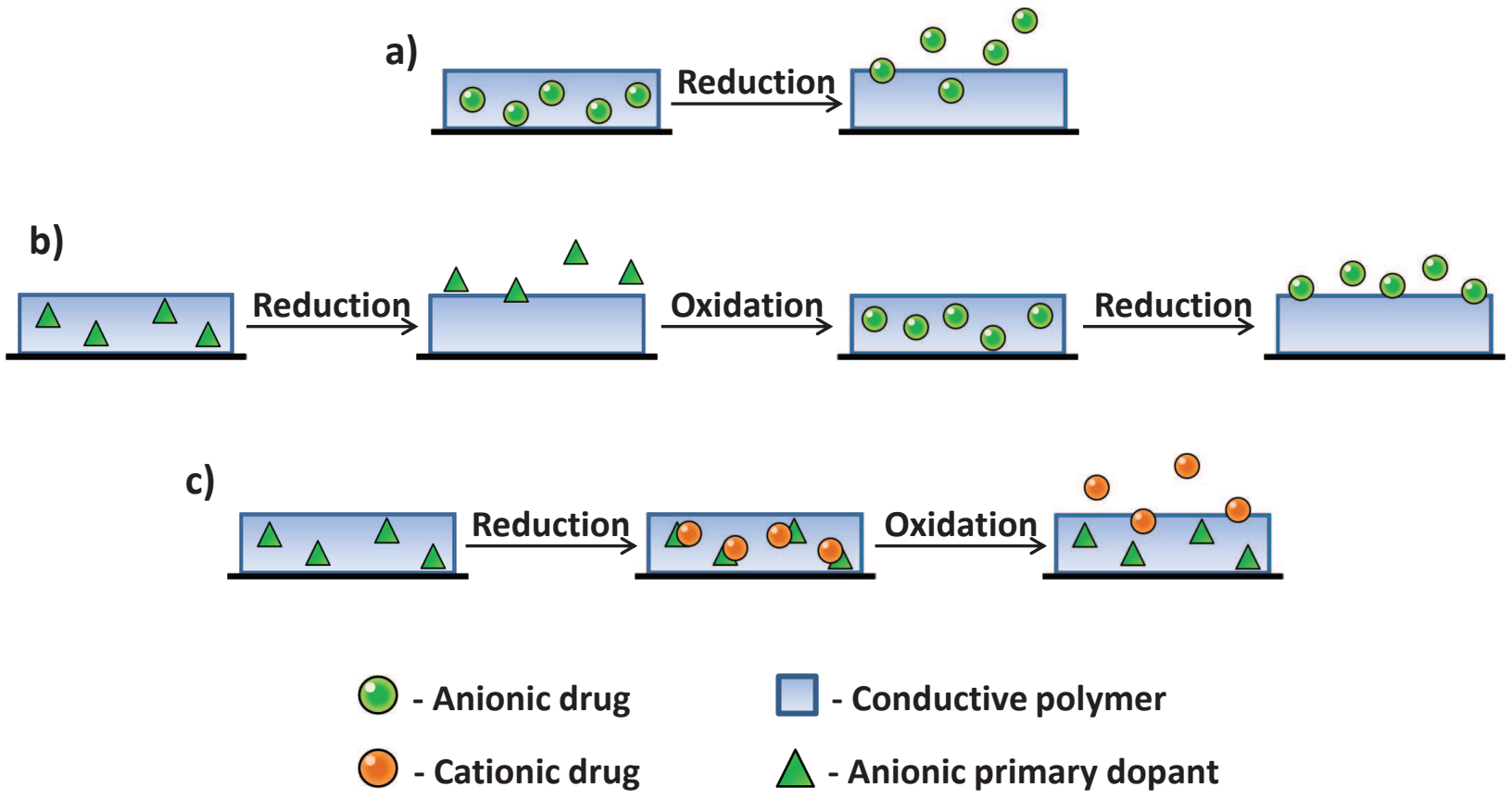

a)
Reduction
b)
Reduction
Oxidation
Reduction
c)
Reduction
Oxidation
- Anionic drug
- Cationic drug
- Conductive polymer
- Anionic primary dopant

Figure 6

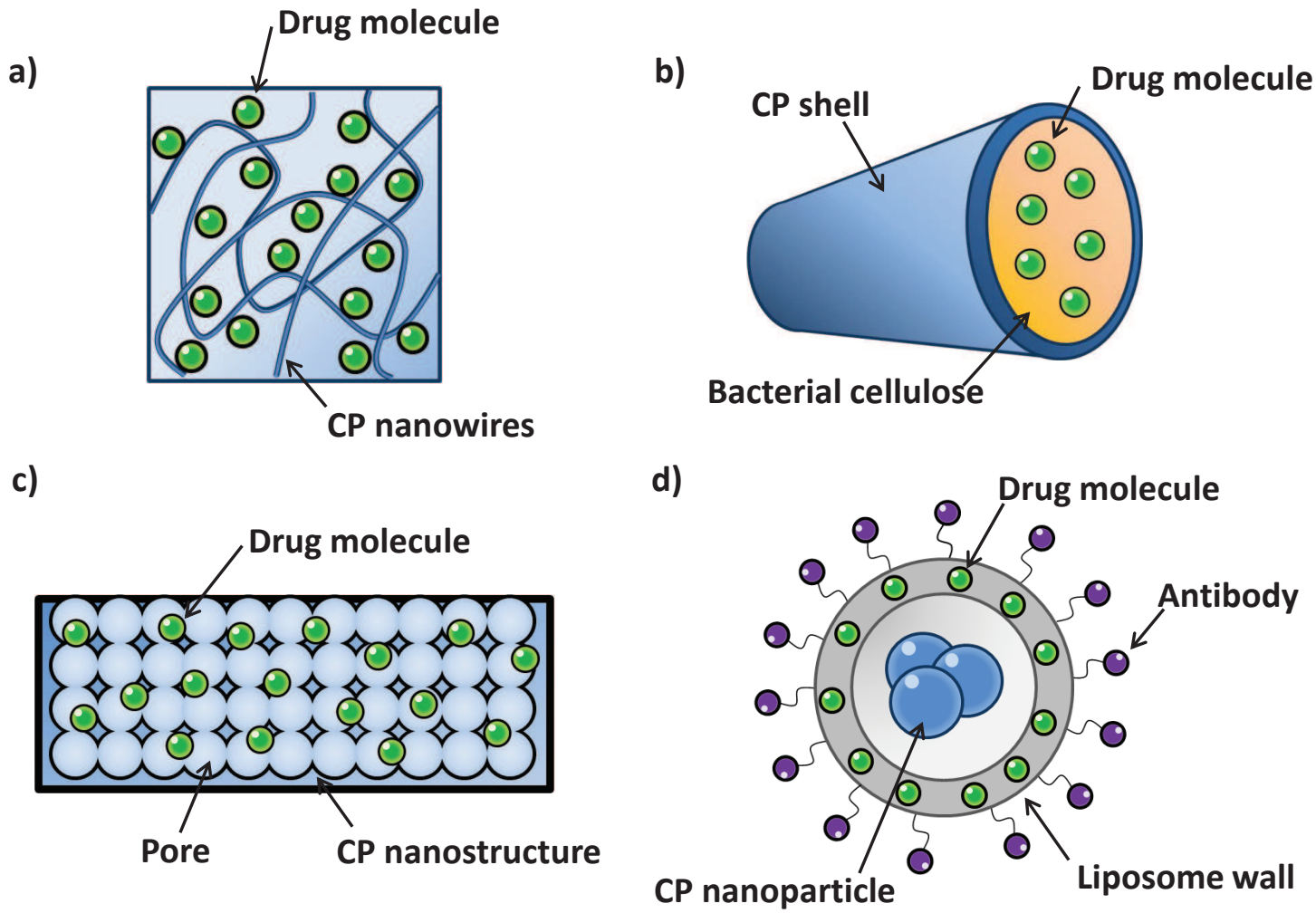
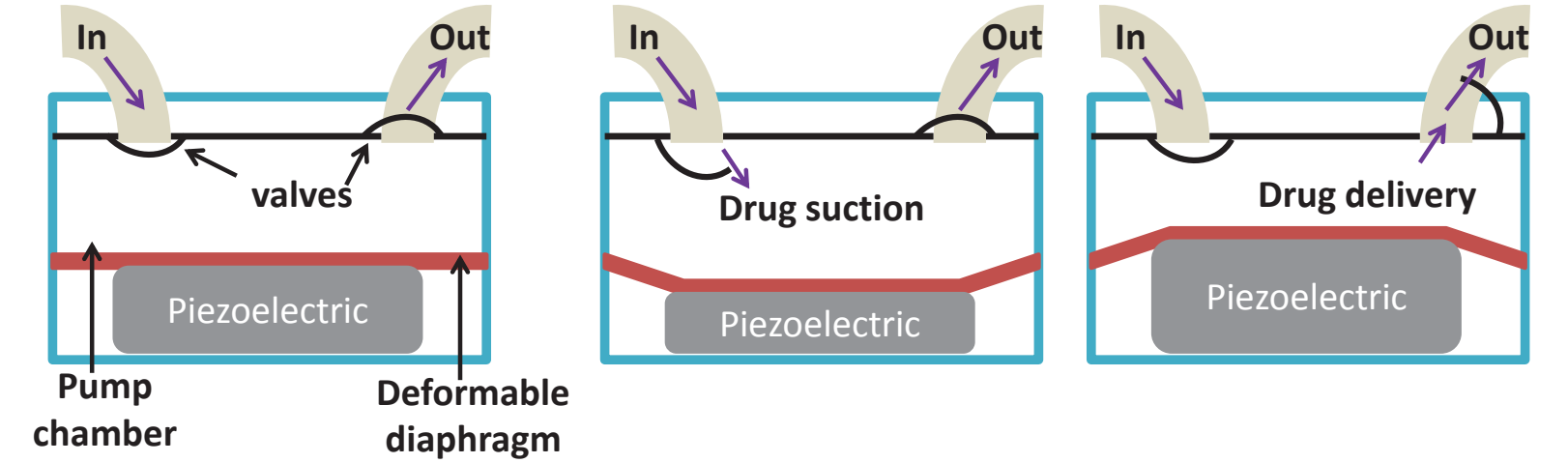
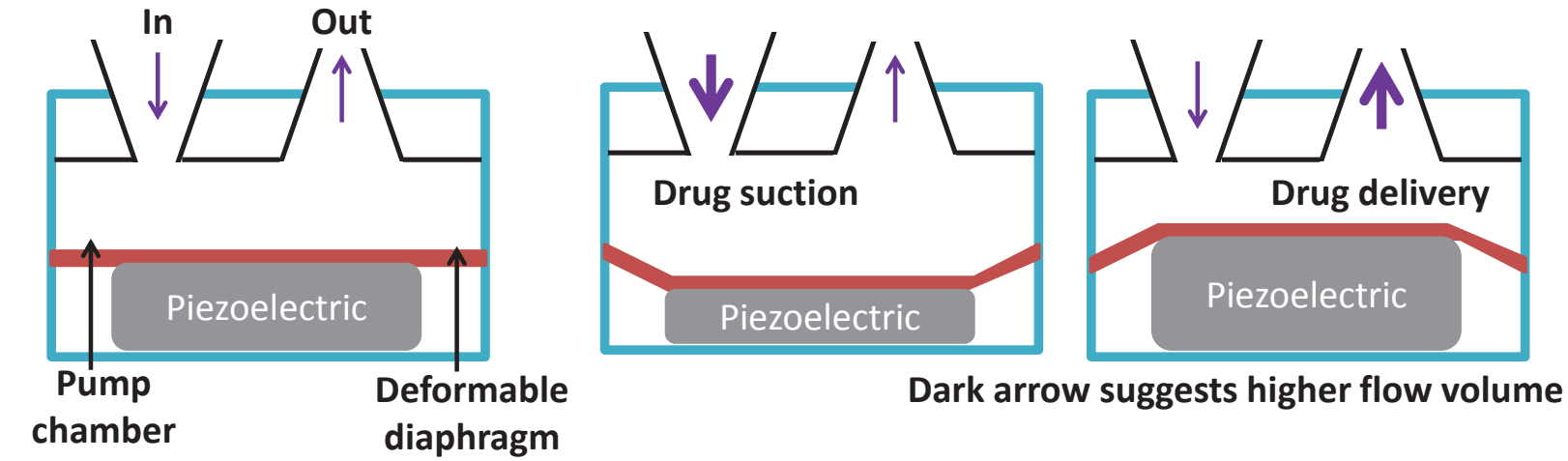

a)
Drug molecule
CP nanowires
b)
CP shell
Drug molecule
Bacterial cellulose
c)
Drug molecule
Pore
CP nanostructure
d)
Drug molecule
Antibody
CP nanoparticle
Liposome wall

Figure 7



Piezoelectric pump with valves



Piezoelectric pump without valves

Figure 8

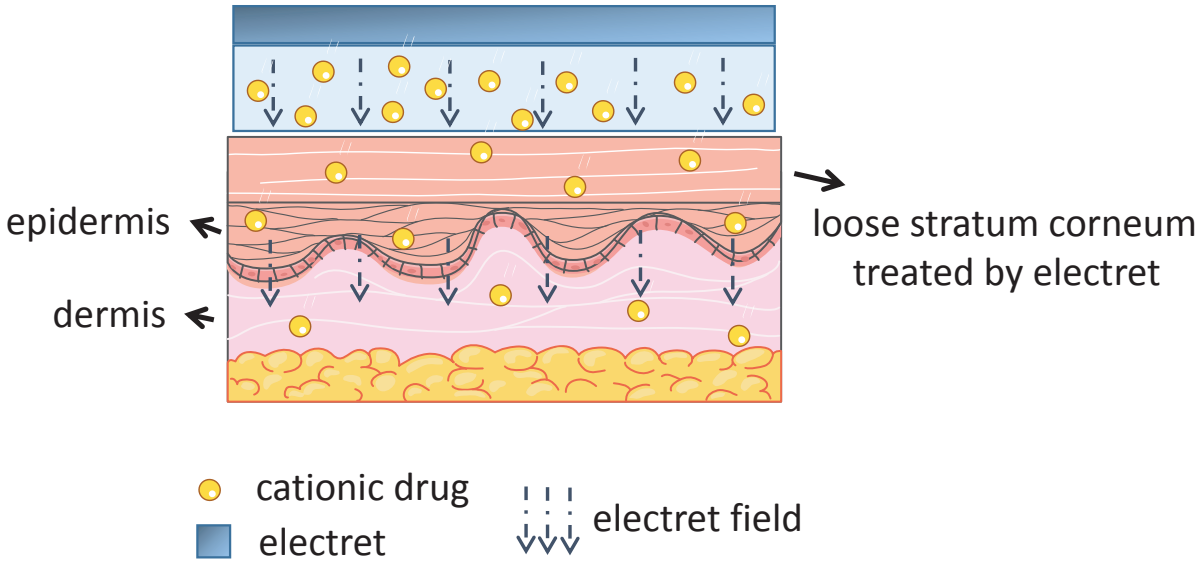

epidermis
dermis
loose stratum corneum
treated by electret
cationic drug
electret
electret field

Figure 9

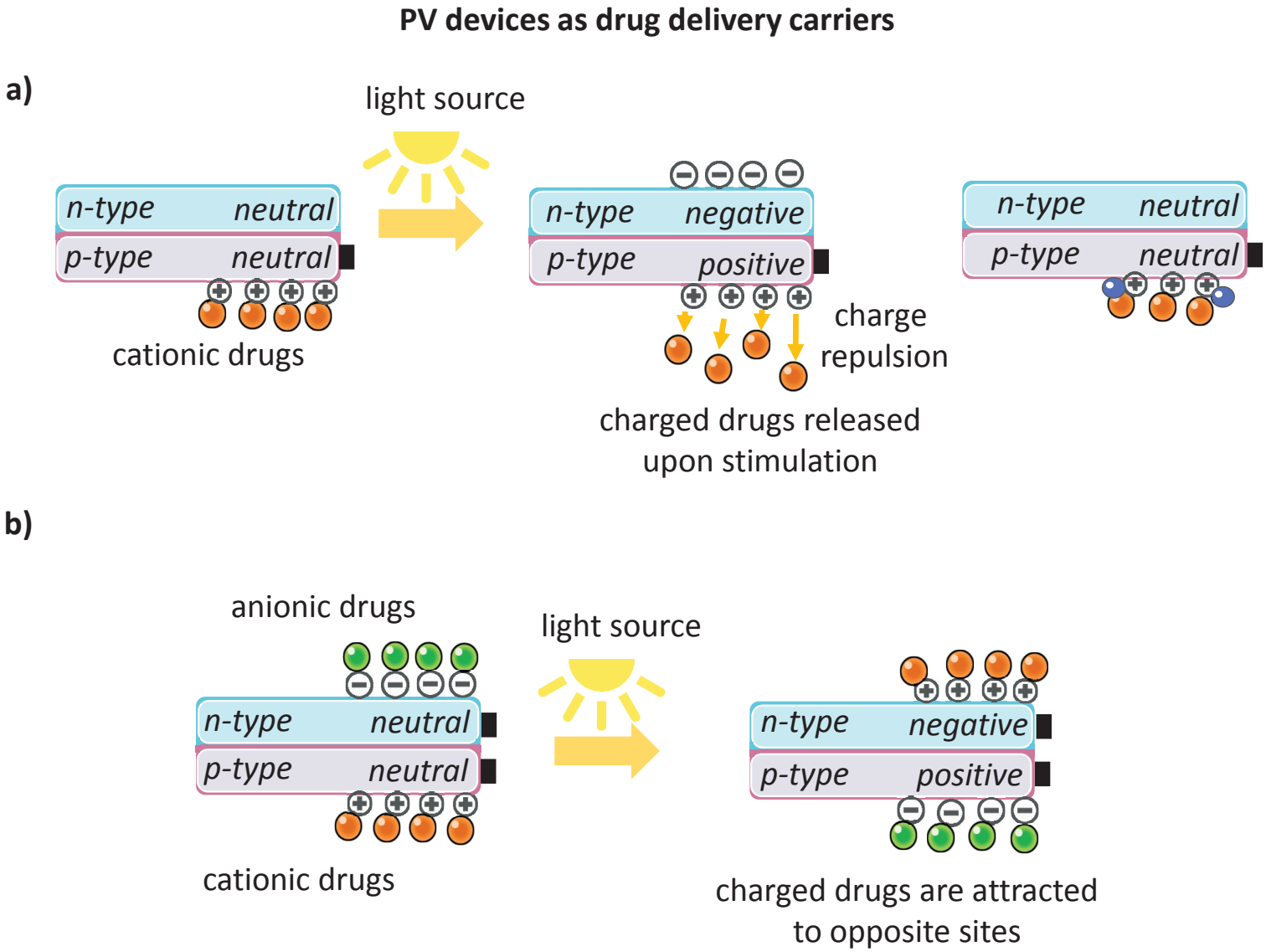
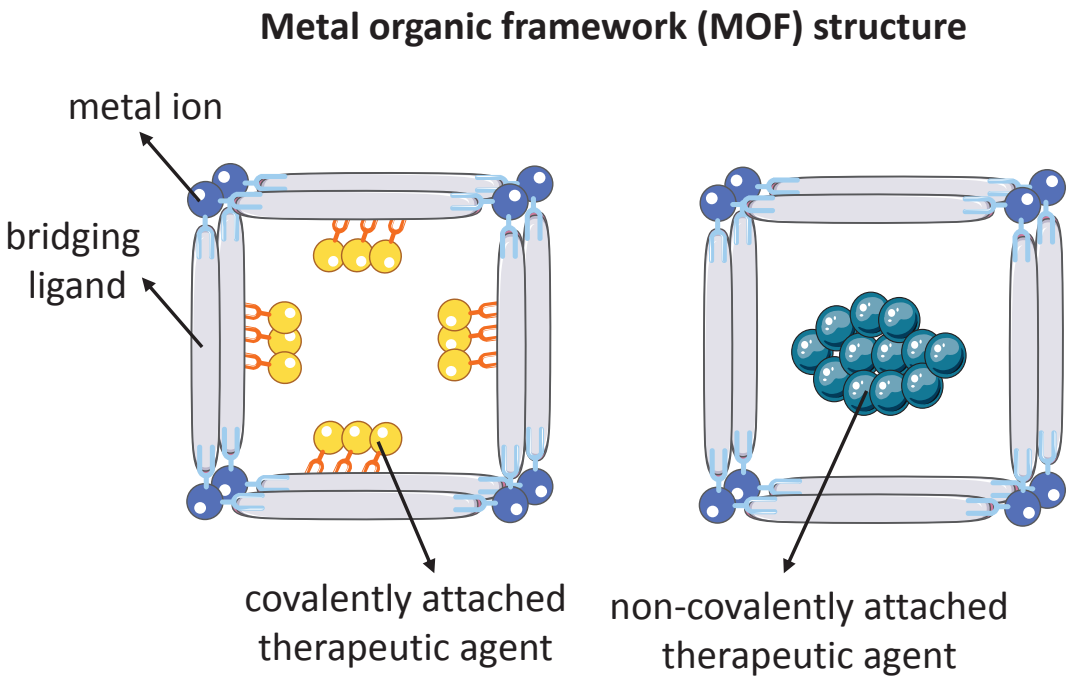

PV devices as drug delivery carriers
a)
light source
n-type
neutral
p-type
neutral
cationic drugs
n-type
negative
p-type
positive
charge
repulsion
charged drugs released
upon stimulation
n-type
neutral
p-type
neutral
b)
anionic drugs
light source
n-type
neutral
p-type
neutral
cationic drugs
n-type
negative
p-type
positive
charged drugs are attracted
to opposite sites

Figure 10


Metal organic framework (MOF) structure
metal ion
bridging ligand
covalently attached therapeutic agent
non-covalently attached therapeutic agent

Tubular structure

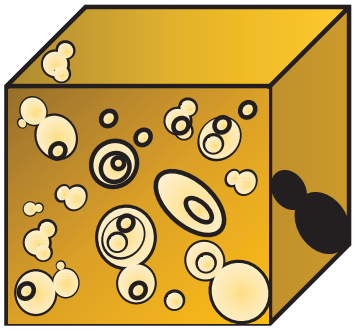


Table 1

Polymers	Ceramics	Others
Poly($_L$-Lactide) (PLLA)	Hydroxyapatite (HA)	Diphenylalanine
Poly (vinylidene fluoride) (PVDF)	Barium titanate (BT)	Collagen
Poly (vinylidene fluoride-trifluro ethylene) (PVDF-TrFE)	Lithium sodium potassium niobate (LNKN)	Boron nitride nano tubes (BNNTs)
Polyhydroxy butyrate (PHB)	Lithium niobate (LN)	Silk
	Lead zirconate titanate (PZT)	
	Zinc Oxide (ZO)	

Table 2

Target tissue	Size particle	Excretion route
Any	3 – 10 nm	Renal filtration [165]
Liver and brain tissue	10 – 30 nm	Phagocyte system [166]
Lung and inflamed tissues	30 – 80 nm	Phagocyte system [167]
Liver and spleen	> 80 nm	Hepatobiliary excretion [166]

Figure legends

Figure 1 The family of electroactive materials and their applications

Figure 2 a) Direct and converse piezoelectric effect mechanisms and b) types of poling procedures to maximize piezoelectricity

Figure 3 Types of electrets: (a) heterocharged and (b) homocharged (*injected charges are those which get deposited on the material surface from the surrounding electrode); and (c) charge carriers involved during the formation of electrets

Figure 4 Photovoltaic mechanism: a) conventional photovoltaic cell where electron-hole pairs migrate to opposite electrodes upon photo stimulation and electric current is produced; b) photovoltaic cells depicting the schematics of a planar heterojunction, a blended bulk heterojunction and an ordered heterojunction; c) model of a conceptual nanoscopic photovoltaic device depicting realistic and optimal design dimensions

Figure 5 Mechanisms of drug loading and release in CPs: a) one-step loading of anionic drug; b) three-step loading of anionic drug; and c) loading of cationic drug

Figure 6 Examples of advanced CP based drug delivery solutions: a) nanowires [89]; b) microtubes [80]; c) nanoporous structure [106]; and d) nanoparticle [121]

Figure 7 Schematic of working principle of piezoelectric micropumps with or without valves, based on deformable piezoelectric based diaphragms that regulate drug suction and delivery

Figure 8 Transdermal drug delivery system based on electrets

Figure 9 Photovoltaic devices used as drug delivery carriers: a) PV device coated with positively charged drugs, which are released upon stimulation and attracted back again in a retractable-wise manner; b) PV device coated with positively and negatively charged drugs that are attracted to opposite sites upon stimulation of the device instead of being repelled towards the environment

Figure 10 Schematic representation of a metal organic framework (MOF) structure used as a delivery carrier

Figure 11 Examples of different piezoelectric based scaffolds

Table of contents