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Application of conducting polymers to wound care and skin tissue engineering: A review

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ABSTRACT

The use of intrinsically conducting polymers (CPs) in wound care and skin tissue engineering presents a novel opportunity for accelerated wound healing, enhanced antibacterial activity and the potential for controlled drug delivery. Through their increased electrical conductivity, CPs can facilitate the application of electrical stimulation directly to the wound area, which has been linked to faster wound healing. The release of drugs or biological agents to the wound site can likewise be modulated through the use of an external electrical stimuli. This review thus summarises the available literature regarding the use of CPs for wound healing and skin tissue engineering applications, in particular the most common CPs, polyaniline (PANI), polypyrrole (PPy), polythiophene (PTh) and their derivates, including poly(3,4-ethylenedioxythiophene) (PEDOT). Results indicated that PANI and PPy, two CPs that have been most extensively studied across a range of applications, including biological, were also most frequently used in wound dressings and hydrogels. PPy was most commonly applied to skin tissue scaffolds. CPs were also frequently combined with biomolecules or biocompatible polymers via doping, the formation of composites, co-polymerisation or blending in order to improve their biocompatibility and physical properties. Overall, CPs offer much potential in terms of promoting enhanced wound healing and in skin tissue engineering.

1. Introduction

1.1. Wounds, dressings and tissue scaffolds

The provision of adequate wound care is a growing priority internationally, particularly in light of the aging population trend observed in many developed countries. Moreover, the management of chronic wounds, including pressure ulcers, diabetic foot ulcers and venous leg ulcers, poses a significant burden to public health care spending (Sen et al., 2009). Novel methods to improve the rate and effectiveness of wound healing are required; this is where nanotechnology in general, and conducting polymers (CPs) in particular, present a potential opportunity for introducing improved wound healing modalities.

Skin on average comprises 15% of adult total body weight (Vig et al., 2017). It serves a protective function against external agents, facilitates thermoregulation, allows for fluid balance, provides sensation and produces vitamin D and immune system components (Harvey, 2005). It is comprised of three layers; the dermis, epidermis and the hypodermis, which is made up of subcutaneous tissue (Zarrintaj et al., 2017). A skin wound is defined as the disruption of the normal anatomic structure and function of the skin (Lazarus et al., 1994). The healing process involves several phases including haemostasis, inflammation, proliferation, maturation and remodelling (Chaudhari et al., 2016; Dhivya et al., 2015; Gonzalez et al., 2016; Zahedi et al., 2009). To facilitate accelerated wound healing, the surface of the wound should generally be kept moist, rather than being exposed to air (Winter, 1963). The application of a dressing over the wound not only protects against infection, but also helps to maintain a moist environment that promotes faster re-epithelization (Hinman and Maibach, 1963). Traditional, passive wound dressings include gauze and tulle. Although these provide coverage, they can adhere to the wound bed and cause disruption and pain upon removal (Dhivya et al., 2015). In contrast, modern wound dressings not only cover the wound but interact with it to actively promote healing (Dhivya et al., 2015). They utilize more advanced materials in their formulations and can be classified as either interactive or bioactive. They include semi-permeable

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films and foams (often constructed of polyurethane), hydrogels, hydrocolloids, alginates, collagens and hydrofibers. Bioactive dressings are comprised of biomaterials with high biocompatibility, biodegradability and a non-toxic nature; common constituents include hyaluronic acid (HA), chitosan (CS) and elastin, among others (Dhivya et al., 2015; Zahedi et al., 2009).

For larger, deeper and chronic wounds, a matrix-like scaffold may be required to guide cell proliferation and provide mechanical support for tissue regeneration. A scaffold should have high porosity, a large surface area to volume ratio, an interconnected geometry, structural strength and be specific to the shape of the wound (Bendrea et al., 2011; Carletti et al., 2011; Kim et al., 2011). Ideally it should be biocompatible and biodegradable, with a degradation profile that is reflective of the wound healing duration (Carletti et al., 2011). Scaffolds can take on various forms including fibrous networks, sponges, foams and hydrogels, among others (Chaudhari et al., 2016). Various naturally derived polymeric materials have been used as tissue scaffolds including collagen, chitosan, fibrin, elastin, gelatin, hyaluronic acid and silk (Kim et al., 2011). However, synthetic polymers have also been utilised (Zhong et al., 2010) including polycaprolactone (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers (Chaudhari et al., 2016; Kim et al., 2011). Moreover, nanofibers produced by electrospinning hold much promise in terms of tissue scaffolds as their structure is reminiscent of that of extracellular matrix. They allow for nutrient exchange, for the removal of waste products and are able to provide physical protection against microorganisms due to their small pore size (Chaudhari et al., 2016).

In the last few decades, the incorporation of conducting polymers into scaffolds and dressings has been investigated. The increased electrical conductivity that can be provided by their inclusion can facilitate the application of therapies such as electrical stimulation to the wound area as well as enabling the controlled release of pharmaceutical and biological agents. Common CPs include polypyrrole (PPy), polyaniline (PANI), polythiophene (PTh) and their derivates, including poly(3,4-ethylenedioxythiophene) (PEDOT).

1.2. Overview of CPs

CPs are polymers that are electrically conductive. Organic polymers had been generally considered as insulators until the discovery of halogen doped trans-polyacetylene (PA), which was characterised by a remarkable ability to conduct electrical charge compared to unmodified trans-PA (Shirakawa et al., 1977). The general structure of CPs consists of a conjugated backbone with alternated single and double bonds. The double bonds comprise π-bonds that are characterised by overlapping p-orbitals; this means that unpaired electrons associated with each atom in the backbone do not actually belong to any single atom but rather overlap with each other in the orbitals and therefore are able to move freely (Balint et al., 2014; Le et al., 2017). It is this delocalization of π-electrons that provides the basis for electrical conductivity (Macdiarmid et al., 1985). However, pristine conjugated polymers show very limited conductivity unless an extra process called “doping” is applied. Although the term doping was originally used to describe the way in which an inorganic semi-conductor could be rendered electrically conductive by the intentional addition of a foreign neutral atom into its lattice, this differs from the type of “doping” applied to CPs; nevertheless this terminology is now commonly used with reference to CPs (Bredas and Street, 1985). In the context of CPs, doping is essentially a redox reaction, with p-doping referring to oxidation of the polymer and n-doping to reduction; the former being more common (Le et al., 2017). There are many different methods of doping applicable to CPs, including chemical doping, electrochemical doping and photo-induced doping (Balint et al., 2014; Bendrea et al., 2011). Importantly, as a result of doping, the conductivity of conjugated polymers can be increased by many orders of magnitude, to be similar to that of some metals (Le et al., 2017; Macdiarmid et al., 1985).

In addition, doping, together with the formation of composites, copolymers and blends, allows for some of the limitations inherent to the pristine forms of CPs to be overcome (Bendrea et al., 2011). For example, by creating a PPy/poly(D,L-lactide) (PDLLA) composite, the brittleness and mechanical rigidity of pure PPy (Guo and Ma, 2018; Huang et al., 2014) can be avoided (Shi et al., 2004). Likewise PPy can be applied as a coating onto other materials, such as poly(D,L-lactide-*co*-Ɛ-caprolactone) in order to produce a flexible yet electrically conductive membrane (Zhang et al., 2007). In a similar manner, while the biocompatibility of CPs such as PPy (Wang et al., 2004), PANI (Humpolicek et al., 2018; Mattioli-Belmonte et al., 2003) and PEDOT (del Valle et al., 2007) has been well established and confirmed in animal models (Kamalesh et al., 2000; Wang et al., 2004), it can be further enhanced through the intentional incorporation of biomolecules (Bendrea et al., 2011; Guimard et al., 2007).

1.3. Electrical stimulation facilitated by CPs

Electrical stimulation (ES) in relation to wound care refers to the application of an external electrical stimuli to the tissue adjacent to, or directly within, a wound (Isseroff and Dahle, 2012). The intent is to exert greater control over cellular differentiation and proliferation, thereby accelerating the wound healing process (Balint et al., 2013). The mechanism behind its functionality is that, in human skin, the epidermis normally maintains a transepithelial potential, analogous to an ‘endogenous battery’ (Foulds and Barker, 1983); any compromise to its structural integrity leads to a short circuit, resulting in a current vector at the perimeter of the wound which acts to guide cell migration towards the wound centre, thus directing wound healing. It also controls the orientation and frequency of cell division (Balint et al., 2013). Researchers have found that by applying an external electric field to the wound area in a similar manner, the rate of wound healing can be further accelerated (Isseroff and Dahle, 2012; Zhao et al., 2006). In fact a recent review provided strong support for the use of electrical stimulation to facilitate improved wound healing of chronic wounds (E Houghton, 2017). The incorporation of CPs into wound dressings and tissue scaffolds provides the opportunity for ES to be more uniformly and routinely delivered to the injured tissue. In addition, some researchers have noted that CP use alone, even without the application of an external electrical stimuli, resulted in accelerated wound healing (Gharibi et al., 2014).

1.4. Antimicrobial properties of CPs

CPs and their composites have been shown to exhibit intrinsic antibacterial properties. For example, Gizdavic-Nikolaidis et al. showed that polyaniline exhibited antibacterial properties against E.coli, S.aureus and *P. aeruginosa*, both the wild type and antibiotic resistant strains, as well as against other types of antibiotic resistant bacteria; the antibacterial activity was further enhanced by use of the composites poly(aniline-*co*-2-aminobenzoic acid) and poly(aniline-*co*-2-aminobenzoic acid)(Gizdavic-Nikolaidis et al., 2011). Similarly, polypyrrole/dextrin composite demonstrated antibacterial activity against E.coli, P.aeruginosa, S.aureus and B.subtilis (Nazarzadeh Zare et al., 2014); the former three being bacterial strains that are commonly found in infected wounds (Bessa et al., 2013). The antimicrobial properties of CPs and composites can further be enhanced through the incorporation of silver nanoparticles (Chowdhury and Al-Jumaily, 2016; Gharibi et al., 2014; Maráková et al., 2017; Zhou et al., 2015). Silver has traditionally been used in wound dressings to endow antibacterial properties (Wilkinson et al., 2011), with silver nanoparticles, in particular, exhibiting more potent bactericidal effects (Morones et al., 2005). For example, the deposition of silver nanoparticles onto PPy or PANI coated cotton fabrics further enhanced their antimicrobial activity (Maráková et al., 2017). Similarly, while microfibrillated cellulose/PPy aerogels inherently showed antimicrobial activity against E.coli, the

incorporation of silver nanoparticles led to significant activity also against S.aureus (Zhou et al., 2015). As an alternative to silver, some authors have even incorporated antibiotics into CP-based materials. For example, the antibiotic mupirocin, used for the treatment of skin infections, was incorporated by Jotiram et al. into PANI nanofibers, resulting in enhanced antimicrobial activity (Kaveeta Pergas et al., 2012). In fact, another key advantage of CP use in wound dressings and tissue scaffolds is that they provide the opportunity for the controlled release of pharmacological and biological agents.

1.5. Controlled drug delivery using CPs

The ability of CPs to be doped with specific agents gives rise to the possibility of controlled release of drugs at the site of the wound. Control of delivery is achieved through the use of an externally applied electrical field. For example, Nguyen et al. examined the use of a PEDOT nanotube patch for transdermal drug delivery in an *ex vivo* porcine skin model. The authors observed that controlled delivery could be achieved via both short potential bursts and long term applied potential. They concluded that the transdermal patch offers a promising drug delivery method, particularly for drugs such as insulin (Nguyen et al., 2014). Other authors have also examined the use of CPs to facilitate transdermal drug delivery (Chansai et al., 2009; Niamlang et al., 2018; Oktay and Alemdar, 2018; Paradee and Sirivat, 2014; Pérez-Martínez et al., 2016). Justin et al. demonstrated the controlled release of the anti-inflammatory and analgesic drug ibuprofen sodium salt from PPy films. Active, on-demand release was achieved via the application of an external potential. The authors also noted a lesser degree of passive release of the drug in the absence of an electrical stimuli (Justin et al., 2012). Overall, CPs present an opportunity for facilitating controlled drug release, which in the case of wound dressings and skin tissue scaffolds, can be targeted specifically to the wound site.

Given the abovementioned advantages that CPs can offer, their incorporation into wound dressings and tissue scaffolds has been investigated in this review. While the literature documents their utilisation for various tissue engineering applications, including for cardiac (Hsiao et al., 2013; Spearman et al., 2015; Tsui et al., 2018; Wang et al., 2017a) and neural tissues (Chen et al., 2000; Guo et al., 2012; Pires et al., 2015; Shi et al., 2014; Sun et al., 2016; Zhang et al., 2007), this review focuses specifically on their use in relation to skin regeneration and wound healing.

2. Results and discussion

Thirty-six relevant articles were identified by the review. The search methodology is described in supplementary material and details of search strategy are shown in Table S1. The characteristics of these studies are summarised in Table S2. For ease of discussion, our results are divided into three sections depending on whether the CPs were utilised for wound dressings, hydrogels or skin tissue scaffolds.

2.1. Wound dressings incorporating CPs

CPs have been incorporated into wound dressings to provide enhanced antibacterial activity, to facilitate cell growth and to enable the provision of electrical stimulation or controlled drug release through the application of an external electric field. A number of studies have combined CPs with polyurethane, a modern wound dressing material that is used for interactive dressings. For example, dos Santos et al. deposited usnic-acid doped PANI onto polyurethane foam (dos Santos et al., 2018). Polyurethane foam is typically utilised in semi-permeable dressings that are designed to absorb a large amount of exudate (Zahedi et al., 2009). Usnic acid is a known antimicrobial agent, whilst PANI also exhibits inherent antibacterial properties. The inclusion of usnic acid-doped PANI onto the foam provided superior antibacterial activity against E.coli and S.aureus (Fig. 1), two bacterial strains frequently found in wounds (dos Santos et al., 2018).

Other authors described the use of aniline tetramer embedded polyurethane/siloxane membranes loaded with silver nanoparticles for wound dressing applications. The authors sought to design an ideal dressing that maintains a moist wound environment, exhibits good mechanical properties under both dry and hydrated conditions, possesses potent antimicrobial activity, antioxidant activity and stimulates fibroblast growth and proliferation. Again, commonly used polyurethane was employed as the backbone, while siloxane was incorporated to supply enhanced mechanical stability. Aniline tetramer was used to provide the other desired aspects of the wound dressing. In general, PANI and oligoaniline derivates have been shown to exhibit inherent antioxidant activity; this was confirmed in the following study by measuring the dressing's scavenging capacity against the free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH). Antibacterial and antifungal properties were demonstrated against E.coli, *P. aeruginosa* and C. albicans. Furthermore cytocompatibility was demonstrated using murine L-929 fibroblasts. Accelerated cell growth and proliferation associated

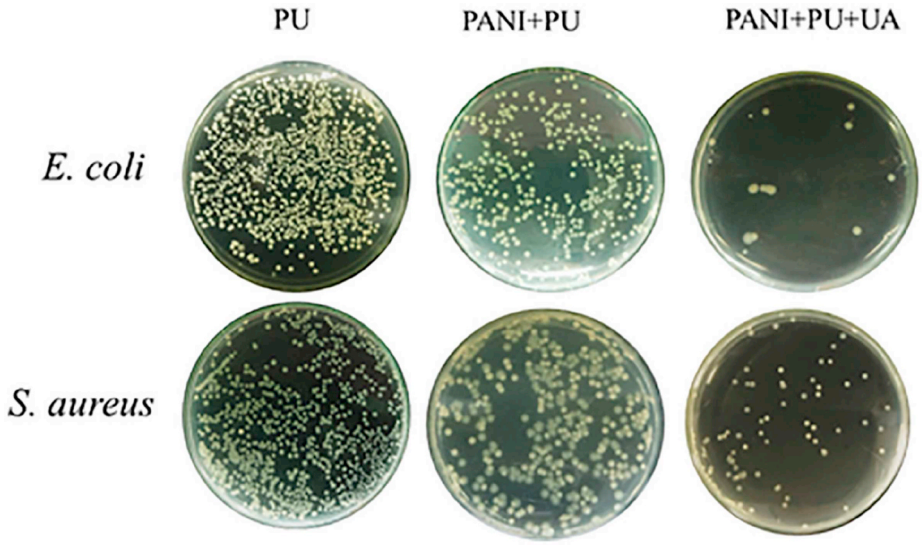

Fig. 1. Quantification of viable bacteria on surface of pristine PU, PANI + PU (undoped) and PANI + PU (doped (UA)) due to the activity of *E. coli* and *S. aureus* (dos Santos et al., 2018).

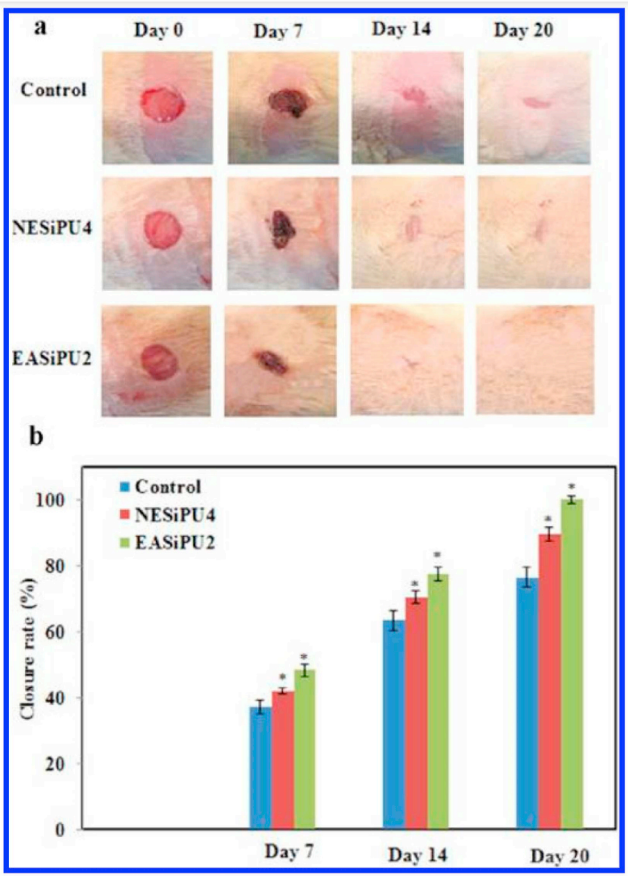

Fig. 2. Photographs (a) and closure rate (b) of wounds treated with gauze (control), NESiPU4 (non-electroactive dressing), and EASiPU2 (electroactive dressing containing aniline tetramer) during the wound healing process for 20 days. According to analysis of variances, *: $P < 0.05$, values are significantly different from the previous compared group (Gharibi et al., 2015).

with the dressing itself, without the employment of electrical stimulation, was recorded by the authors, when compared to a control membrane that did not contain the conducting aniline tetramer component (Gharibi et al., 2014). This dressing provided many advantages and warranted further *in vivo* testing by the authors. Subsequent work was carried out on similar membranes using full thickness skin wound models in Wistar rats. Incisions of 1.5 cm^2 were inflicted and monitored for up to 20 days. Inclusion of the aniline tetramer in the membrane was associated with greater re-epithelialisation, collagen deposition and vascularisation of the wound area. In fact, on day 20, the aniline tetramer-containing membrane was associated with complete wound closure in the animal model (compared to 90% closure with the non-electroactive dressing and 76% in the control group that used cotton gauze to cover the wound) (Fig. 2). (Gharibi et al., 2015) This work highlights the role of CPs in providing desirable wound dressing characteristics.

The previously mentioned studies were all conducted using either PANI or an oligoaniline derivate. Other authors also utilised PANI to create electrospun nanofibrous membranes for use in wound care. The advantages of electrospun nanofibrous dressings in general are that they promote haemostasis, provide high absorption of wound exudate due to their high surface area to volume ratio, allow for atmospheric oxygen permeation, maintain control of an appropriately moist environment due to their semi-permeability, protect against bacterial infection due to their small pore size and provide 3D conformability to the wound contour (Zahedi et al., 2009). Moutsatsou et al. created nanofibrous membranes comprised of PANI and chitosan (Moutsatsou et al., 2017). Chitosan is a biocompatible, biodegradable and antimicrobial natural polymer and a commonly used ingredient for bioactive dressings (Zahedi et al., 2009). The resultant PANI/CS membranes were assessed for cytotoxicity and effect on cell proliferation using human dermal fibroblasts and human osteoblasts (hOST-T85 cell line). It was found that even with higher ratios of PANI to chitosan (for example, 3:5), cell attachment and proliferation was supported (Fig. 3). This highlights the potential for use of PANI/CS nanofibrous membranes for wound dressing applications (Moutsatsou et al., 2017). Other authors to investigate electrospun nanofibrous membranes included Karim et al. and Gizdavic-Nikolaidis et al. Karim et al. created membranes based on PANI with o-aminobenzenesulfonic acid copolymer (PANI-*co*-PABSA) and poly(vinyl alcohol) (PVA)/chitosan oligosaccharide (COS) biopolymers. These membranes were tested in a full thickness skin defect model in Sprague Dawley rats, together with the application of the commercially available topical ointment Fucidin®. Wounds of diameter 8 mm were inflicted and monitored for up to 15 days; those treated with the PANI-co-PABSA/PVA/COS membranes plus Fucidin® demonstrated a statistically significant reduction in wound area compared to the control (Karim et al., 2016). Gizdavic-Nikolaidis et al. created nanofibrous mats comprised of HCl-doped poly(aniline-*co*-3-aminobenzoic acid) (3ABAPANI) and poly (lactic acid) (PLA) via electrospinning. The growth of African Green Monkey COS-1 fibroblasts was supported at various ratios of 3ABAPANI to PLA, ranging from 5:95 to 45:55. Furthermore the nanofibrous mats were found to demonstrate antimicrobial properties against S.aureus. The authors highlight their potential use in wound dressings and tissue engineering scaffolds, particularly where the application of ES is desired (Gizdavic-Nikolaidis et al., 2010).

PPy was also incorporated into wound dressing materials. Da Silva Jr. et al. deposited PPy and carbon nanotubes (CNTs) onto polyurethane sponge (Fig. 4), citing its possible application as a 'smart' dressing. Polyurethane is again a common wound dressing component. Carbon nanotubes have been previously examined as a potential material for use in biomedical applications such as tissue engineering (Abarrategi et al., 2008; Hirata et al., 2011). However, at high concentrations, they have been shown to exhibit cytotoxicity (Jia et al., 2005). To address this issue the authors stated that when adhered to polyurethane and coated in PPy, direct contact of CNTs with skin is minimised, therefore the potential cytotoxicity of the overall material is significantly reduced. Cytotoxicity was not directly assessed in this study, however the enhanced antimicrobial activity of the PPy/CNT/PU composite was demonstrated against S.aureus, K.pneumoniae and E.coli. Further work is required to explore the possible use of this composite for 'smart' wound dressings (da Silva et al., 2018). Chowdhury et al. likewise utilised PPy to generate a novel potential wound dressing material (Fig. 5). They produced composite films of regenerated cellulose coated with PPy and silver nanoparticles, loaded with ionic liquid, for use as wound healing patches. Cellulose is a biocompatible and biodegradable natural polymer, whilst, as described previously, silver nanoparticles exhibit bactericidal activity. Ionic liquid loading further enhances this effect. The antimicrobial activity of the composite was confirmed against S.aureus and S.infantis (Chowdhury and Al-Jumaily, 2016). Overall, both PANI and PPy have been reported to be utilised for the exploration of enhanced wound dressings.

2.2. CP hydrogels and aerogels in wound care

Hydrogels are used both as wound dressings and tissue scaffolds. As a wound dressing they provide the advantage of a high water content (70–90%) which maintains a moist environment, important for wound healing (Dhivya et al., 2015). Additional advantages include that they can be easily applied and removed without inflicting damage to the wound bed and they can elicit a soothing and cooling effect to the wound area. Hydrogels can be comprised of natural polymers (for example, collagen and gelatin) or synthetic polymers such as poly

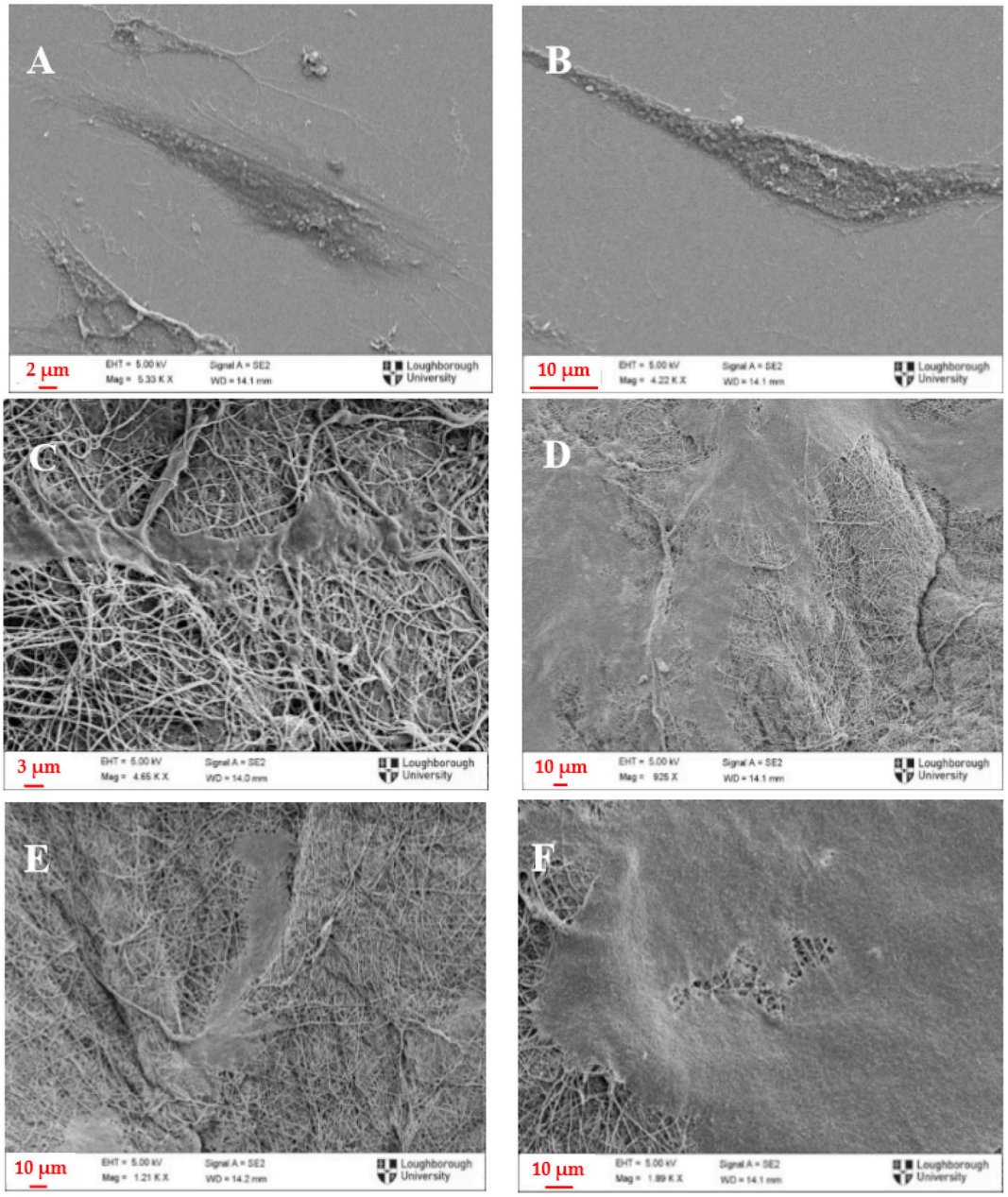

Fig. 3. Scanning Electron Microscope Images of: (A,B) fibroblasts on glass slide; (C) 1:3 PANI/CS membrane; (D) 3:5 PANI/CS membrane; and (E,F) 1:1 PANI/CS membrane (Moutsatsou et al., 2017).

(ethylene glycol) (Ahmed, 2015), poly(methacrylate) and polyvinyl pyrrolidine (Dhivya et al., 2015). Some of their disadvantages however include the fact that excessive accumulation of wound exudate can lead to tissue maceration, whilst overall they exhibit low mechanical strength (Dhivya et al., 2015). They can also be used to manufacture aerogels by replacing the liquid component with gas (usually air). The resultant aerogels are characterised by very high porosity and low density and can likewise be used as wound dressings (Zhou et al., 2015).

Zhao et al. created a series of quaternized chitosan-g-polyaniline and benzaldehyde group functionalised poly(ethylene glycol)-co-poly (glycerol sebacate) hydrogels as wound dressings. The gels were designed to possess self-healing qualities; after being separated into four pieces and then allowed to rest for 2 h at 25 °C without external intervention, the four adjacent, individual pieces were found to re-assemble into one complete hydrogel unit. This unit maintained its integrity when lifted and bent into a U-shape. The antibacterial properties of the hydrogels were confirmed by testing against E.coli and S.aureus, while their antioxidant capacity was demonstrated by their ability to scavenge the free radical DPPH. Lack of cytotoxicity was confirmed *in vitro* using mouse L-929 fibroblasts. The performance of the hydrogel was tested in an *in vivo*, murine, full thickness skin defect model. Circular wounds of diameter 7 mm were inflicted in mice and monitored for up to 15 days. Results indicated that the PANI-containing hydrogel promoted greater wound closure compared to controls, which included a commercially available film dressing (Fig. 6). Furthermore, the PANI-containing hydrogel promoted haemostasis, upregulated several growth factors (vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and transforming growth factor-β (TGF-β), all of which promote wound healing), promoted granulation tissue formation and promoted collagen deposition. This led to enhanced wound healing capacity (Zhao et al., 2017). Other authors also formulated a PANI-containing hydrogel in the form of type 1 bovine skin collagen and carbon nanobrushes (consisting of a carbon nanotube (CNT) core

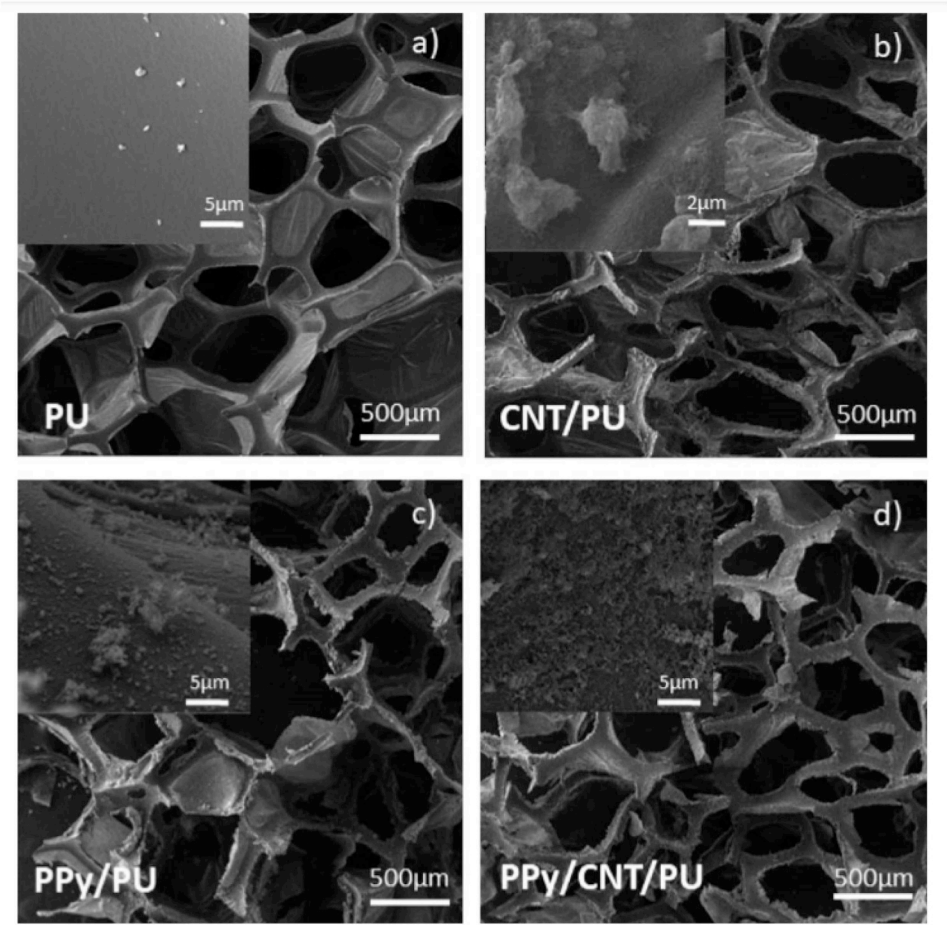

Fig. 4. Scanning Electron Microscope images of (a) pristine polyurethane (PU), (b) polyurethane with deposited carbon nanotubes (CNT/PU), (c) polyurethane with deposited polypyrrole (PPy/PU), and (d) PPy/CNT/PU composites (da Silva et al., 2018).

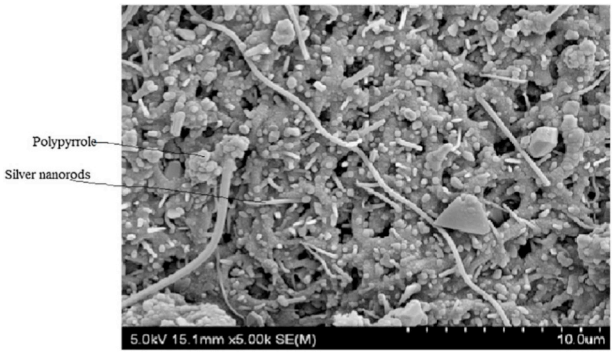

Fig. 5. Scanning Electron Microscope image of polypyrrole and silver nanoparticles deposited on regenerated cellulose film (Chowdhury and Al-Jumaily, 2016).

coated with polystyrene and polyaniline copolymer 'bristles') (Dombi et al., 2015). However, although the intention was to provide structural support through the incorporation of the CNTs, the opposite effect was observed. Moreover the *in vitro* biocompatibility of such a hydrogel would need to be investigated because CNTs, although proposed for use in various biomedical applications (De Volder et al., 2013), have shown potential cytotoxicity unless suitably chemically functionalised (Smart et al., 2006).

Hydrogels have also been created incorporating PPy. Satapathy et al. created a thermoresponsive gelatin hydrogel containing a polyethylenimine(PEI)–polypyrrole nanocomplex for use in tissue engineering. Gelatin is one of a number of traditional materials utilised for the manufacture of hydrogels. The inclusion of the PEI-PPy composite allowed for the gel to exhibit photothermal performance; with the application of near-infrared light, the gel was found to elicit a hyperthermic response. This meant that the gel was able to melt to fit into the potential wound area. Its cytocompatibility was confirmed using mouse L-929 fibroblasts. It was then applied to a full thickness skin defect model in Wistar rats. Circular wounds of diameter 20 mm were inflicted and monitored for up to 21 days. Results indicated that there was a significantly greater degree of wound contraction with the use of the photothermal gel compared to the control ($p < 0.05$) (Fig. 7). (Satapathy et al., 2018) Other authors created PPy-containing aerogels for use as a dressing. Specifically Zhou et al. produced a series of microfibrillated cellulose/PPy/silver nanoparticles hybrid aerogels. Microfibrillated cellulose was used because it provides a ductile capacity to the aerogel. PPy and silver nanoparticles provided antibacterial properties. The authors confirmed the antibacterial nature of the aerogels against E.coli and S.aureus bacteria. Cytocompatibility was demonstrated using murine L-929 cells. The manufactured aerogels exhibited a porosity of greater than 99% (Zhou et al., 2015). They may be useful as wound dressings and for controlled drug delivery to the wound area (Maleki et al., 2016; Zhou et al., 2015). Overall, both hydrogels and aerogels incorporating CPs were used to provide enhanced skin tissue healing capabilities.

2.3. CP scaffolds for skin tissue engineering

Although there are numerous studies in the literature documenting the use of CP scaffolds for a range of tissue engineering applications, the focus of this review was specifically on skin tissue regeneration and

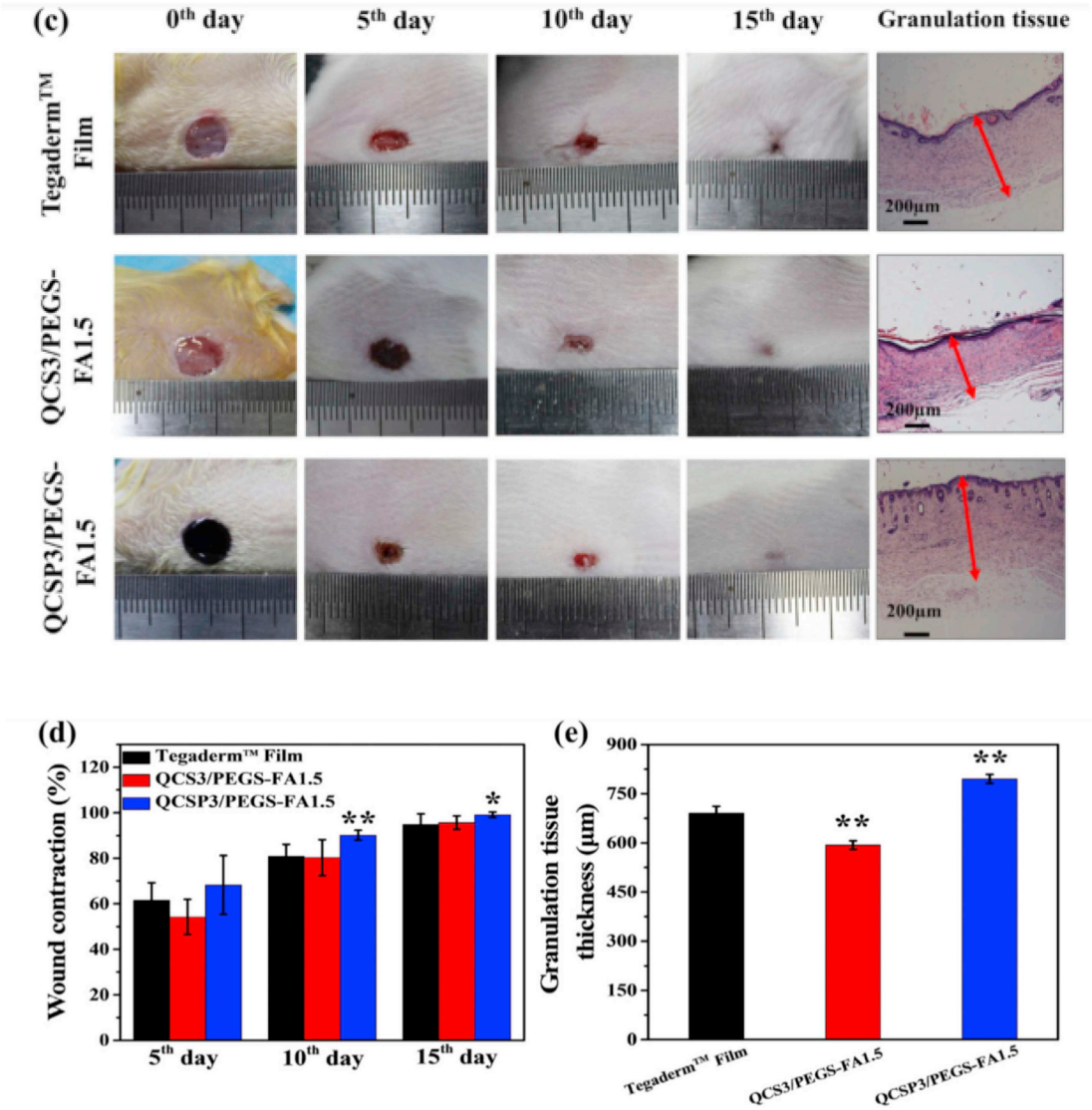

Fig. 6. (c) Photographs of wounds at 0th, 5th, 10th and 15th day and granulation tissue at 15th day for commercial film dressing (Tegaderm™), hydrogel QCS3/PEGS-FA1.5 and polyaniline-containing hydrogel QCSP3/PEGS-FA1.5; (d) Wound contraction for commercial film dressing, hydrogel QCS3/PEGS-FA1.5 and hydrogel QCSP3/PEGS-FA1.5; (e) Granulation tissue thickness for commercial film dressing (Tegaderm™), hydrogel QCS3/PEGS-FA1.5 and hydrogel QCSP3/PEGS-FA1.5 at 15th day. Scale bar: 200 mm *P < 0.05, **P < 0.01 (Zhao et al., 2017).

wound healing. Therefore, this review reports only the findings of studies that demonstrate CP scaffold use *in vitro* with human skin cells (for example, human dermal fibroblasts or keratinocytes) or those that have been tested in rodent wound models. It does not report on scaffold use with other types of human or animal cells, unless the authors have explicitly stated that it is directly applicable to skin wounds. Likewise, the review does not elaborate on scaffolds targeted for use in other areas of the body such a cardiac, bone and neural tissue, although

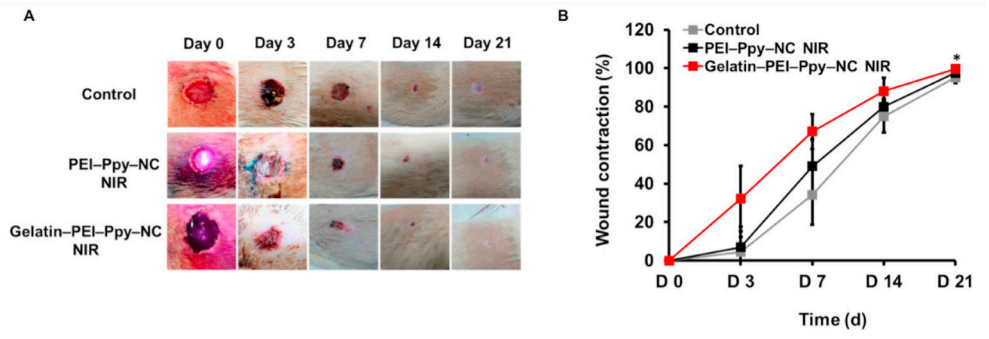

Fig. 7. (A) Periodical wound healing evaluation (full thickness wound in the Wistar rat model): macroscopic images of the wound site and wound area of the control and two experimental groups (polyethylenimine–polypyrrole nanocomplex subject to near infrared light (PEI-Ppy-NC-NIR) and gelatin hydrogel containing polyethylenimine–polypyrrole nanocomplex subject to near infrared light (Gelatin-PEI-Ppy-NC-NIR)) at different time points (day (d) 0, 3, 7, 14, and 21) (n = 3); (B) Wound contraction (%) at various stages of wound healing and complete wound closure from day 0 to day 21(n = 3) ($p < 0.05$) (Satapathy et al., 2018).

similar materials as are used in these applications may likewise be applicable to skin tissue engineering in some cases.

Skin tissue scaffolds for use *in vivo* should ideally be comprised not only of biocompatible and biodegradable components, but also of those that are bioresorbable. This means that they are able to be broken down into products that are completely eliminated from the body, for example, through the citric acid cycle or directly in urine (Gupta et al., 2007; Hutmacher, 2000; Lopes et al., 2012; Vert et al., 1992). Naturally derived bioresorbable materials frequently used for the construction of tissue scaffolds include chitin, hyaluronic acid, fibrin and silk (Generali et al., 2014). Commonly used synthetic bioresorbable materials include aliphatic polyesters such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and polycaprolactone (PCL), and their copolymers. Other alternatives include polyhydroxyalkanoates (PHA), such as poly-3-hydroxybutyrate (P3HB) and copolymers of 3-hydroxybutyrate and 3-hydroxyvalerate (PHBV).

Of the twenty-four studies that reported on skin tissue scaffolds, three reported on PANI-containing scaffolds. Two studies described PANI-containing electrospun nanofibers, whilst one described PANI- or PPy-coated silk fibroin fibers. Gu et al. created chitin/PANI electrospun nanofibrous scaffolds and examined their effect on cell viability and proliferation using human dermal fibroblasts. The nanofibers were either structurally aligned or randomly distributed. The structurally aligned nanofibers were found to better support cell growth and to promote cell distribution in a bipolar, as opposed to multipolar, direction (Gu et al., 2018). Other authors generated electrospun nanofibrous scaffolds comprised of camphorsulfonic acid (CPSA)-doped PANI blended with poly(L-lactide-*co*-Ɛ-caprolactone) (PLCL) (Jeong et al., 2008). Doping with CPSA increases the electrical conductivity of PANI (Balint et al., 2014). PLCL on the other hand is a bioresorbable, elastic polymer that awarded elastic properties to the composite nanofibers. The resultant scaffolds were found to promote cell adhesion of human dermal fibroblasts, murine NIH-3T3 fibroblasts and murine C2C12 myoblasts, compared to the PLCL-only control. Furthermore, growth of NIH-3T3 cells was enhanced through the application of an external electrical stimuli (Jeong et al., 2008). A third paper reported the use of Antheraea mylitta silk fibroin fibers coated with either PANI or PPy (Fig. 8). Silk fibroin is a bioresorbable tissue scaffold constituent that has good mechanical properties, while inciting minimal inflammatory response. Coating with either PANI or PPy adds electrical conductivity and promotes cell adhesion. The cytocompatibility of the coated fibers was confirmed using human immortalised keratinocytes (HaCaT). As expected, both the PANI/silk fibroin and PPy/silk fibroin scaffolds were found to better support cell adhesion than silk fibroin fibers alone (Gh et al., 2017).

PPy was by far the most commonly reported CP incorporated into skin tissue engineering scaffolds or membranes; it was described in sixteen out of the twenty-four studies, although several originated from the same research group. In a similar manner to Gh et al., (2017), Aznar-Cervantes et al. constructed scaffolds made of silk fibroin coated with PPy. The fibers were electrospun into a mesh prior to coating with the CP. Cell viability and growth was tested using primary human dermal fibroblasts and undifferentiated multipotent adult mesenchymal stem cells. However, as opposed to the previous study, the uncoated silk fibroin meshes were found to better support cell adhesion than the PPy-coated silk fibroin mesh. The authors attributed this potentially to contaminants that may have been present from the synthesis stage (Aznar-Cervantes et al., 2012).

PPy was frequently used in combination with polymers of lactic acid or its cyclic di-ester, lactide, which have been favoured in tissue engineering because of their bioresorbable nature, biocompatibility, thermoplasticity and favourable mechanical properties. Many authors sought to maintain the PPy contribution at below 5–10 wt%, leaving predominantly the bioresorbable constituent (Akkouch et al., 2010; Meng et al., 2008; Shi et al. 2004, 2008a, 2008b). Much of the work in this area originated from a Canadian research group based at Laval

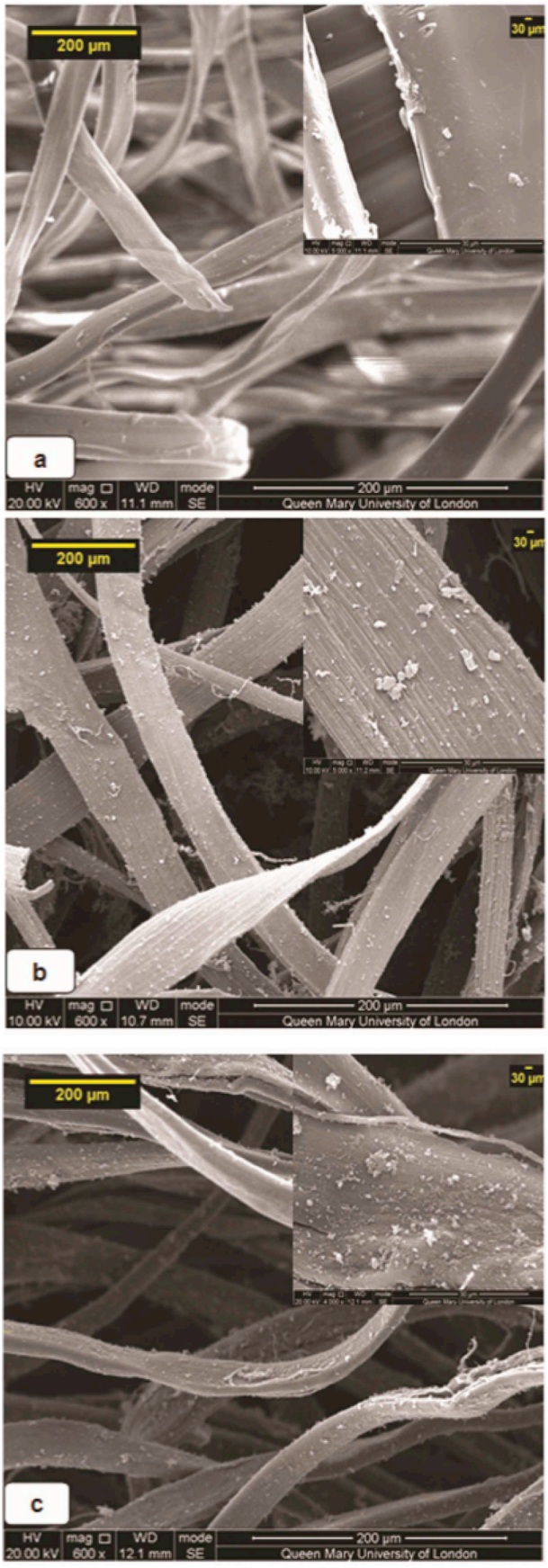

Fig. 8. The surface morphology of a) silk fibroin fibers, b) PPy-coated silk fibroin fibers, and c) PANI-coated silk fibroin fibers (Gh et al., 2017).

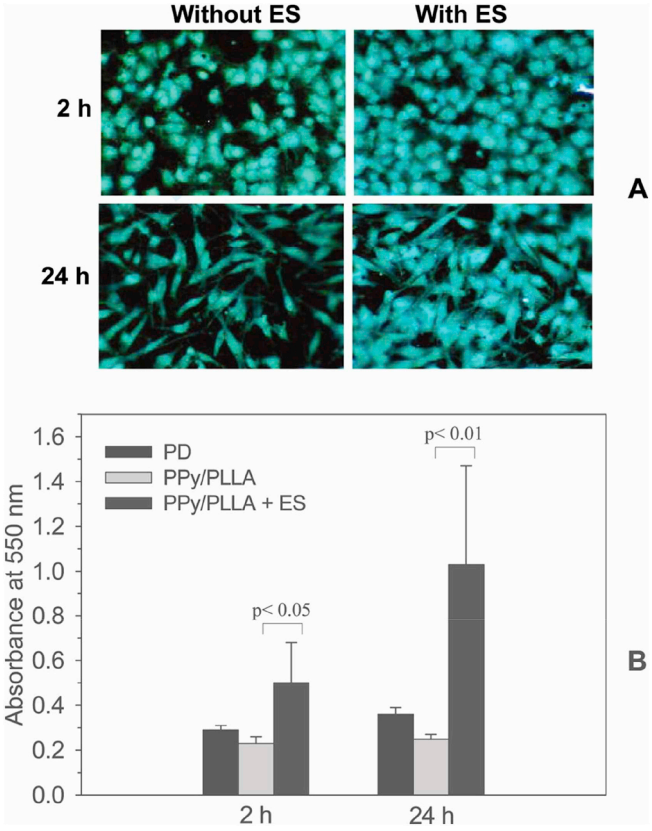

Fig. 9. Fibroblasts on the polypyrrole/poly(L-lactic acid) (PPy/PLLA) membranes at 2 and 24 h with or without electrical stimulation (ES). Note the comparable cell distribution and high cell density on the ES membranes (A). Panel (B) shows a significantly higher cell viability on the membranes with ES (100 mV/mm) (Shi et al., 2008a).

University and the Saint-Franois d'Assise Hospital Research Centre in Quebec City. From this group, Shi et al. created a membrane comprised of PPy and poly(D,L-lactide) (PDLLA) and confirmed its ability to support the growth of human dermal fibroblasts under applied electrical stimulation. Furthermore this composite material was found to maintain its electrical conductivity at biologically meaningful levels after 1000 h of applied 100 mV DC voltage (Shi et al., 2004). Similarly, authors from the same group examined the adhesion and proliferation of human skin fibroblasts on a PPy/poly(L-lactic acid) (PLLA) membrane, both with and without ES. As expected, cell growth was significantly enhanced when a direct electrical field of strength 100 mV/mm was applied (Fig. 9). (Shi et al., 2008a) Authors from this group subsequently demonstrated that ES was linked to a large and significant increase the secretion of inflammatory cytokines (specifically interleukin-6 and interleukin-8, which are involved in wound healing) from human cutaneous fibroblasts, which likely mediated the beneficial effects of ES on cell growth (Shi et al., 2008b).

Authors from the Canadian group also investigated the advantages of doping PPy with heparin prior to its incorporation into the PLLA composite membrane. Heparin is an endogenous glycosaminoglycan and its inclusion was intended to improve cell adhesion as well as provide increased electrical stability in an aqueous environment. This was found to be the case (Fig. 10) when tested with human skin fibroblasts (Meng et al., 2008). With the application of ES at either 50 mV/mm or 200 mV/mm for up to 6 h, the secretion of fibroblast growth factors FGF-1 and FGF-2 was upregulated and consequently cell growth was enhanced. Furthermore, the advantages provided by ES were found to be available even after ES had stopped to be supplied; the membranes previously exposed to 4 and 6 h of ES were found to show significantly better support of fibroblast growth compared to the unexposed membranes, particularly at 72 h of subculture (Fig. 11). In an *in vitro*, mono-layer scratch-wound assay, prior exposure to ES was linked to subsequent faster cell migration and more pronounced cell contractile activity, resulting in faster wound healing (Rouabhia et al., 2013). Additionally ES was found to modulate the expression of a number of important wound healing genes in human dermal fibroblasts (Park et al., 2015).

Other authors likewise investigated the effect of functionalising PPy with various constituents. Ruiz-Velasco et al. utilised iodine as a dopant for PPy/poly(L-lactic acid) (PLLA) and PPy/poly(glycolic acid) (PGA) scaffolds. While the iodine-doped PPy/PLLA scaffolds were found to support the adhesion and proliferation of keratinocytes and dermal fibroblasts, the iodine-doped PPy/PGA scaffolds degraded rapidly and were not conducive to cell viability (Ruiz-Velasco et al., 2017). On the other hand Akkouch et al. created PPy/poly(L,L-lactide) membranes that incorporated fibronectin (Fn), a glycoprotein known to play a role in endogenous wound healing. As expected, the FN-containing membranes were found to promote the adhesion and proliferation of human skin fibroblasts (Akkouch et al., 2010).

Other authors investigated the incorporation of various molecules into PPy films; Collier et al. looked at the ability of hyaluronic acid (HA)-doped PPy films to support the growth of PC-12 rat adrenal gland pheochromocytoma cells *in vitro*. The authors then implanted these films subcutaneously in Sprague Dawley rats and monitored them for up to 6 weeks to assess *in vivo* tissue response (Collier et al., 2000). Hyaluronic acid is a glycosaminoglycan found in extracellular tissues of the human body, with a known impact on wound healing and angiogenesis. It has been used for the manufacture of both wound dressings and tissue scaffolds, the latter due to its endogenous degradation via enzymatic cleavage (Collins and Birkinshaw, 2013). After an initial period of 2 weeks, a bilayer film containing HA/PPy situated on PPy/PSS was found to promote greater vascularisation at the implantation site compared to the PPy/PSS film alone. The authors postulated that this was largely due to the rapid, early degradation of HA and the resultant promotion of angiogenesis by its degradation products. At 6 weeks however, vascularisation around both the single layer and bilayer implants was not statistically different (Collier et al., 2000).

Ateh et al. on the other hand examined PPy films loaded with a range of substrates including chloride, polyvinyl sulphate and polysaccharides and proteins such as heparin, fibrinogen, fibronectin, dermatan sulphate and collagen, describing their effect on the proliferation of SVK14 human keratinocytes. The most effective at promoting cell growth was found to be dermatan-loaded PPy. Like HA, dermatan sulphate is a glycosaminoglycan; it is the most abundant glycosaminoglycan featured on skin and is involved in wound repair (Ateh et al., 2006).

As an alternative to using known biomolecules to promote cell adhesion and tissue growth, Lee et al. investigated the use of amine-functionalised PPy. This was generated via the polymerisation of 1-aminopropyl pyrrole monomer with pyrrole monomers at various molar ratios. The authors found that the resultant material promoted cell attachment of human dermal fibroblasts and Schwann cells (Lee and Schmidt, 2015). The latter three studies were not strictly representative of endogenous resorbable tissue scaffolds, but rather functionalised PPy films, however they do provide insight into the use of various agents with PPy to enhance skin cell adhesion and proliferation, while the authors described their potential application to future skin tissue engineering scaffolds.

Researchers from the Canadian group likewise showed that PPy-coated polyethylene terephthalate (PET) fabrics (Fig. 12) subjected to an applied, pulsed, square wave, DC electrical stimulation can promote human skin fibroblast cell growth and accelerate wound healing (Wang et al. 2013b, 2016, 2017b). Although these materials possess some of the desirable characteristics of a scaffold, namely non-cytotoxicity, porosity and processability, they lack the bioresorption capacity common to some of the other *in vivo* tissue scaffolds discussed thus far.

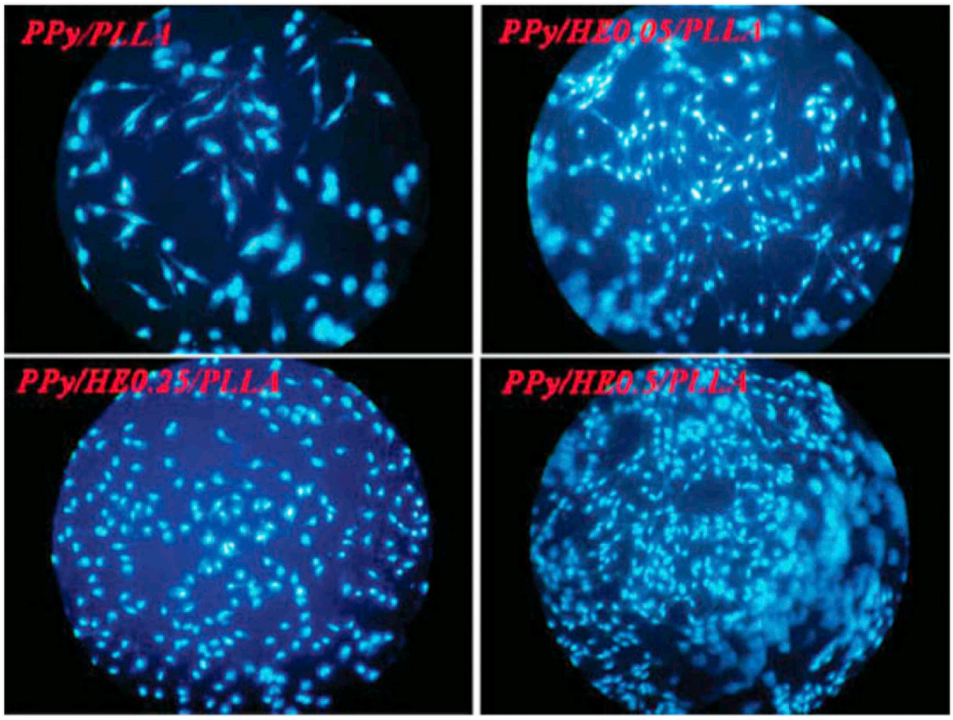

Fig. 10. Hoechst staining of human skin fibroblasts cultured on polypyrrole/poly(L,L-lactide) membranes (PPy/PLLA) membranes for 24 h, showing apparently higher population of cells on heparin-containing membranes (Meng et al., 2008).

In fact they are more commonly used as medical fabrics to manufacture surgical meshes and implants designed to remain in the body for an extended period of time, such as vascular grafts and hernia patches (Maitz, 2015). They can also be used as wound dressings or *ex vivo* tissue scaffolds. In fact, researchers from the same group used the PPy coated PET scaffold to apply pulsed ES to primary human dermal fibroblast, then reseeded the fibroblasts on a collagen scaffold and successfully implanted them subcutaneously into mice. The researchers therefore demonstrated the potential of using *ex vivo* electrically stimulated cells for *in vivo* tissue regeneration (Wang et al., 2016).

PEDOT-containing scaffolds, membranes and films were also investigated in the literature; they were described in four out of the twenty-four studies that related to scaffolds in this review. The Canadian research group explored the application of a thin PEDOT coating onto a nonwoven microfibrous poly(L-lactic acid) (PLLA) web. Again, PLLA offers the advantage of being bioresorbable, while PEDOT is electrically conductive and able to facilitate ES. The scaffold was found to support the attachment and growth of human dermal fibroblasts, which was further enhanced through the application of ES. However, the electrical stability of the PEDOT/PLLA scaffold was found to be inferior to that of the previously described PPy/PLLA composite membrane after 400 h under a constant potential of 5 mV/mm. Nevertheless, the authors noted that the PEDOT/PLLA scaffold offers higher porosity and more physical flexibility than the PPy/PLLA membrane, therefore still making it a useful material for skin tissue engineering applications (Niu et al., 2015).

Stewart et al. produced PEDOT-glycol composites via vacuum vapor phase polymerisation. By utilising glycol the authors were able to increase the overall electrical conductivity of the material. The resultant composites, at various glycol concentrations, supported the adhesion and proliferation of human immortalised keratinocytes (HaCaTs). The authors state that one of the potential applications of this material could be in *ex vivo* tissue engineering (Stewart et al., 2013).

Other authors examined the ability of PEDOT doped with poly (styrene sulfonate) (PSS) to support cell growth. While Marzocchi et al. showed that PEDOT:PSS films alone were able to support human dermal fibroblast proliferation (Marzocchi et al., 2015), Chang et al. further investigated fibroblast growth on PEDOT:PSS coated polylactide (PLA) and poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) electrospun membranes. Both PLA and PHBV are bioresorbable scaffolding materials; PLA is degraded via hydrolysis into simple products that are metabolised by the human body, while PHBV degradation yields a low toxicity product, D-3-hydroxybutyrate, which is a natural component of blood (Wang et al., 2013a). The authors found that fibroblast attachment and growth was better supported by the PEDOT:PSS coated membrane compared to the uncoated membrane (Chang et al., 2016).

Other polythiophene derivatives were explored as potential components of tissue scaffolds. Polythiophene phenylene (PThP) polymers were blended with bioresorbable poly(lactic-*co*-glycolic acid) (PLGA) and electrospun into porous fiber mats by Chan et al. These mats were found to exhibit cytocompatibility with both human dermal fibroblasts and human epidermal melanocytes. Functionalisation of PThP with arginylglycylaspartic acid (RGD) was found to further promote cell proliferation. These findings highlight the potential application of PThP to the manufacture of tissue engineering scaffolds (Chan et al., 2018). Lee et al. on the other hand investigated carboxylic acid-functionalised polyterthiophene (PTTh) and found that when grafted with RGD, it significantly promoted the adhesion of human dermal fibroblasts. This again illustrates the potential use of polythiophene derivatives in skin tissue scaffold design (Lee et al., 2013).

2.4. Additional features that can be incorporated into CP-based wound care products

A number of papers documented additional features that can be incorporated into CP-based wound care products. They include the use of temperature responsive polymers, photosensitive polymers used together with light stimulation, and pH sensitive materials. Patra et al. investigated composite nanofibrous scaffolds comprised of PANI, multiwalled carbon nanotubes (CNTs) and poly(N-isopropylacrylamide) (PNIPAm). CNTs were thought to provide mechanical strength, while

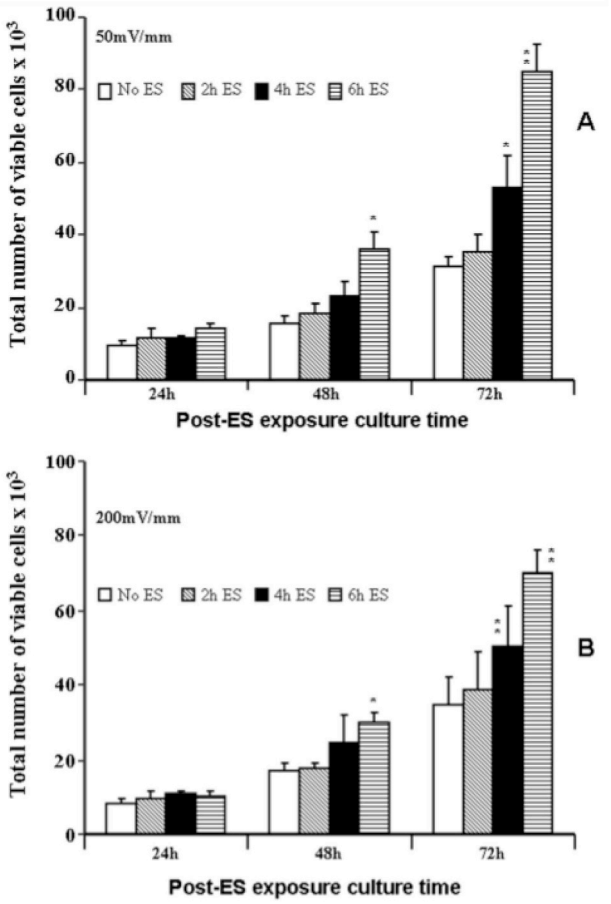

Fig. 11. The proliferative capacity of fibroblasts was maintained and elevated following exposure to electrical stimulation (ES) for 2, 4, or 6 h. The cells were then detached and used to investigate their proliferative capacity at longer periods (24, 48, and 72 h) post-exposure to ES. Viability was determined by trypan blue exclusion assay. Values are means 6 SD, (n = 6). The ES-exposed and non-exposed cultures were compared, with the difference considered significant at p, 0.05 (Rouabhia et al., 2013).

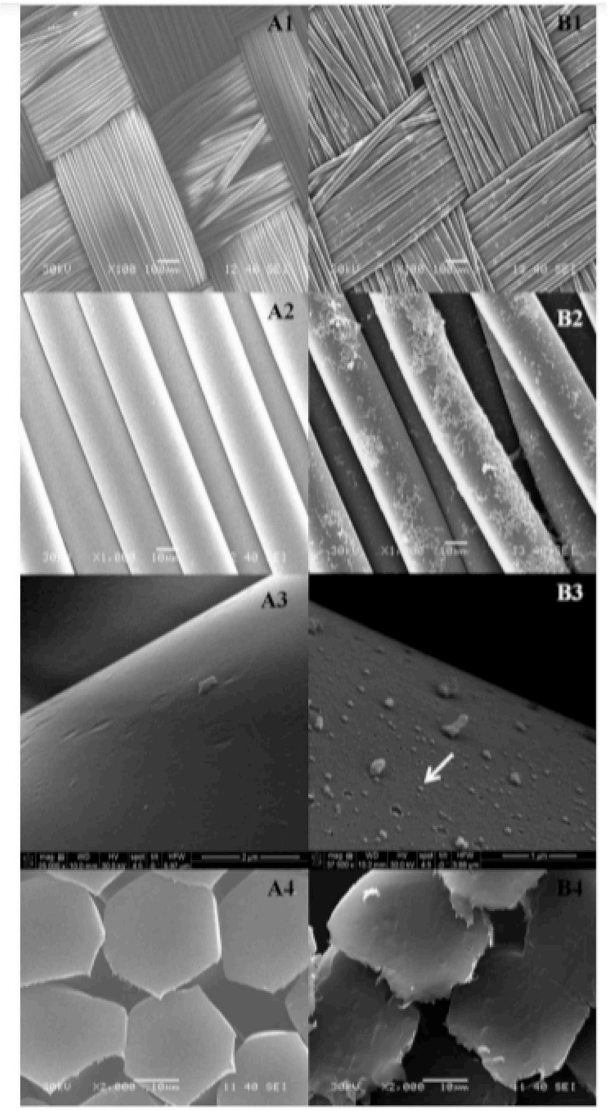

Fig. 12. Scanning Electron Microscopy photomicrographs of the polyethylene terephthalate (PET) (A) and polypyrrole (PPy)-coated PET fabrics (B), showing thin and uniform PPy on the surface of the microfibres without blocking inter-fibre space. The arrow indicates a PPy granule less than 100 nm in size (Wang et al., 2013b).

PNIPAm exhibits a temperature responsive nature. Above a lower critical solution temperature (LCST) of 32 °C, the PNIPAm chains exhibit hydrophobicity and become characterised by a compact and collapsed structure; as a result, cell attachment is better supported. By subsequently lowering the temperature to below 32 °C, the chains exhibit hydrophilicity and become elongated, allowing the cells to be detached and transplanted without the scaffolding material. This scaffold was confirmed to promote the attachment and growth of murine L-929 fibroblasts and displayed inflammation-sensitive properties, as observed using human umbilical vascular endothelium cells (HUVEC) and leukocytes (Patra et al., 2016).

Jin et al. described the use of a photosensitive semi-CP, poly(N,N-bis (2-octyldodecyl)-3,6-di(thiophen-2-yl)-2,5-dihydropyrrolo[3,4-c]pyrrole-1,4-dione-*alt*-thieno[3,2-*b*]thiophene), applied to an electrospun poly(ε-caprolactone) scaffold. Upon continuous exposure to red LED light stimulation for 9 days, it was found to promote the proliferation of human dermal fibroblasts. It presents an alternative mode for accelerating wound healing through the use of light-induced electrical stimulation (Jin et al., 2017).

Other authors looked at measuring pH in the wound bed to elucidate the presence and distribution of bacterial infection. This could be particularly useful for the monitoring of chronic wounds. Rahimi et al. created a pH sensor array comprised of carbon electrodes coated with proton-selective PANI and Ag/AgCl reference electrodes. This sensor array can be incorporated directly into wound dressings. It was found to detect pH with sufficient sensitivity, repeatability and stability, whilst its biocompatibility was demonstrated using human keratinocytes (Rahimi et al., 2016). Subsequent work by the same group demonstrated that a similar sensor was able to monitor pH changes associated with *S. epidermis* infection *in vitro* (Rahimi et al., 2018). This was preceded by work by Guinovart et al. to likewise create a PANI-based pH sensor for incorporation into wound dressings (Guinovart et al., 2014).

Korupalli et al. on the other hand utilised the acidic conditions present in the case of subcutaneous abscess bacterial infection to promote the assembly of PANI-conjugated glycol chitosan nanoparticles, leading to the aggregation of bacteria within the infected area. This subsequently allowed for the application of near-infrared light to facilitate photothermal ablation of the bacteria (Korupalli et al., 2017). A similar technique was earlier employed by Hsiao et al. using a chitosan (CS) derivative with self-doped polyaniline (PANI) side chains to likewise induce photothermal lysis of focal bacteria (Hsiao et al., 2014). Although subcutaneous abscesses are a type of localised infection situated beneath the skin, as opposed to an open skin wound, the employment of CPs to address their treatment nevertheless offers insight into the widespread utility of CPs in facilitating wound care.

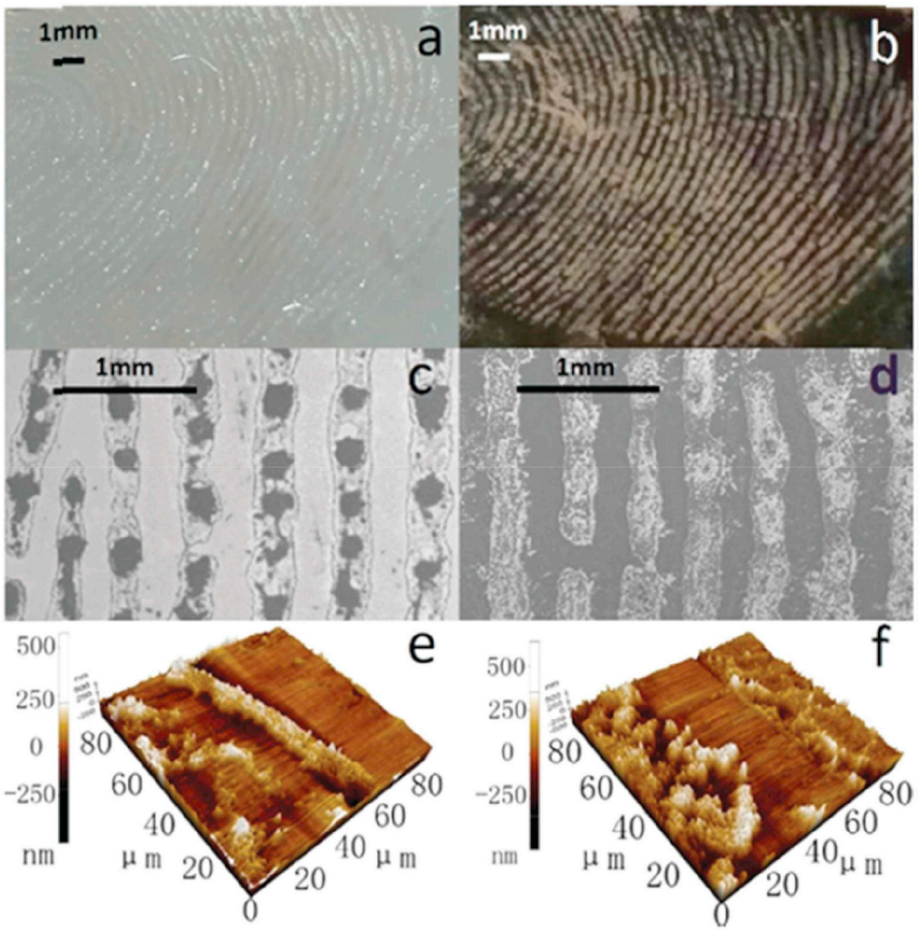

Fig. 13. Skin patterns on gold surface before (a, c and e) and after electropolymerization (b, d and f), taken with: high-resolution camera (a and b), FE-SEM (c and d) and AFM (e and f).

Lisak et al. have also investigated conducting-polymer-based materials for skin-related applications, namely application of CPs for a 3-D and electrically conducting skin mapping. For that, the PEDOT(PSS) was synthesized via electrochemical route after deposition of natural sebum on the surface of gold coated plastic substrates (Fig. 13). Since sebum acts as insulator, the CP deposited only on sebum unoccupied areas, thus the skin 3D features were recorded with sufficient resolution. Using this approach, various features of the human skin were patterned, such as fingerprints, scars, moles and pores. Moreover, the method was used for the direct polymerisation on live human skin, which was found feasible for 3-D and electrically conducting skin mapping. The method itself is under evaluation for the possible use in wound healing or treatment of pathological skin conditions (Fu et al., 2018).

3. Summary and conclusions

CPs offer much promise in terms of their potential clinical utility for wound management and skin tissue engineering. They may be used in the manufacturing of wound dressings, hydrogels, aerogels and skin tissue scaffolds that have increased electrical conductivity due to the intrinsically conductive properties of CPs. When used either alone or with the application of an external electrical stimuli, they have been shown to promote the proliferation of human skin cells. In addition, various rodent models have demonstrated a greater rate of wound healing when CP-containing materials were applied to full thickness skin wounds, compared to the application of non-CP controls. Another key advantage of CP incorporation into wound healing materials is that their inclusion has been shown to provide enhanced antimicrobial properties against a range of bacteria, including those commonly found in human skin wounds. In some cases this has been further increased with the use of silver nanoparticles. Finally, the incorporation of CPs into wound healing products also provides the opportunity for controlled drug delivery. Taking advantage of the electrical conductivity provided by CPs, an external electrical stimuli can be used to trigger the release of drugs or biological agents to the wound area. However more studies are required, particularly in relation to minimising the passive release of agents. Moreover, many studies thus far have only investigated one of the potential advantages of CP-containing materials at a time (for example antimicrobial activity or the effect of applying an external electrical stimuli) and have not looked at maximising cumulative advantages. Various CP-based materials mentioned in this review show promising function or potential in wound management or skin tissue engineering, but more and deeper investigations are needed to take better advantage of CPs and move closer towards clinical applications.

This review found that PANI and other oligoaniline derivatives were the most frequently reported CPs used in the fabrication of wound dressings. Both PANI and PPy were reported for the manufacture of hydrogels and aerogels. PPy was most often used for skin tissue scaffolds, although several of the studies originated from one research group. The findings of this review were limited to papers that focused specifically on skin tissue engineering and wound healing. Therefore, the results of studies that investigated CP use in other types of tissues such as cardiac and neural tissue are not discussed here. Nevertheless they may offer insights which could be applicable to skin tissue and

should be examined separately. Despite these limitations, this review found that CPs offer several advantages in regards to wound healing and skin tissue engineering and warrant further scientific investigation.

4. Future perspectives

Future research should continue to investigate the use of CPs in wound care and skin tissue engineering, as there appears to be further scope to capitalise on the various special properties of CPs. Specifically, authors should continue to examine which doping agents or other incorporated materials provide superior wound healing capacity, as well as biocompatibility and the required level of stability. Maximising the controllability and durability of CP-based materials under an electric field also requires further investigation. Further work is likewise needed in regards to the controlled delivery of drugs and other useful agents. The majority of studies conducted thus far, although providing promising results, have been primarily preliminary and explorative in nature, reporting findings mainly from *in vitro* models. Further work using more sophisticated *ex vivo* skin models or animal studies is required in order to provide increased support for potential human trials.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Credit author statement

Authors choose not to include the statement.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bios.2019.04.001.

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