Self-Responsive Electrospun Nanofibers Wound Dressings: The Future of Wound Care

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1. Introduction

The ability to absorb wound exudate, suitable strength, maintaining a moist environment around the wound, permeability to gas, nontoxic, biocompatible, nonadherent, readily detachable, and infection control capabilities are some of the key qualities of an excellent wound dressing (see Figure 1) [1, 2].

In our earlier assessment, it was said that conventional wound dressings were merely used to cover the wound; however, today’s wound dressings include functional components for improved skin repair, infection prevention, and healing. Figure 2 depicts the development of wound dressings throughout various time periods. Due to their distinctive qualities, including morphological similarity to the natural extracellular matrix (ECM), higher surface area
to volume ratio, porosity, applicability as drug delivery systems, support tissue regeneration, wound fluid transportation, and ensure breathability for cellular growth and proliferation, drug delivery polymer nanofibrous by electrospinning are a promising research area for the wound healing process [2–5].

Electrospinning is one technique for producing nanofibers that makes use of electrostatic forces. When used in electrospinning, the polymeric solution acts as an electrode with a positive charge at the needle tip and a negative charge at a collector plate, creating a large potential difference between the two [6], then the Taylor cone is freed, and the rotating fluid core-sheath jet is propelled from the cone apex to produce fibers when the electrostatic forces are greater than the force of molecular bonding [7]. Figure 3 shows the working principles of electrospinning.

Every skin wound that develops for a variety of reasons contains some bacterial contamination that might not affect or delay wound healing. There is a cut-off point for bacteria, such as 105 colony-forming units per gram of tissue, which can cause infection and destroy skin tissue, as well as cause inflammation, discomfort, purulent discharge, and edema. As a result, to avoid tissue damage and sluggish wound healing, the wound infection must be identified and monitored at an early stage [8].

Researchers are currently focusing more on drug delivery systems utilizing electrospun nanofibers, however, conventional antibacterial or drug-loaded electrospun nanofibrous wound dressings constantly elute biocides based on the diffusion of the drug through the carrier matrix or nanofibers (referred to as passive delivery), even in the absence of bacteria, i.e., not in a systematic way that leads to overuse of antibiotics and antimicrobial agents that may cause toxic effects to the patients, increase costs and decrease healing [9, 10].

Therefore, it is important to avoid overusing antibiotics and antimicrobial agents in favor of an active delivery system drug delivery system that can release the drug payload at a controlled rate in the wound area. Releasing the drug could be activated by biochemical biomarkers such as bacteria, oxygen, cytokine, enzyme, metabolic by-product, pH [11, 12], and physical biomarkers such as temperature, pressure, and moisture content. Alternatively, the release could be triggered in response to external stimuli including magnetic fields, electric fields, light, ultrasound, etc., as well as environmental factors like pH, temperature, enzymes, chemical reactions, and redox reactions [10, 13, 14]. Self-responsive electrospun nanofibrous wound dressings made from self-responsive materials are the name given to the electrospun nanofibrous produced by adding these kinds of materials [15]. This will reduce the frequency of dressing
changes, the cost of health care, and patient pain [16]. As a result, the purpose of this review is to study the latest self-responsive smart electrospun nanofibrous wound dressings and the materials used to develop these smart nanofibrous wound dressings in detail.

2. Self-Responsive Materials for Electrospun Nanofibrous Wound Dressings

Smart materials are those that can be integrated and respond to actions during the complicated wound healing process [1]. Different smart materials or compounds such as halochromic chemical compounds [17] hydrogels [4], UV-photo-cross linkable materials [18, 19], and shape memory polymers [20] can be electrospun into nanofibrous wound mats.

Halochromic pH sensing materials may be of synthetic or natural origin, such as bromothymol purple, bromothymol blue, bromocresol green, fluorescent dye, and anthocyanins (from plant extracts such as carrot and cabbages), can change color when exposed to pH changes [21]. Different researchers incorporated these materials into nanofibers for wound monitoring. Different wavelengths of visible light can absorb by pH-detecting dyes [17].

There are also hydrogels that respond to external stimuli like pH, temperature, and light that could be used to develop self-responsive wound scaffolds. Thermo-responsive hydrogels are among smart hydrogels that respond to temperature change and are biocompatible, degradable, and reversible sol-gel conversion controlled by temperature change used in biomedical applications [4].

Self-responding drug delivery systems can also be made with thermo-sensitive polymers. At some critical solution temperatures in an aqueous medium, these polymers will quickly undergo a phase transition. These polymers are classified into two types based on how they react to heat: upper critical solution temperature polymers and lower critical solution temperature polymers [15]. Poly(N-isopropylacrylamide) is one of the temperature-sensing polymers used as drug delivery nanofibers [22]. Polymers that respond to pH, such as Eudragit L100, are also widely used in the development of self-responsive nanofibers for drug delivery as they can dissolve at some pH value but not dissolve in another pH [5, 23]. Some polymers, such as shape memory polyurethane polymer, change their shape in response to external stimuli (temperature, pH, and force) and then return to their original shape when the external stimuli are removed, making them suitable for use as controlled drug release self-responsive nanofibers [20]. The different responsive materials used in the wound dressing development process for nanofibers are shown in Table 1.

3. PH-Responsive Electrospun Nanofibrous Wound Dressings

The pH of the wound bed is one of the key factors related to wound physiology in the wound bed [17], and the pH value varies for a variety of reasons. Healthy skin has a pH of 4–6 [24–27], which is slightly acidic and helps to block or inhibit the spread of bacteria. In the wound-healing phase, the pH ranges from 5.5–6.5, while the pH of the infected wound is greater than 6.5 (pH shifted from acidic to alkaline) [15, 28], and the pH of chronic wound ranges from 7.15–8.9 [25]. Active substances (antibacterial, antibiotics, and drugs) incorporated into nanofibrous materials can be either weak bases or weak acids, with pH variations causing their dissolution and release into the wound [17]. As a result, in order to achieve releasing effectiveness or to control the release of active substances (drugs) to the wound part, the wound pH should be adjusted.

The pH of the wound site can change due to dissimilar factors, including bacterial colonization, wound healing phases [17], and the healing process [29]. Figure 4 depicts the pH values of acute versus chronic wound types at various wound stages (different times). As a result, the pH of the wound site could be used as a parameter to indicate the progress or status of the wound [25]. Active substances...
To incorporate antibacterial, antibiotics, and other drugs into nanofibrous can be either weak bases or weak acids, with pH variations causing their dissolution and release into the wound [17]. As a result, in order to achieve releasing effectiveness or to control the release of active substances (drugs) to the wound part, the wound pH should be adjusted in a continuous manner by incorporating pH-sensitive materials into wound dressings [27].

To fabricate electrospun nanofibrous wound dressings, various different pH sensing materials (halochromic dyes, polymers) are used in textiles. Synthetic halochromic pH sensing dyes (bromocresol-bromocresol green) to “bromocresol green” for clarity. Please confirm. “green, bromothymol blue” or natural halochromic pH sensing dyes (anthocyanin) are available. Because halochromic dyes contain pH-sensitive chromophore groups, they can change their color under different pH conditions. Halochromic dyes can absorb different wavelengths of visible light due to the change in pH of the examined sample. These dyes can be incorporated into nanofibers to indicate wound pH through color change. As a result, an electrospun nanofibrous wound dressing with pH-sensitive dyes can help with wound follow-up or monitoring without removing the wound dressing [25, 29, 30].

Bromothymol blue and bromocresol green are pH-sensitive halochromic dyes that change color at different pH levels and can be used in medical applications. Bromothymol blue and bromocresol green are halochromic pH-sensitive dyes that change color at different pH levels and can be used for medical applications. Bromothymol blue has
a yellow color when the pH is less than 6.0, and the color gradually changes from green to blue as the pH rises.

Based on this knowledge, Kurečić et al. [17] used needleeless electrospinning to incorporate bromocresol green dye into cellulose acetate nanofibrous mat containing benzocaine (pain-reducing drug). In vitro study, the nanofibrous mat showed maximum drug release at pH 9.0, which is similar to the pH of an infected wound. Bromothymol blue dye was also incorporated into two-layer poly(methyl methacrylate-co-methacrylic acid)/poly(acrylic acid) nanofibers by Bazbouz and Tronci [31]. Bromothymol blue has a yellowish color at pH less than 6.0 and changes color gradually from green to blue as pH increases. It has been reported to be used for biomedical applications. Poly(methyl methacrylate-co-methacrylic acid) nanofibers demonstrated high pH indicator dye loading efficiency (>80% by weight) and a change in color pH > 7. The network of thermally-cross-linked poly(acrylic acid) network allowed high water uptake and swelling. However, when the same building blocks were configured in a single layer mesh of core-shell fibers, the dual functionality will be lost at which bromothymol blue will be released (70wt.%) even at acidic pH.

Synthetic halochromic pH indicator dyes, on the other hand, may be toxic or allergic [32], have negative environmental effects, and have a limited pH range that may require a combination of several dyes [33]. As a result, natural halochromatic pH sensing dyes derived from plants of colored fruits or vegetables, such as anthocyanins (compatible with human health, soluble in water, coloration at extended pH range, stable in photodegradation, and excellent color resistance at a higher temperature), have an advantage over synthetic halochromatic pH indicator dyes for medical applications [34, 35]. Anthocyanins extracted from purple cabbage are attractive due to their wide color spectrum depending on pH change, good water solubility, inexpensive, and easily accessible products [36]. Many researchers published their findings on anthocyanins extracted from purple cabbage and electrospun into various polymer nanofibers such as cellulose acetate, zein, and PVA nanofibrous. Devarayan and Kim [33] developed cellulose acetate electrospun nanofiber containing purple cabbage anthocyanin. The color of nanofiber mat changes when the pH changes from 1–14, having a unique color for each pH within the given range. Prietto et al. [21] also incorporated anthocyanin from purple cabbage into zein polymer nanofiber with pH-sensing ability, explaining the utility for pharmaceutical applications in wound care. In addition to pH sensing of PVA/purple cabbage anthocyanin nanofibers, Pakolpakçıl et al. [37] incorporated sodium alginate polymer to PVA/purple cabbage anthocyanin nanofibers to increase the healing efficacy. Pakolpakçıl et al. [35] extracted natural anthocyanins from red cabbage leaves and incorporated them into sodium alginate and PVA mixture solution to fabricate electrospun nanofibrous wound mat. The mat displayed different colors at various pH levels, which can be used to monitor wound healing. Devarayan and Kim [33] also incorporated anthocyanins extracted from red cabbage into cellulose acetate solution and fabricated nanofiber mat by electrospinning. The mat showed a capability to detect pH from 1–14 with a unique color code against each pH, stable pH sensing at different temperatures, at a prolonged time, reversible colors, and pH sensor was recoverable. Pakolpakçıl et al. [25] incorporated natural pH indicator anthocyanins extracted from black carrot into alginate/PVA nanofibers to develop pH-sensing sodium alginate/polyvinyl alcohol/anthocyanins composite nanofibrous wound dressing for monitoring wound healing. The color of the nanofibrous mat was different at different pH values in short period of time (red color in acidic medium, blue color in neutral medium, and black-green color in basic medium).

Another type of pH-stimuli material is pH-sensitive polymers, which have pH-dependent functional groups in their structure, such as hanging acidic groups (carboxylic and sulfonic acids) or basic (ammonium salts) groups that respond to pH changes in their environment by gaining or losing protons [38]. These polymers can be used to create responsive nanofibers for controlling wound status, controlled drug release, and controlled oxygen release to the wound, as oxygen, is essential for wound healing. Eudragit L100, Eudragit S100, Eudragit RS100, and their copolymers are among pH-sensitive polymers used in developing responsive nanofibrous mats. Eudragit L100-55 is methacrylic acid and methyl methacrylate acid ionic synthetic copolymer, that is, insoluble in an acidic medium but soluble in the alkaline medium above pH 6.0 [22, 39]. As a result, Eudragit L100-55 can be used as a pH-triggered drug delivery mat, preventing drug dissolution in an acidic medium and allowing drug release in an alkaline medium [22]. Drug-loaded Eudragit nanofibers demonstrated slow drug release at pH 1.2 and complete drug release at around pH 6.8. Eudragit L100-55 polymer was electrospun for wound mat with drugs such as diclofenac sodium [22] and moxifloxacin hydrochloride [39], resulting in drug release when the pH is in an alkaline medium. Because diclofenac sodium is soluble at neutral pH, Eudragit L100-55 loaded with diclofenac sodium nanofibers dissolved quickly at 6.8 pH. Rivero et al. [40] also fabricated pH-sensitive Eudragit S100/nitrofurazone electrospun nanofibrous mat from Eudragit S100 polymeric solution loaded with nitrofurazone via single and coaxial electrospinning. The mat can release nitrofurazone at pH values greater than 7.

Oxygen is required for wound healing because it regulates cell proliferation, migration, and angiogenesis while also promoting collagen deposition and epithelialization of regenerative tissue. There are oxygen-releasing biomaterials that can be electrospun with synthetic polymers in a specific pH solution media, such as peroxide-based biopolymers (sodium percarbonate). There is research being done on nanofibers that can generate oxygen at certain pH levels in the wound site [41] developed oxygen-releasing sodium percarbonate loaded PCL (PCL-sodium percarbonate) nanofibers for full-thickness wound healing. In a pH range of 7.3 to 7.6, the mat can produce increasing amounts of oxygen for up to 10 hours.
The incorporation of halochromic dyes into electrospun nanofibrous wound dressings only tell us the change in pH on the wound site for monitoring purpose. Combining these dyes with pH-sensing drug-releasing polymers improves the smartness of the mat. A pH-responsive hydrophilic polyacrylic acid polymer capable of loading and releasing drugs at higher pH values can be combined with halochromic dyes to produce an electrospun nanofibrous mat, resulting in color change and on-demand drug release at different pH. Arafat et al. [42] used electrospinning to develop a polyvinyl alcohol/polyacrylic acid nanofibrous mat loaded with bromothymol blue and the antibacterial drug ciprofloxacin. Polyacrylic acid was used as an on-demand ciprofloxacin release and halochromic bromothymol blue as monitoring the condition of the wound by a change in color. When the pH of the wound changes, the mat changes color and releases ciprofloxacin on-demand. The mat started out yellowish, and then turned green at pH 7, then blue at pH 8.5.

Materials with pH-dependent fluorometric properties could be used to monitor the acidifying microenvironment representative of healthy wound healing, which is important for visually identifying healthy wounds without removing wound dressings. The pH-responsive fluorescent magnesium hydroxide nanosheets can be to investigate the pH of wound acidification. Fluorescent magnesium hydroxide nanosheets were incorporated into polycaprolactone/poly(ethylene oxide) electrospun biocompatible nanofibers that could help to identify the health of the wound visually without removing the dressings to minimize invasive operations [24].

In order to regulate cell proliferation, migration, and angiogenesis, as well as improve collagen deposition and epithelialization of regenerative tissue, adequate oxygen must be supplied to the wound site during the normal wound healing process [43]. However, in diabetic wounds, blood vascular tissues may be damaged, resulting in prolonged hypoxia (a lack of enough oxygen in tissues) and a delay in wound healing [44]. In this regard, electrospun nanofibrous wound dressings with oxygen-releasing properties at pH values (chronic wounds) are extremely important for diabetic wounds. Combining oxygen-releasing biomaterials like peroxide-based biopolymers with nanofibers could lead to this discovery. When decomposed, sodium percarbonate (0.01% at 20°C) produces hydrogen peroxide and, eventually, oxygen for the treatment of dermal wounds [45] [41] fabricated an oxygen-releasing polycaprolactone-sodium percarbonate salt blend nanofiber that can generate oxygen chemically in situ. The results showed that the mat released oxygen uniformly at pH levels ranging from 7.3 to 7.6.

Wound care benefits from dual-drug-loaded electrospun nanofibrous wound dressings. Guo et al. [46] coaxial electrospinning was used to fabricate core-shell chitosan–PEO–lidocaine hydrochloride/PCL-curcumin-sodium bicarbonate nanofibrous mats, with chitosan/PEO as the shell, and PCL as the core. When sodium bicarbonate reacts with hydrogen ions in an acidic environment, carbon dioxide is produced. The produced carbon dioxide microbubbles increase material internal pressure, causing holes on the surface and hastening drug release.

4. Thermo-Responsive Electrospun Nanofibrous Wound Dressings

The temperature of the wound site may vary due to differences in inflammation, oxygenation, and infection; this could indicate the wound status. Normal skin temperature ranges from 32°C to 34°C [15]. Researchers designed and developed temperature-responsive nanofibrous mats loaded with drugs for controlled drug release and wound healing using wound temperature as a parameter. Thermo-sensitive drug delivery systems, which are typically based on temperature-responsive polymers such as poly(N-isopropylacrylamide) or poly(N-vinyl caprolactam) [23], have exceptional characteristics that can be used in the development of scaffolds. They have unique solid-gel transition properties above a certain temperature, some of which are close to physiological human body temperature, 37°C [47].

Traditional hydrogels and nanofibrous hydrogels both have limitations in terms of drug release as the wound environment changes. To address this issue, thermo-sensitive hydrogels or phase change materials with a specific shape, swelling ability, charge on the surface, and drug-releasing characteristics can be designed as controlling drug-releasing materials in nanofibrous wound dressings [48, 49].

A thermo-sensitive hydrogel is a 3D polymer network that expands in response to temperature changes. When drugs are encapsulated in such polymers, the encapsulated drug is squeezed out of the polymer matrix when the temperature changes. As a controlling material in the drug release, thermo-sensitive hydrogel can be incorporated and electrospun into nanofibers [50] (see Figure 5). There are different thermo-sensitive hydrogels used for drug-releasing materials such as poly(N-isopropylacrylamide), poly(2-acrylamido-2-methylpropane sulfonic acid), poly(N-vinyl caprolactam-cohydroxymethyl acrylamide)-co-methacrylic acid, poly(N-vinyl caprolactam-cohydroxymethyl acrylamide), poly(N-vinyl caprolactam)-NMA, and poly(N-vinyl caprolactam)-ZnO [4]. Lin et al. [51] used electrospun poly(N-isopropylacrylamide) polymer with poly(2-acrylamido-2-methyl propane sulfonic acid)/nifedipine nanofiber to control nifedipine drug release. Another work by Tran et al. [52] used electrospinning to design and fabricate composite thermo-responsive nanofibers made of poly(N-isopropylacrylamide) and PCL containing ibuprofen. Without any burst effects, the mat released controlled ibuprofen at controlled room temperature (22°C) and above lower critical solution temperature.

Under physiological conditions, polymer glass transition temperature would be a stimulus to activate drug release. Pan et al. [13] used an electrospinning process to incorporate Eudragit RS100 and poly(methyl methacrylate) with octenidine (antimicrobial agent) to control drug release at the physiological temperature of 37°C. Temperature-based shape memory polymers are also used in controlled drug-release nanofibers. Berberine hydrochloride, a natural antibacterial agent, was sequential electrospun into shape memory polyurethane polymer in three stages. The nanofiber is sensitive to near-body temperature (approximately 42°C) [20].
5. Light Responsive Electrospun Nanofibrous Wound Dressings

Light triggers one of the external stimuli used in the design of light-degradable drug delivery smart nanofibers in various situations [53]. The O-nitro benzyl group is a common photocleavable linkage, that is, harmful to skin tissues and cells that require UV radiation. Low-energy near-infrared light must be used to irradiate the dressing and wound for wound dressing wound to be safe; however, low near-infrared light may not cleave any chemical bonds. As a result, nano-materials can be used as transducers, converting near-infrared radiation to UV light; thereby reducing UV light’s negative effect on skin tissues. Lanthanide-doped upconverting nanoparticles are ideal to change near-infrared radiation to UV light, which reduces the negative effect of UV light on skin tissues. Electrospun PVA fibers for wound dressings that are embedded with upconverting nanoparticles as NIR-to-UV light transducers and levofloxacin conjugates as a model drug.

Huang et al. [54] fabricated a hybrid electrospun nanofibrous with PVA embedded with upconverting nanoparticles and UV-cleavable levofloxacin conjugates for wound healing. When exposed to NIR light, the upconverting nanoparticles emit UV light, which can cleave the o-nitrobenzyl linkage of the levofloxacin conjugates in the PVA fiber, allowing the drug to be released in a controlled way. Only NIR and UV irradiation causes the drug to be released, not in the dark. Ballesteros et al. [53] developed an electrospun biodegradable polycaprolactone nanofiber loaded with photo-responsive silver nanoparticles nanogels as smart nanofibrous mats by electrospinning.

6. Bacteria Responsive Electrospun Nanofibrous Wound Dressings

Bacteria enzymes are another parameter for designing self-responsive nanofibers for wound healing, known as bacteria-responsive nanofibers. Bacteria-responsive nanofibrous can be designed in such a way that bacteria enzymes can degrade the nanofiber, resulting in releasing antimicrobials [10, 18]. The method could be designed by incorporating biocide inside bacteria-degradable polymers in two ways: by incorporating biocide inside single nanofibers, and by incorporating biocide in the core polymers in core-shell nanofibers by the same polymers. Polymers degradable by bacteria, such as polycaprolactone and poly(ethylene succinate), are used to develop such responsive polymers [10].

Some bacteria, such as methicillin-resistant Staphylococcus aureus, are antibiotic-resistant. As a result, researchers began to use silver nanoparticles, because the interaction of silver nanoparticle ions with thiol groups present in respiratory enzymes in the bacteria can inhibit the growth of bacteria. However, using a sliver is toxic and may cause healing to be delayed. To address this issue, efforts have been made to employ novel natural and synthetic antimicrobial peptides, but still, some remain ineffective. To solve those abovementioned issues, pathogens must be treated in a controlled and systematic manner. Nanofibrous, which changes color in response to bacteria, provides a valuable platform for continuous monitoring of wound status, allowing for early detection of bacterial infections. Gelatin methacrylate hydrogel is UV photo-cross-linkable and is made by incorporating methacrylate groups into the amine-containing side groups of gelatin, which can inhibit the growth of Gram-positive methicillin-resistant S. aureus and Gram-negative. Bacterial infection monitoring is one option that shows whether or not there is an infection. Methylene blue is a blue-colored cationic dye that turns colorless when it comes into contact with bacteria. The surface mesh was made of sodium carboxyl methyl cellulose nanofiber and was double layered with dye/antibacterial drug/PVA foam as the second layer. If the wound has a bacterial infection, that is, easily controlled, the dye will fade in color [55].

Self-monitoring electrospun wound dressing is another option for developing a bacterial infection by P. aeruginosa. Zhou et al. [18] developed a dual-layered gel with a lower layer of GeLMA encapsulating antimicrobial vesicles and an upper layer of colorimetric/fluorimetric encapsulating vesicles containing the self-quenching dye carboxyfluorescein. The gelatin-based membrane containing fluorescent vesicles lysable by bacterial toxins from methicillin-resistant Staphylococcus aureus or Pseudomonas aeruginosa, a bio-compatible UV-photo cross-linkable methacrylated gelatin encapsulating silver nanoparticles (antimicrobial) and fluorescent vesicles that can respond to the microbiological environment of the wound by a change in color and release antimicrobials only when pathogenic bacteria exist. In vitro and in vivo studies were approved to kill/inhibit the growth of methicillin-resistant S. aureus and P. aeruginosa, while also providing visual warning of infection due to vesicle bilayer membrane lysed by toxins secreted by these pathogens but not by a nonpathogenic Escherichia coli species. To inhibit bacterial growth, pathogenic bacteria secrete membrane-destructing toxins that lyse the vesicles and release silver nitrate and gentamicin sulfate.

Xiong et al. [56] manufactured a lipase-sensitive polymeric triple-layered nanogel as a drug carrier for delivering antimicrobials to bacterial infection sites from poly(ethylene
glycol)-poly(ε-caprolactone). Based on lipase-sensitive polymerase, Abdali et al. [10], fabricated bacteria-responsive core-shell nanofibers incorporated with biocide, PCL/poly(ethylene succinate) nanoparticles as shell blended into poly (vinyl pyrrolidone)/benzyl dimethyl tetradeyl ammonium chloride (model biocide) as the core. Poly (vinyl pyrrolidone) improved electrospinnability of the core solution and encapsulated antibacterial. When there is bacterial development in the wound, the contacted polymers are degraded and antibacterial released (see the details in Figure 6).

It has been demonstrated that adding bacterial enzymes to hemicyanine-based chromogenic dye causes the dye’s color to change from yellow to red. Currie et al. [8] developed bacterial responsive color-changing core-shell chitosan-polyurethane: polyvinyl pyrrolidone nanofiber membrane by electrospinning process a hemicyanine based chromogenic probe and using polyvinyl pyrrolidone as a dopant to enhance charge transfer in hemicyanine to detect bacteria. Chromogenic probes with a labile ester linkage can be enzymatically cleaved by bacterial lipase, resulting in a rapid chromogenic response that can be used to continuously monitor the wound bed and detect bacterial infections early.

Polyhydroxyalkanoates (Mw 100,000 to 500,000) and poly(ethylene succinate) (Mw approximately 10,000) are both biocompatible and biodegradable, with hydrolyzable ester bonds that can be hydrolyzed by bacterial lipases. The researchers are inspired by the hydrolysis of these polymers by bacteria to use the nanofibers of these polymers as drug carriers and bacteria-responsive for controlling the release of drugs when there is a bacterial infection in the wound. Li et al. [57] used coaxial electrospinning to develop a core-shell bacterial lipase responsive poly hydroxyl alkanoates/Poly(N-isopropylacrylamide)/Poly(ethylene succinate)/PVA copolymer nanofibers having a dual response to thermal and pH changes and encapsulated antibacterial. When there is bacterial infection, the polymers are degraded and antibacterial released.

7. Oxygen Species-Responsive Electrospun Nanofibrous Wound Dressings

Reactive oxygen species include hydrogen peroxide (H₂O₂), superoxide anion radical (O₂⁻), and hydroxyl radical (OH⁻), all of which play an important role in wound healing at various stages [58]. H₂O₂ can aid in cell growth, immune response, and senescence. On the other hand, too many reactive oxygen species may be produced in an infected wound, resulting in oxidative stress and delayed formation of new tissue [59]. As a result, the level of H₂O₂ in the wound must be detected and monitored in order to determine its relationship with wound healing status. Some polymers, such as europium (III) coordination, change color when exposed to H₂O₂. Based on this concept, Wu et al. [16] designed and manufactured H₂O₂-responsive nanofiber mat by combining polycrylonitrile and europium (III) coordination polymers using electrospinning. The nanofiber mat can detect H₂O₂ levels. The study shows that H₂O₂ concentration and intensity of fluorescence have a linear relationship in the range of 20–200 μM. Furthermore, when H₂O₂ is present in vitro, the color of the mat changes from bright to weak, and when an inflammatory wound is present in vivo. Furthermore, when H₂O₂ is present in vitro, the color of the mat changes from bright to weak, and when an inflammatory wound is present.

8. Dual Stimuli-Responsive Electrospun Nanofibrous Wound Dressings

Two or more stimulus-responsive materials can be combined and incorporated into multi-stimulus-responsive electrospun fibers called electrospun nanofibrous wound mats. This will improve drug delivery and monitoring quality. Better drug delivery electrospun nanofibrous wound materials will be produced by combining pH and thermos-responsive polymers with drugs. Blend electrospinning was used to electrospin thermo-responsive poly(N-isopropylacrylamide) polymer and pH-sensitive Eudragit L100–55 polymer solution loaded with a model drug ketoprofen. The study showed that the release of ketoprofen profiles from poly(N-isopropylacrylamide)/Eudragit L100–55 composite is dependent on both temperature and pH for the composite fibers. The drug release studies showed a release of the drugs at different pH (4.5 or 7.4) or temperatures (25 and 37°C) in vitro study [23]. Poly(N-isopropylacrylamide) polymer also combined with pH-sensitive N-methylolacryl amide-acrylic acid) polymer to be used as dual-responsive smart nanofiber loaded with two antimicrobial agents (gatifloxacin hydrochloride and silver nanoparticles) having a dual response to thermal and pH was obtained via radical copolymerization and electrospinning. Both antimicrobial agents were released in max amounts at 37°C or pH 4.0 [60].

In another work, Li et al. [5] prepared hybrid poly(N-vinyl caprolactam)/ethyl cellulose/ketoprofen-Eudragit/ketoprofen dual stimuli-responsive nanofiber mats. Combining the pH-responsive properties of Eudragit with thermos-responsiveness of poly(N-vinyl caprolactam)/ethyl cellulose results in dual-responsive drug delivery system hybrid mats, with the latter drug released at 25°C faster than at 37°C and at pH 7.4 faster than at pH 4.5.

Table 2 shows the different self-responsive electrospun nanofibrous wound dressings and the properties studied by
<table>
<thead>
<tr>
<th>No.</th>
<th>Electrospun nanofibrous wound dressing mat</th>
<th>Responsive material</th>
<th>Responsive to</th>
<th>Functional properties studied</th>
<th>Properties not studied</th>
<th>In vivo/ In vitro</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cellulose acetate-bromocresol green-benzocaine</td>
<td>Bromocresol green</td>
<td>pH</td>
<td>(i) Drug release (ii) Contact angle (iii) Swelling (iv) Biocompatibility (v) Halochromic property</td>
<td>(i) Mechanical (ii) Gas permeability (iii) Infection prevention (iv) Porosity</td>
<td>In vitro</td>
<td>[17]</td>
</tr>
<tr>
<td>2</td>
<td>Poly(methyl methacrylate-co-methacrylic acid)-poly(acrylic acid)-bromothymol blue</td>
<td>Bromothymol blue</td>
<td>pH</td>
<td>(i) Porosity (ii) Swelling (iii) Drug release (iv) Halochromic property</td>
<td>(i) Mechanical (ii) Mechanical (iii) Gas permeability</td>
<td>In vitro</td>
<td>[31]</td>
</tr>
<tr>
<td>3</td>
<td>PCL-PEO-fluorescent Mg(OH)2 nao sheets</td>
<td>Bromothymol blue</td>
<td>pH</td>
<td>(i) Antibacterial (ii) Absorbency (iii) Biocompatibility (iv) Nontoxic (v) pH change</td>
<td>(i) Mechanical (ii) Swelling (iii) Porosity (iv) Gas permeability</td>
<td>In vitro</td>
<td>[24]</td>
</tr>
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<td>4</td>
<td>Sodium alginate-PVA-anthocyanins extracted from black carrot</td>
<td>Anthocyanins extracted from black carrot</td>
<td>pH</td>
<td>(i) Thermal (ii) Halochromic/pH change</td>
<td>(i) Mechanical (ii) Porosity (iii) As exchange (iv) Swelling (v) Biocompatibility</td>
<td>In vitro</td>
<td>[25]</td>
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<td>5</td>
<td>Zein-anthocyanins extracted from red cabbage</td>
<td>Anthocyanins extracted from red cabbage</td>
<td>pH</td>
<td>(i) Contact angle (ii) Color changing</td>
<td>(i) Porosity (ii) Biocompatibility (iii) Thermal (iv) Mechanical property (v) Swelling</td>
<td>In vitro</td>
<td>[21]</td>
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<td>6</td>
<td>Eudragit®L100-55-diclofenac sodium</td>
<td>Eudragit®L100-55</td>
<td>pH</td>
<td>(i) Drug release (ii) Thermal (iii) Compatibility</td>
<td>(i) Porosity (ii) Mechanical property (iii) Swelling (iv) Gas exchange (v) Absorbency</td>
<td>In vitro</td>
<td>[22]</td>
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<td>7</td>
<td>PCL-sodium percarbonate</td>
<td>Sodium percarbonate</td>
<td>pH</td>
<td>(i) O2 release (ii) Wound closure</td>
<td>(i) Swelling (ii) Porosity (iii) Gas exchange (iv) Compatibility (v) Mechanical property</td>
<td>In vitro</td>
<td>[41]</td>
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<td>No.</td>
<td>Electrospun nanofibrous wound dressing mat</td>
<td>Responsive material</td>
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<td>Functional properties studied</td>
<td>Properties not studied</td>
<td>In vivo/ In vitro</td>
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<td>8</td>
<td>Cellulose acetate-anthocyanins extracted from red cabbage</td>
<td>Anthocyanins extracted from red cabbage</td>
<td>pH</td>
<td>(i) Halochromic behavior</td>
<td>(i) Swelling</td>
<td>In vitro</td>
<td>[33]</td>
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<td>(ii) Porosity</td>
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<td>(iii) Gas exchange</td>
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<td>(iv) Compatibilty</td>
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<td>9</td>
<td>Sodium alginate-PVA-Red cabbage extract</td>
<td>Red cabbage extract</td>
<td>pH</td>
<td>(i) Biocompatibility</td>
<td>(i) Swelling</td>
<td>In vitro</td>
<td>[35]</td>
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<td>(ii) Halochromic</td>
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<td>(iii) Gas exchange</td>
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<td>(iv) Mechanical property</td>
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<td>Sodium alginate-PVA-anthocyanins extracted from purple cabbage</td>
<td>Anthocyanins extracted from purple cabbage</td>
<td>pH</td>
<td>(i) Contact angle</td>
<td>(i) Swelling</td>
<td>In vivo</td>
<td>[37]</td>
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<td>(ii) Halochromic</td>
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<td>(iii) Healing efficiency</td>
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<td>(iv) pH sensing</td>
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<td>11</td>
<td>Eudragit S100-nitrofurazone</td>
<td>Eudragit S100</td>
<td>pH</td>
<td>(i) Contact angle</td>
<td>(i) Porosity</td>
<td>In vitro</td>
<td>[40]</td>
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<td>(ii) Thermal</td>
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<td>(iii) Drug release</td>
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<td>(iv) pH release</td>
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<td>(v) Antibacterial</td>
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<td>12</td>
<td>PVA- poly acrylic acid-bromothymol blue dye-ciprofloxacin (antibacterial drug)</td>
<td>Bromothymol blue dye</td>
<td>pH</td>
<td>(i) Drug release</td>
<td>(i) Porosity</td>
<td>In vitro</td>
<td>[42]</td>
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<td>(ii) Water vapor transmission rates</td>
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<td>(iii) Swelling</td>
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<td>(iv) Antibacterial</td>
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<td>(v) Halochromic</td>
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<td>(vi) Mechanical strength</td>
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<td>13</td>
<td>Core-shell chitosan–PEO-lidocaine hydrochloride/PCL-curcumin-sodium bicarbonate</td>
<td>Lidocaine hydrochloride</td>
<td>pH</td>
<td>(i) Drug release</td>
<td>(i) Porosity</td>
<td>In vitro</td>
<td>[46]</td>
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<td>(ii) Mechanical property</td>
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<td>(iii) Hemolytic %</td>
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<td>(iv) Blood clotting</td>
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<td>(v) Cytotoxicity</td>
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<td>14</td>
<td>Poly(methyl methacrylate)-Eudragit RS100- octenidine (antimicrobial agent)</td>
<td>Eudragit®RS100</td>
<td>Temperature</td>
<td>(i) Drug release</td>
<td>(i) Gas exchange</td>
<td>In vitro</td>
<td>[13]</td>
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<td>(ii) Thermal</td>
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<td>(iii) Antibacterial</td>
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<td>(iv) Cytotoxicity</td>
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</table>
| 15  | Polyurethane-berberine hydrochloride (antibacterial agent) | Polyurethane | Temperature | (i) Mechanical property  
(ii) Drug release  
(iii) Antibacterial  
(iv) Surface wettability | (i) Porosity  
(ii) Swelling  
(iii) Gas exchange | In vitro | [20] |
| 16  | Poly(N-isopropylacrylamide)/poly(2-acrylamido-2-methyl propane sulfonic acid)-nifedipine (drug) | Poly(N-isopropylacrylamide) | Temperature | (i) Drug release  
(ii) Thermo-responsive/contact angle  
(iii) Gas exchange  
(iv) Swelling  
(v) Cytotoxicity | | In vitro | [51] |
| 17  | Poly(N-isopropylacrylamide)-PCL-ibuprofen(drug) | Poly(N-isopropylacrylamide) | Temperature | (i) Drug release  
(ii) Mechanical property  
(iii) Porosity  
(iv) Gas exchange  
(v) Swelling | | In vitro | [52] |
| 18  | Core-shell PCL-poly(ethylene succinate)/PVP-benzyl dimethyl tetradecyl ammonium chloride | PCL-poly(ethylene succinate) gel | Bacteria | (i) Antibacterial  
(ii) Drug release  
(iii) Cytotoxicity | (i) Mechanical property  
(ii) Porosity  
(iii) Gas exchange  
(iv) Swelling | In vitro | [10] |
| 19  | Core-shell chitosan-polyurethane/PVP-hemicyanine based chromogenic probe dye | Hemicyanine based chromogenic probe dye | Bacteria | (i) Color changing by bacteria | (i) Swelling  
(ii) Mechanical property  
(iii) Porosity  
(iv) Gas exchange  
(v) Cytotoxicity | In vitro | [8] |
| 20  | Silver nitrate- gentamicin sulfate/10,12-tricosadiynoic acid-phospholipid vesicles | Phospholipid vesicles | Bacteria | (i) Antibacterial  
(ii) Cell viability, proliferation  
(iii) Wound closure  
(iv) Bacteria sensing  
(v) Colorimetric sensitivity | (i) Swelling  
(ii) Mechanical property  
(iii) Porosity  
(iv) Gas exchange  
(v) Cytotoxicity | In vivo & in vitro | [18] |
| 21  | PCL-photo responsive nanogels containing silver nanoparticles | Photo responsive nanogels containing silver nanoparticles | Light | (i) Antibacterial  
(ii) Release | (i) Swelling  
(ii) Mechanical property  
(iii) Porosity  
(iv) Gas exchange | In vitro | [53] |
the researchers. As seen from the table most of the studies are in vitro study that needs in vivo study as well. Almost most of the developed self-responsive nanofibrous mats have not studied their mechanical properties.

9. Conclusion and Future Challenges

Researchers are currently focused on materials that respond to wound pH, temperature, light, and bacteria for developing electrospun nanofibrous for wound monitoring, and controlled drug release. When temperature, pH, and hydration are critical parameters influencing the wound healing process because they serve as indicators of the wound status, detect an infection, monitor, and detect nonhealing wounds early. Researchers in biomedical textiles have paid more attention to these types of materials for emerging responsive smart electrospun nanofibrous wound dressings.

In general, responsive smart nanofibrous wound dressings can recognize wound environment information and reduce changing frequency of dressing, saving health treatment costs and reducing patients’ pain. In the treatment of wounds, tremendous progress has been made in the use of self-responsive/electrospun nanofibrous wound dressings. These dressings are primarily based on controlling the pH and temperature of the wound, infection detection, and the use of multiple responsive systems.

However, there are some challenges for self-responsive electrospun nanofibrous wound mats at this time. The challenges and future directions for developing self-responsive electrospun nanofibrous mats for wound treatment are given as follows:

(1) Many studies, as shown in Table 2, did not include the studied in vivo studies or clinical trials.

(2) Most studies did not pay much attention to the main characteristics of ideal wound dressings, such as mechanical property, gas exchange, selling, porosity, and permeability tests.

(3) Incorporating sensory materials into nanofibrous wound dressings aids in wound monitoring because they make direct contact with the wound. As a result, researchers in this field must focus on selecting biocompatible materials.

(4) In the near future, real-time monitoring, infection warning, and self-drug release wound dressings will be required.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


[44] H. Li, J. Yang, Q. Deng et al., "Au nanoparticle@silica@europium coordination polymer nanocomposites for enhanced fluorescence and more sensitive monitoring reactive oxygen species," *Science China Materials*, vol. 61, no. 3, pp. 401–408, 2018.
