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Electroactive composite for wound dressing

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ABSTRACT

Skin tissue engineering and wound healing are two applications where conductive biomaterials based on metal compounds, conductive polymers, or piezoelectric polymers have great potential. This is because of their excellent antibacterial and antioxidant activities, similar conductivity to human skin, photothermal effect, and electrically controlled drug delivery. Wound healing can be accelerated by using conductive materials to stimulate the activity of electrically responsive cells. Electroactive wound dressings can be made by combining non-conductive polymers with conductive compounds, and this article focuses on current developments in this area. It is detailed how these electroactive dressings (conductive polymers, metal-based, and piezoelectric-based dressings) accelerate the healing process, and the properties of these electroactive dressings are examined. Furthermore, electrical stimulation techniques for accelerating wound healing are discussed. The possibility for electroactive wound dressings to be used in vivo to track the progress of wound healing is also mentioned, as are future development directions.

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1. Introduction

The epidermis and dermis are two independent layers of the skin, which is the body's largest organ. The epidermis, the outermost skin layer, acts as an obstacle against pathogen entrance; the next layer, the dermis, provides elasticity and tensile strength [1]. Ions are transported across the epidermis by epithelial tissues, acting as an epidermal battery and creating a transepithelial potential (TEP). The epidermis maintains a TEP of 10–60 mV, corresponding to the entire polarized distribution of charges in the channels of ions in epithelial cells.

The epidermal battery is short-circuited in a skin wound that destroys

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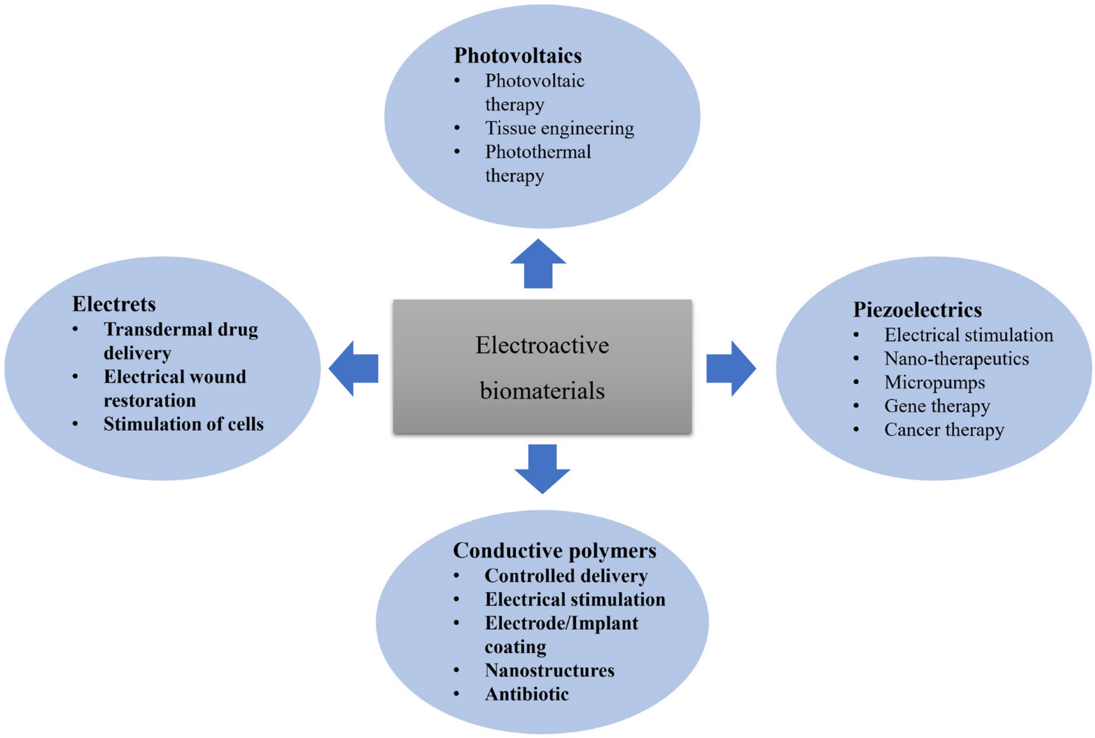

Fig. 1. Electroactive materials and their variable applications.

the epithelial barrier, causing the TEP to drop. In a wound that cuts the epidermis through completely, TEP is zero, which establishes an endogenous electric current or potential gradient from the unwounded epidermis to the wound. During the healing of the damaged skin, the endogenous wound current decreases as the resistance increases. Because the rise in resistance correlates to the process of epidermal repair, it may be used to monitor wound healing [2, 3].

As a new generation of smart materials, the electroactive biomaterials family (Fig. 1) provides direct transmission of electrical signals through the modulation of the electric potential. They have the benefit of being very active (that is, stimulating tissues while also activating controlled/responsive release therapies). By such systems, substitute delivery mechanisms in the care of the wound can be provided for scientists and clinicians which facilitate developing new therapeutic methods for the patients [4]. Electroactive biomaterials can have their electrical, physical, and chemical features proportional to their functional needs. Conductive polymers, piezoelectrics, photovoltaic materials, and electrets are examples of electroactive biomaterials [5, 6].

Up to now, wound healing physiology has been well known [7]. Hemostasis, inflammation, proliferation, and remodeling with various enzymes, cytokines, and growth factors are all overlapping aspects of the healing process, which exert a considerable effect on the synergistic modulation of relevant cell activities [8, 9]. There are different wound types, including excision wounds and acute incisions which have normal healing conditions, and chronic wounds with aberrant healing processes. Wound healing management differs depending on the tissue characteristics, inherent regeneration potential, wound categorization, and environmental factors. Vacuum-assisted closure, negative-pressure therapy, auto/allograft and xenograft, hyperbaric oxygen therapy, electrotherapy, engineered skin graft and cell-based therapy, ultrasound, growth factor, and topical drug delivery are all viable wound treatment options [10, 11]. The open wounds are hardly fit by conventional passive dressings such as bandage, cotton wool, and gauze. They also do not have an active influence on wound healing. Further, their adhesion to the skin leads to dehydration and secondary injury when they are replaced. Modern biomaterial-based dressings are recently in high demand for wound healing and have shown enormous advantages in more complicated situations, as they integrate many functions such as exudate management and protection against pathogens, maintenance of a moist environment, adhesiveness, injectability, self-healing capacity, antioxidant property, antibacterial capacity, and appropriate mechanical properties [12, 13]. In the last decade, a strategy of wound healing has emerged based on the conductive nature of the human skin and because of its high effectiveness, flexibility of processing, and simplicity of handling and maintenance has attained a lot of attention. Notable increment in wound treatment has been achieved by the advanced conductive biomaterial-based dressings which have similar conductivity to human skin [14, 15]. Their great potential has also been demonstrated in different wound types including diabetic wounds, infected wounds, and full-thickness acute wounds. Incorporation of electroactive substances which mostly include metal-based materials, conductive polymers (CPs), or carbon nanomaterials, into the polymeric biomaterial is the basis of conductive wound dressing fabrication [16-19]. To date, several conductive wound dressings have been developed in various forms such as electrospun nanofiber, cryogel, film, foam, hydrogel, and membrane [20, 21]. Furthermore, with the advanced development of regenerative medicine and tissue engineering, conductive scaffolds mimicking bioactive cells or extracellular matrix (ECM)-loaded molecules have also been developed for more drastic wounds such as chronic wounds with weak regenerative capabilities and open or large wounds, modulating cell activities and providing mechanical support. Highly porous structures of foam, hydrogel, sponge, and nanofibrous network make them ideal for scaffolds. Even so, the design and usage of conductive biomaterials have not been comprehensively reviewed for the skin tissue engineering and wound healing [22-24].

This review paper thoroughly describes the recent enormous success and tremendous promise of conductive wound dressings for skin tissue engineering and wound healing.

2. Principal of Wound Dressing Design

It is critical that a dressing not only serves the purpose that it states, but that it does so in a cost-efficient and therapeutically successful manner. Accurate clinical evaluation and diagnosis, as well as the selection of suitable therapy, result in cost efficiency. This might not be accomplished by selecting the cheapest product, and the duration of dressing wear might be as effective as the product selection [25]. When choosing a product for wound dressing, factors such as nursing costs, frequency of dressing changes, healing time, and additional needed products such as analgesics, antibiotics, and secondary dressings must all be considered. Sometimes it may be necessary to use multiple products, but this should generally be avoided. Some wound dressings, such as antimicrobial ones, may have an unfavorable effect on the function of cells; thus, their use should be limited to specific cases. Optimal healing is achieved by a perfect dressing or a combination of dressings that permit gaseous exchange, maintain high humidity, allow thermal insulation, remove excess exudate of the wound, minimize scar formation, conform to the surface of the wound, and facilitate debridement if necessary [26]. Except for an initially closed surgical wound, a single dressing type rarely provides a change in the wound bed condition of a non-healing acute or chronic open wound. The peri-wound tissues and the wound should carefully be assessed for dressing selection, and an evaluation of their performance should be done at each dressing change [27].

A different approach is required for the closed surgical wounds. The significance of preserving the optimal physiological conditions upon anesthesia and surgery is emphasized in the NICE guideline NG125. Selection of the dressing plays a role in wound outcome as a secondary factor, and the use of simple interactive dressings like a pad with the occlusive film is advised; moreover, topical antimicrobial components should not be used consistently [28]. To eliminate traction blistering upon exerting a post-operative dressing, a fitted dressing should be used to permit joint or limb mobility. Depending on the anticipated bioburden, alginate or hydrofiber with or without an antibacterial agent, should be used to manage the cavity of surgical wounds. Then, a secondary dressing like a foam or a hydrocolloid dressing should be applied to cover them [29]. Topical negative pressure (TNP) can also be effective. For diabetic patients, it is routinely used after digital ray amputation if the loss of a large area of tissue and exposure of bone and tendon in traumatic wounds occur and in an open abdomen or dehisced surgical wound management. An overall management plan is needed to use the dressings, which may include offloading for diabetic foot ulceration or pressure ulcers or compression therapy for venous disease. Dressings for non-healing acute or chronic open wounds should be chosen based on the wound bed condition and treatment goal, and regularly evaluated with the progress of treatment [30]. For example, debridement, as an ongoing procedure, might need to be repeated periodically all over the healing process, and different debridement methods are often used. This process is termed ‘maintenance debridement’. The wound bed color or percentage tissue type can be used to describe and document the wounds. Wound bed condition is commonly indicated by four basic descriptors [29].

Each Dressing has specific functions and is chosen based on wound site, the condition of the surrounding skin, exudate levels, wound hydration, and any background of dressing contact allergy or sensitivity. Three main issues require careful evaluation during conductive biomaterials design for wound healing. Matrix material selection is the first one. Naturally produced polymers with versatile biological properties, biodegradability based on hydrolytic or enzymatic reactions, and good biocompatibility can promote the healing of wounds; however, their quality differs from category to category. In contrast, great mechanical properties and more controlled structures have been provided by synthetic polymers, but because of their hydrophilicity, they have weak cell attachment [31, 32]. Other critical issues are degradability and biocompatibility, which limit their biomedical application. In addition, functionalization of synthetic polymers needs to be done for meeting biological requirements due to the lack of bioactivity. As a result, a combination of synthetic and natural polymers either by crosslinking or simple blending is used to integrate multifunction, such as suitable mechanical strength, specific bioactivity, degradability, and biocompatibility. Different synthetic and natural polymeric materials such as polyurethane, poly(lactic acid), polyvinyl alcohol, polyethylene glycol, poly(glycolic acid), polycaprolactone, hyaluronic acid, chitosan, alginate, silk fibroin, fibrin, cellulose, and gelatin have been employed to make wound dressings [33-35]. Because of the inherent unique qualities of the components and the production procedures, these biomaterials have a wide range of properties [36]. In addition to the composition, the structural morphology of biomaterials is another determining factor in the properties, performance, and fabrication method. typically, fibers, membranes, and films possess a two-dimensional (2D) structure, which provides tough mechanical properties, resistance to water, and good oxygen permeability. Hydrogels, sponges, and foams have porous structures and three-dimensional (3D) networks and can act as cell and bioactive substance carriers, preserve a moist environment, and absorb high levels of exudate [37]. Furthermore, the morphology of these biomaterials affects their application. Biomaterials with the 2D structure are usually utilized as wound dressings, while 3D ones can be fabricated as wound dressings and tissue scaffolds. Particularly, nanofibers have high potential in skin scaffolds through their programming into ECM-like architecture. Meanwhile, the morphology of these conductive biomaterials somewhat limits their application [38]. Biomaterials with 2D structure could not adapt to chronic and deep wounds, and tough foams cannot be applied on dry wounds and delicate skins. At the same time, hydrogel, which is soft in nature, might lead to dehydration of wounds and fail long-term applications because of the permanent wound movement and inevitable evaporation of water. It should be noted that in hybrid polymers (i.e., a combination of synthetic and natural polymers), choosing the fabrication techniques of these biomaterials is affected by their structural morphology. Meanwhile, to design 3D biomaterials, crosslinking is required resulting in a tough matrix via firm covalent bonds, while soft biomaterials usually result from dynamic covalent bonds and physical crosslinking [39, 40].

Incorporating conductive materials is one of the important step. Up to now, different types of these materials have been explored and examined. Their morphologies can be well adjusted and controlled in different forms such as nanosheets, nanoparticles, nanotubes, and nanowires, and have a notable effect on their properties [41]. Conductive materials have been extensively utilized in diverse fields, such as conductors, energy storage, supercapacitors, sensors, medical instrument and tissue engineering, etc. because of their relevant photothermal and antibacterial properties, excellent electroconductivity, and special optical properties [42-44]. However, most metals, metal oxides, carbon nanomaterials, and CPs are not soluble in aqueous solution and tend to aggregation which causes lower conductivity. As a result, their incorporation into the biomaterials is highly challenging and requires elaborate pretreatment to disperse homogeneously. Surface modification is a well-established approach for increasing the stability and solubility of these substances via noncovalent interactions or chemical conjugation, and with that grafting of hydrophilic substances including polymers and small molecules onto the conductive nanomaterials can be done. Polymer wrapping through

Table 1.
Wound type and color description.

Tissue type	Color
Necrotic	Black
Sloughy	Green/yellow
Granulating	Red
Epithelializing	Pink

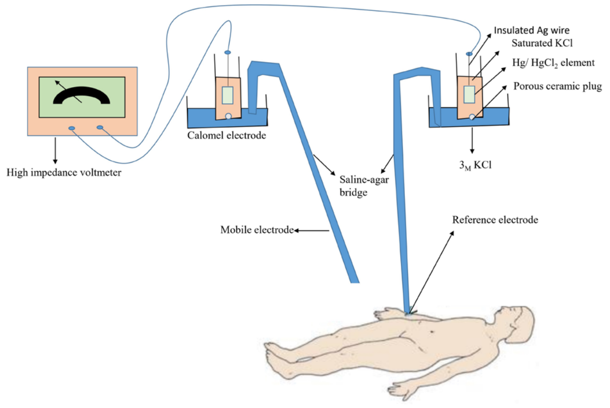

Fig. 2. A schematic of skin potential recording apparatus.

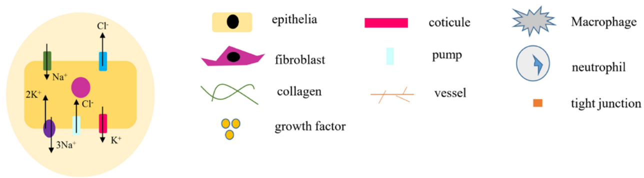

Fig. 3. Distribution of ion channels in epithelial cells. Epithelial cell Na + and Cl-channels are located in the apical cell membrane, and K + channels and Na + / K + ATPase are located in the basal protoplasmic membrane. Right side of the figure demonstrates skin compartments.

sonication and strong stirring has been effective to disperse conductive nanomaterials uniformly and prevent their aggregation. Furthermore,

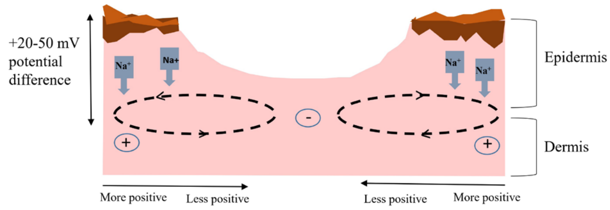

Fig. 1. FThe injury current is high in the initial stages of repair. Epithelial disruption generates wound electrical current.

conductive polymers can be functionalized via a doping mechanism [45, 46]. The degradability, cytotoxicity, and stability of CPs are also very important under physiological conditions. Degradation of metal nanomaterials and carbon nanomaterials cannot even occur in-vivo. The degradability, cytotoxicity, and stability of CPs are also very important under physiological conditions. Degradation of metal nanomaterials and carbon nanomaterials cannot even occur in-vivo. Furthermore, the mechanical features of the pristine biomaterials would greatly change by the conductive substance incorporation. The compromise and balance between the mechanical properties, biocompatibility, and conductivity should be comprehensively studied before in-vivo usage [47-49].

Novel inorganic conductive nanomaterials with the 2D structure such as transition metal nitrides and carbides (MXene) and black phosphorus (BP), due to their electroactivity, have recently gained a lot of interest and shown high potential in biomedical usage for antibacterial activities biodegradability, and photothermal effect. However, poor stability of these nanomaterials in liquid medium in ambient conditions hinders their application. While MXene and BP face many challenges and opportunities, their use in the healing of wounds is still in the early stages [50]. These conductive biomaterials are divided into two catego-

Table 2.
Example of conductive composite wound dressings.

Conducting polymer	Non-Conducting Polymer	Dressing Components	Dressing Form	Fabrication Technique	Conductivity [mS cm^{-1}]	External Electrical Stimulation	Ref.
PPy	PLLA	PPy/PLLA/FN/BSA	Membrane	Casting	2×10^2	No	[73]
	PAM	PPy-PAM/CS	Hydrogel	Crosslinking	10^{-3}	No	[74]
	PET	RC/PPy/Ag/IL	Film	Casting/Dipping	100	No	[75]
	PolyHEMA	PPy/polyHEMA	Hydrogel	Crosslinking	0.05–0.8	Yes	[76]
PANI	PCL	PCL/QCSP	Nanofiber	Electrospinning	-	No	[77]
	Chitosan	QCSP/PEGS-FA	Hydrogel	Crosslinking	2.25–3.50	No	[72]
	PU	PU/AT/Siloxane/Ag	Membrane	Sol−Gel Reaction	2.7–45	No	[78]
	PVA	PVA/PANI/PDA/AgNPs	Hydrogel	Crosslinking	-	No	[79]
PEDOT	PLA/PHBV	PEDOT/PSS/PLA/PHBV	Membrane	Electrospinning/Dipping	$0.22–1.45 \times 10^{-3}$	No	[80]
	PEG–PPG–PEG	PEDOT/Glycol	Film	Vacuum Vapor Phase Polymerization	$2–15 \times 10^5$	No	[81]
	Guar Gum	PEDOT: PSS/CG	Hydrogel	pH-dependent Sol-Gel transition	1.04–2.22	No	[82]

PLA, polylactide acid; PHBV, poly(3-hydroxybutyrate-co-3-hydroxyvalerate); PSS, poly-(styrenesulfonate); PEG–PPG–PEG, poly (ethylene glycol–propylene glycol–ethylene glycol); PLLA, poly(L-lactic acid); CG, cationic guar gum; FN, fibronectin; BSA, bovine serum albumin; PAM, polyacrylamide; CS, chitosan; Ag, silver; RC, regenerated cellulose; IL, ionic liquid; PET, polyethylene terephthalate; polyHEMA, poly(2-hydroxyethyl methacrylate); QCSP, polyaniline-grafted quaternized chitosan; PEGS-FA, benzaldehyde group-functionalized poly(ethylene glycol)-co-poly(glycerol sebacatePCL, poly(ϵ-caprolactone); PU, polyurethane; PVA, polyvinyl alcohol; AT, aniline tetramer;; PDA, polydopamine; AgNPs, silver nanoparticles

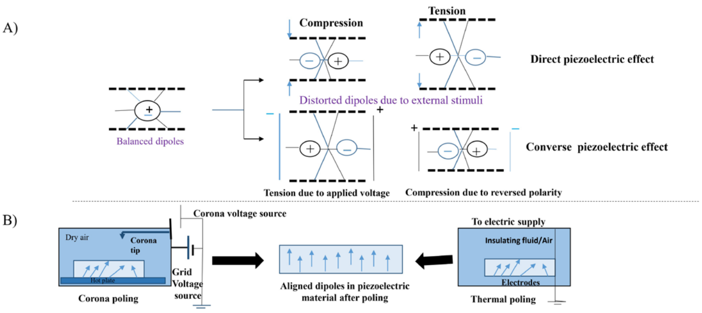

Fig. 5. a) Direct and converse piezoelectric effect. b) Poling procedures for maximizing piezoelectricity.

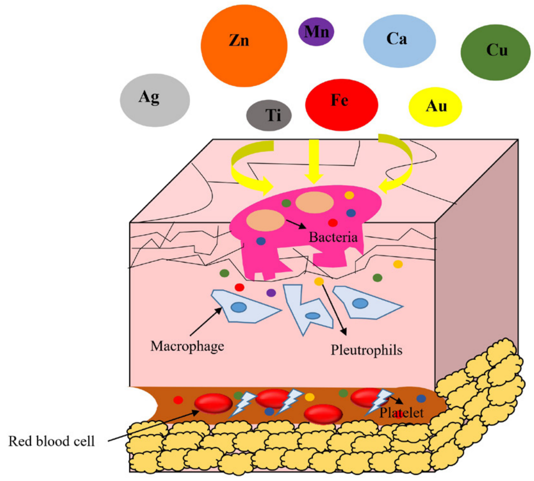

Fig. 6. Metal elements and their role in wound repair and gene and protein transduction.

ries: 2D conductive biomaterials and 3D conductive biomaterials. We also provide a quick overview of the manufacturing process for adding conductive materials into wound dressings and scaffolds [51, 52].

3. Wound Endogenous Electrical Field

Generation of endogenous electrical signals on the plasma membrane by electrical synapses (gap junctions), pumps, and ion channels are referred to as bioelectricity. Barker et al. introduced the “skin battery” theory after measuring the voltage (10–60 mV) in skin wounds of human and hamster with a recording instrument (Fig. 2) [53]. The intensity of the electric field (EF) was believed to be negatively proportional to the distance from the wound’s edge. In acute skin wounds, the endogenous electric field (EED) has been reported to be related to wound surface size. Then, the generation of EED on skin wounds has been found to be connected with the directional ion transport by polarized epithelial cells [2]. The channels of Cl– and Na+ ions are placed in the apical plasma membrane (PM) of epithelial cells, while the Na+/K+-ATPase and K+ channel are placed in the basal PM (Fig. 3A). The current is established across the cell by this asymmetrical distribution of ion channels. Meanwhile, trans-epithelial potentials (TEP) are formed by the directional ion transport via epithelial cells (Fig. 3B). It has been reported that short-circuiting TEP causes the wound current after epidermis damage (Fig. 3C) [54, 55]. The wound site acts as a cathode in comparison to the surrounding normal skin. A direct current with low intensity transfers from the intact skin to the wound because of the difference of electric potential between the intact skin around the wound and the damaged site. The major components of wound current are Na+ and Cl–, which means the ion flow is responsible for the wound current; hence pumps of Na+ and Cl– ions play a critical role in wound electric potential maintenance [56].

Table 3.
Classification of piezoelectric materials.

Ceramics	Polymers	Others
Barium titanate	Poly-L-lactic acid	Diphenylalanine
Lithium sodium potassium niobate	Polyvinylidene fluoride	Boron nitride nanotubes
Lead zirconate titanate	poly(vinylidene fluoride-trifluoroethylene)	Collagen
Hydroxyapatite	Polyhydroxy-butyrate	silk
Lithium niobate		
Lithium niobate		

In addition, the endogenous electric potential of the skin, known as the endogenous skin battery, affects the wound healing process. In intact skin, between the sub-epidermal and epidermal layers exists a natural electrical potential of 10–60 mV. Mainly, the ions transmission via ion channels and frequentative cell depolarization and repolarization are responsible for this. Around a wound, TEP largely rises [57]. As seen in Fig. 4, a short-circuit is created to the TEP by epithelial disruption via an injury, which drives positive electrical flow to the wound. In fact, an electric current is produced by Injuries and the voltage difference between the intact skin and wound site has shown to be in the range of 100-150 mV/mm [58].

Endogenous currents act as a sign for migration of the cells, which simultaneously aid wound healing; hence these EEDs play an important role in the healing process of the wound. It should be noted that the average rate of healing is estimated to decrease by 25%. This phenomenon has prompted researchers to utilize electrical stimulation (ES) to accelerate wound healing [59, 60].

4. Conductive-Based Composite for Wound Dressing

A compromise between the optical, electrical, and magnetic features of metals and mechanical properties and the simplicity of processing of polymers can be provided by conductive polymers. The available conductive polymer systems are currently over 25 [61, 62]. Poly(3,4-ethylenedioxythiophene) (PEDOT), polyaniline (PANI), and polypyrrole (PPy) are the ones that have been widely studied. Easiness of jump of electrons between and within polymer chains of CPs makes them electrically conductive. The “dopant” is a critical factor of this conductivity. Synthesis of CPs is done in an oxidized state and to enter the polymer they need anion molecules (dopant) [63, 64]. This can cause the stabilization of the polymer backbone. Acharge carrier is introduced into the system by this dopant since it adds or removes electrons to/from the polymer chain and thereby creates bipolarons or polarons. Bipolarons and polarons are localized, weakly bonded electrons surrounded by a distortion in the crystal lattice. With applying an electrical potential, the dopant molecules’ movement within or outside of the polymer disrupts the backbone. This provides passage of electrical charge (in the form

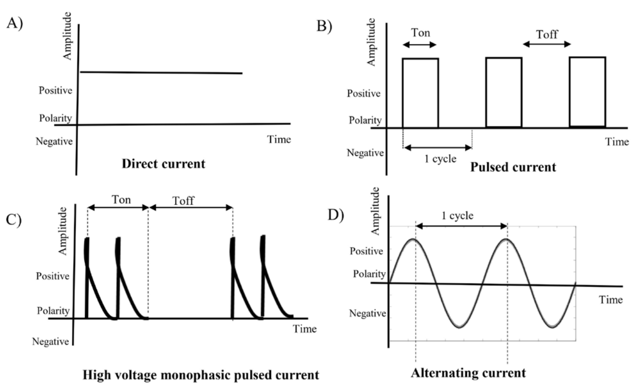

Fig. 7. Waveform characterization a) DC b) PC c) HVMPC d) AC

of bipolarons and polarons) through a polymer. It has been shown that many of the conductive polymers display good biocompatibility in animal models and are cell friendly, which means they support the growth of a wide variety of cells. For instance, it has been reported that PPy supports the differentiation, growth, and adhesion of glial, bone, neural, and endothelial cells in addition to fibroblast, mesenchymal, and keratinocyte stem cells [65-67]. Similarly, the biocompatibility of PEDOT has been shown with epithelial cells, neuroblastoma, neural cells, the NIH3T3 and L929 fibroblasts cell lines [68].

It has been proven that conductive materials promote the activities of the keratinocyte and fibroblast cells [6]. In addition, antibacterial property has been shown by CPs like PANI. These advantages make CPs ideal biomaterials for usage in wound healing [69]. For instance, a double full-thickness skin wound model was employed on the dorsum of SD rats to evaluate the wound healing efficacy of conductive nanofiber composites (CNCs) composed of chitosan oligosaccharide, poly(vinyl alcohol), and poly(aniline-co-amino-benzenesulfonic acid). Compared to the control group, CNC dressing displayed fewer provocative responses. After 15 days of treatment, the complete healing and increased granulation and collagen were presented by conductive dressing relative to the control group. This suggests the promising application of CNC for wound healing [70]. A synergistic effect in the improvement of both fibroblast and osteoblast growth was shown by PANI/chitosan (1:3) nanofiber due to its proper conductivity and hydrophilicity, which indicates its potential for wound healing usage [71]. Injectable benzaldehyde-functionalized poly- (ethylene glycol)-co-poly(glycerol sebacate) (PEGS-FA)/quaternized chitosan-g-PANI hydrogels were developed and showed free radical scavenging capacity, good electroactivity, robust mechanical properties, adhesiveness, biocompatibility, conductivity, and antibacterial activity. In a full-thickness skin defect model, remarkably increased wound healing and great blood-clotting capacity in-vivo was presented by the hydrogel with a 1.5 wt.% cross-linker in comparison with Tegaderm film (commercial dressing) and nonconductive quaternized chitosan/PEGS-FA hydrogel. The results have shown that, it could promote the deposition of collagen and thickness of granulation tissue and upregulate the gene expression by growth factors such as TGF-β, EGF, and VEGF. Some examples of conductive composite dressings are presented in Table 2 [72].

5. Piezoelectric-Based Composite for Wound Dressing

Since the Curie brothers discovered piezoelectric materials in 1880, they have been used in a variety of fields, including biomedical equipment, energy harvesting, drug delivery, and tissue engineering. These materials respond to applying the mechanical deformations by charge generation (i.e., direct effect) and also to applying the EFs by deformation (i.e., converse effect). Non-centrosymmetric chemical/crystal structure of these materials is responsible for this effect since their deformation with applying a force leads to a net dipole formation, causing electric polarization. In spite of being piezoelectric inherently, the dipoles in the bulk material are oriented randomly and should be rearranged for enhancement of their piezoelectric properties. To perform such rearrangement, the procedure termed poling is used. In this procedure, a high EF is applied at a specific temperature, and the material is subsequently cooled under the same EF [83]. Fig. 5 illustrates the poling procedures and representation of piezoelectric effects.

Piezoelectric materials can be based on ceramics or synthetic polymers, hydrogel systems or natural materials (a list of piezoelectric materials is presented in Table 3). These materials can be made in macro-, micro-, or nano- structures. Hence, they can be used for the controlled and efficient release of therapeutic agents and drugs. The scientific community should pay a lot of attention to how these materials could be

Table 4.
PENGs for wound healing.

Piezo materials	Structure	Features	Ref.
BTO*	TiO2/BTO/Au heterostructure	In vitro: photodynamic bacteria-killing via ROS* generation In vivo: enhanced infected wound healing	[86]
ZnO, P(VDF-TrFE)*	P(VDF-TrFE)/ZnO nanocomposite scaffolds	In vitro: higher cell viability, adhesion, and proliferation In vivo: angiogenesis promotion	[87]
Polydopamine	Polydopamine coating on chitosan film (CM@DA)	In vivo: wound regeneration promotion in rats via upregulation of Hsp90 and HIF-1Î±* expression	[88]
PVDF*	Polyurethane/PVDF scaffolds	In vitro: enhanced fibroblast migration, adhesion, and secretion In vivo: higher fibrosis level	[84]
P(VDF-TrFE) nanofibers	P(VDF-TrFE) nanofiber scaffolds	In vitro: 1.6-fold increase in fibroblast cell proliferation rate; electric output: 1.5Â V, 52.5 nA In vivo: maximal 6-mV and ~6-Î¼A electric output via rat leg motion	[89]
ZnO, P(VDF-TrFE)*	P(VDF-TrFE)/ZnO nanocomposite scaffolds	In vitro: higher cell viability, adhesion, and proliferation In vivo: angiogenesis promotion	[87]
PVDF nanofibers	Bioinspired hybrid patch with PVDF nanofibers aligned on mussel-inspired hydrogel matrix	In vitro: fibroblast proliferation and migration promotion, facilitating collagen deposition, angiogenesis, and re-epithelialization In vivo: mouse wound closure time reduction of approximately one third	[90]
ZnO NRs*	ZnO NRs aligned on PDMS*	Bidirectionally grown ZnO NR-based piezoelectric patch In vitro: enhanced skin-cell regenerative activity In vivo: enhanced wound healing in rats	[91]

used in medicine.

Guo et al.[84] used electrospun polyvinylidene fluoride (PVDF)/ polyurethane (PU) blends to investigate the piezoelectricity effect on fibroblast activity and wound healing. They employed flexible-bottom culture plates with the ability of biaxially stretching for mechanical deformation. Since the increase in PVDF/PU ratio was accompanied by decreasing the mechanical properties and also increasing the piezoelectric coefficient of the composite scaffolds, PVDF/PU of 1 was used as the optimum composition to culture mouse embryo fibroblasts. According to Arinzeh et al.'s findings, a comparison of the DSC thermograms, FTIR spectra, and XRD patterns of electrospun PVDF/PU scaffolds and PVDF powder revealed that electrospinning causes phase transition from α to β [85]. With comparing the wound healing rates of the cultured fibroblasts on the three groups, the electrospun PVDF/PU scaffolds deformation at 0.5 Hz by 8% was shown to nearly double the migration of the cells towards the scratched area after 24h over deformed PU and undeformed PVDF/PU scaffolds (control specimens). In addition, in comparison with control specimens, the number of attached cells to the PVDF/PU was greater. Their findings showed the piezoelectric response caused to the enhancement of adhesion and migration, not just microstructure or deformation. Guo et al. also did the implantation of PU and PVDF/PU scaffolds in three parts of the rat body: abdomen and back with higher deformation; vertex with higher blood flow and less deformation. By histological imaging, similar fibrosis levels of the three scaffolds were shown in PVDF/PU group, triggering the piezoelectric response from the PVDF/PU scaffold. Whereas in the PU group, the vertex scaffold was shown to have increased fibrosis over the abdomen or back scaffolds. Further, fibrosis levels in PU scaffolds were lower than in PVDF/PU scaffolds in all parts of the body. This was attributed to the change of the intracellular ion channels resulting from the alternation in the cell membrane permeability [84]. The summary of investigations on PENGs (piezoelectric nanogenerators) for the healing of the wound and their key results are presented in Table 4.

A wound dressing based on polyhydroxybutyrate/chitosan (PHB/ CTS) and PVDF nanofibers was fabricated and loaded with gentamicin. It was reported that the addition of the PVDF layer dramatically improves the mechanical properties. This membrane can be employed to treat post-surgical ulcers [92]. PVDF, as a porous membrane, possesses chemical stability and high durability. It is commercialized under different trade names. Its average pore size is about 0.45µm. The high porosity of this membrane makes it the ideal substance for carrying a drug [93]. However, in an aqueous media the application of PVDF is limited because of its hydrophobic characteristics [94]. The grafting of inclusion compounds or hydrophilic polymers including poly (dimethylamino ethyl methacrylate) (poly (DMAEMA)), Maltodextrin, polyacrylic acid (P (AAc)), etc. onto the membrane have been used to solve this problem. In this regard, Jarvinen grafted pH-sensitive acrylic acid (PAA) onto porous PVDF membranes and used them for FITC dextran, DL-Propranolol-HCl, and sodium salicylate delivery. Stimuli-responsive drug delivery system contains a negatively pH-responsive cross-linked hydrogel and a positively pH-responsive grafted gating inside the PVDF porous membrane [95]. Because of the pumping effect of hydrogels and linear grafted gates, this system presents high release and fast response. In smart controlled-release systems, the synthesized pH-responsive membrane can be a viable option for a drug carrier [96].

6. Metal-Based Composite for Wound Dressing

The repair of the wound is a set of interactions of complicated processes including expression of genes, synthesis of proteins, and transduction of signals. Copper, zinc, calcium, iron, and other common metal elements must be considered in the wound repair management and the wound infection prevention (Fig. 6) [97-101].

Biomaterials based on metals have been employed for wound healing. Metals like Cu and Au, and metal oxides like ZnO are the main types of metal-based materials, prepared in different nano-forms for wound healing application. Due to their large surface areas, these materials in nanoscale could be easily physically or chemically modified and exhibit notable conductivity and good biocompatibility [102-105]. The summary of previous research on metal-based composite dressings is presented in Table 5.

HPMC, methylcellulose; PF127, Pluronic F127; PET, polyethylene terephthalate; PTFE, polytetrafluoroethylene; CS, chitosan; MMT, 2-mercapto-1-methylimidazole; PDMS, polydimethylsiloxane; BDG, bidirectionally grown; NR, nanorod;

The cellular structures of bacteria get significantly damaged in contact with gold nanoparticles (AuNPs), leading to their death [109]. The blending of AuNPs into thermoresponsive hydrogels containing hydroxypropyl methylcellulose (HPMC) or Pluronic has been recently done. The in-vivo histopathological results show that wound healing properties with excellent antibacterial activity can be achieved by as-prepared thermoresponsive hydrogels [108].

It was reported that mechanical displacement resulting from the movement of the skin could be converted into an alternating discrete EF by a wearable nanogenerator fabricated by overlapping the electropositive (Cu) and electronegative (Cu/polytetrafluoroethylene) layers. This nanogenerator was developed for wound healing. In the rat model, the results show promoting the wound closure along with the EF and facilitating the fibroblasts differentiation into myofibroblasts via the alternating discrete EF generated by the nanogenerator. Hence a contraction force is provided by this EF which accelerates the regeneration of the wound [104].

According to the studies, ZnO nanoparticles have been employed in wound healing. A piezoelectric patch was produced as an electroactive wound dressing by aligning bidirectionally grown ZnO nanorods over polydimethylsiloxane (PDMS). The as-fabricated piezoelectric patch can induce ES at the bed of the wound by creating a piezoelectric potential in response to mechanical deformation caused by animal motion.

Table 5.
Metal-based conductive wound dressings

Non-Conducting Polymer	Dressing Components	Dressing Form	Fabrication Method	External Electrical Stimulation	Ref.
PDMS	BDG/ZnO/NR/PDMS	Hydrogel	Spin Coating	Yes	[91]
Gelatin	CS-Au@MMT/Gelatin	Hydrogel	Crosslinking	No	[103]
Nylon	Silver/Nylon	Pad	Impregnation	Yes	[106]
Polyester	Ag/Zn Dots	Sheet	Printing	No	[107]
PET	Cu/PTFE/Cu/PET	Bandage	Deposition	Yes	[104]
Cotton	Ag/Zn@Cotton	Nonwoven	Magnetron Sputter	No	[102]
HPMC	AuNPs/PF127/HPMC	Hydrogel	Crosslinking	No	[108]

In-vitro and in-vivo studies reveal that the applied piezoelectric patch can aid protein synthesis, cellular metabolism, and migration, accelerating the process of wound hea [91, 110].

7. Electrical Stimulation Techniques for Wound Healing

ES is utilized for different clinical applications including wound healing, fracture repair, and pain management. Electricity is used in a variety of ways, including alternating current (AC), direct current (DC), low-intensity direct current (LIDC), and high-voltage pulsed current (HVPC). Pulsed electromagnetic field (PEMF) and transcutaneous electrical nerve stimulation (TENS) are more familiar to physicians to repair the fracture and control the pain, respectively [107]. Frequency rhythmic electrical modulation systems (FREMS) are a type of transcutaneous electro treatment employing ES which differs in terms of duration, frequency, voltage, and pulse. Even though the wound healing and ES research have employed several types of ES, they all have seemed to achieve positive results [112].

7.1. Direct Current (DC)

DC is also referred to as galvanic current. As displayed in Fig. 7A, DC is a unidirectional electric current flow with the flow duration greater than 1s, giving DC no waveform. Two polarities exist: the positive pole, referred to as the anode, and the negative pole, referred to as the cathode [113]. The current direction is from the cathode toward the anode. In DC, until the polarity is not manipulated manually, it remains constant. The electrothermal effect occurs when a continuous current flows through an object. The living tissue may be faced with the burn injury by the exceeding electrothermal effect, and it causes an electrophysical effect. Meanwhile, constant usage of anode and cathode can result in the electrochemical effect whereby attraction of chloride and sodium ions are occurred, respectively, forming acidic hydrochloric acid and sodium hydroxide that cause a chemical burn. In the DC ES study, polarity, current or voltage to express field strength, and exposure duration are the important parameters [114, 115].

7.2. Pulsed Current (PC)

As demonstrated in Fig. 7b, PC is a bi-directional/uni-directional pulsating current flow with a duration shorter than 1s and a longer inter-pulse interval, in which there is no current [116]. PC can be classified various ways according to amplitude, waveform, frequency, and duration. PC has been widely investigated since its pulsating characteristics lead to lesser electrochemical, electrothermal, and electrophysical side effects relative to DC. Delivered current in the majority of PC protocols is less than 20mA. The most common PC is high voltage monophasic pulsed current (HVMPC) (shown in Fig. 7C) possessing twin spikes of high-voltage (100–500V) current. It delivers 2–50mA in a pair. The cellular galvanotaxis is affected by exposure time, field strength, and duty cycle, but not by frequency. Therefore, adjustment of PC can be done, since the high-frequency (≥4000Hz) PC is shorter than the refractory period of nerve, and is sensed by the skin without pain stimulus [117].

7.3. Alternating Current (AC)

AC is the continuous bidirectional current flow, changing its magnitude and direction (at least once per second), periodically. The delivery of AC can be done in different asymmetrical/symmetrical waveforms. Sine-wave (Fig. 7D) is the most common one, which reverses its direction every half cycle. In AC, the electrodes' polarity alters every cycle, thereby chemical by-products and heat do not constantly accumulate over the electrodes. However, AC has not been widely investigated in the field of wound healing [114, 115].

8. Future Perspective

Conductive materials have the potential to improve the efficiency of exogenous/endogenous ES by aligning/guiding the migration of the cells to the wound, hence accelerating the healing process. Some commonly used wound-healing agents may lose their conductivity over time because of reducing or losing their dopant in the physiological media. This may limit their ability to promote wound closure. Covalent organic frameworks (COFs) and metal organic frameworks (MOFs) have recently gained a lot of interest as drug carriers for therapeutic usage [118]. The conductivity can be maintained constant in physiological media by COFs- and MOFs- based materials. Hence, these materials may have the potential for wound healing by their incorporation into electroactive dressings. Aside from their cytotoxicity, the degradation of metal- and carbon-based materials do not occur in-vivo because of their structure, surface functionality, size, or porosity. Hence, they should be comprehensively evaluated before their incorporation into the composite wound dressings. The regeneration process of the skin is considered to be complex and involve continuous and sometimes overlapping phases. Effective management and care of the wound depend on practical, reliable, and noninvasive monitoring of the wound healing progress. Conventional healing monitoring focuses mostly on visual evolution, which lacks applicatory standards and is subjective. In addition, for each visual examination, wound dressing removal may disrupt the newly formed tissues, leading to secondary injury and prolonged healing [119, 120].

To collect objective information about the wound condition, the development of smart wound dressings has been recently noticed. These dressings enable scientists to detect the physicochemical indications including inflammatory cytokines, lactate, temperature, glucose, or pH at the wound site, without removing the dressing. Nevertheless, to fully monitor the entire process of healing, these approaches may not be sufficient, as they are mainly effective only in one phase of wound healing. Hence, new techniques are needed to continuously monitor the progress of wound healing. The use of electrodes for daily measurement of the transcutaneous impedance or electrical resistance at the wound site has been proposed and studied as a new healing approach. According to the results, both impedance and electrical resistance enhance with wound healing progression, which provides valid measures of the wound status [121, 122]. To sense impedance and electrical resistance at the wound site, conductive dressings can be employed as the electrodes. However, it should be considered the distinction between skin tissue resistance and conductive biomaterial resistance. There is a great opportunity to develop conductive materials that provide the ability to simultaneously promote activities of the cells, which is accompanied by wound healing, and monitor the healing progress. Individualized treatments can be realized in different stages of wound repair and regeneration by dual-function electroactive dressings, which accelerate healing processes.

9. Conclusions

Endogenous electrical potentials are naturally generated surrounding a wound, and guide cell migration to the injury site, causing acceleration of the healing process. To mimic this physiological process, exogenous ES is utilized and has been shown to accelerate wound healing. As expressed in this paper, ES enhances fibroblast migration, stimulates keratinocyte activity, controls the growth of bacteria, enhances wound blood perfusion, induces angiogenesis, and limits inflammation. This is relevant for both chronic and acute wounds. In addition, ES (particularly pulsed current) notably decreases chronic wound size relative to control groups (specimens without ES). ES can be used as an adjunct treatment to manage chronic wounds. Nevertheless, because of the variations in the experimental protocol of the studies, the most efficient ES cannot be deduced from this paper. Furthermore, research on chronic wounds did not compare various ESs to determine an optimal type. Comparing the different types of ES and monitoring any long-term side effects can be subjects of future trials to prescribe a certain type that leads to the most successful healing. Additionally, we anticipate that electroactive biomaterials can be used in advanced technologies of wound healing. Recent advances in nanogenerator technology that allow the production of self-sustaining ES for use as a wearable wound-healing device highlight the possibility of novel prospects in wound care management.

In summary, the typical strategy for the conductive biomaterial's fabrication is the incorporation of minute quantities of conductive material into the nonconductive polymers, and as a result their properties are mainly affected by the crosslinking methods and the matrix polymer selection. Meanwhile, conductive biomaterials can be combined with other bioactive components and cells to accelerate the process of wound healing in multiple channels. This is an efficient approach and requires more investigation. Additionally, in the next decades, with the bioelectronics and nanogenerators development, the real-time assessment and electrotherapy of the wounds by conductive biomaterials will progress considerably. Significant achievement in real-time wound diagnosis, skin tissue regeneration, and wound healing has been made by conductive biomaterials used as an electrode or wound dressing. On the basis of these accomplishments and the burgeoning development of new technology, we anticipate that conductive biomaterials will make remarkable advancements in wound healing.

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