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# Drug Delivery Systems and Materials for Wound Healing Applications

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## Abstract

Chronic, non-healing wounds place a significant burden on patients and healthcare systems, resulting in impaired mobility, limb amputation, or even death. Chronic wounds result from a disruption in the highly orchestrated cascade of events involved in wound closure. Significant advances in our understanding of the pathophysiology of chronic wounds have resulted in the development of drugs designed to target different aspects of the impaired processes. However, the hostility of the wound environment rich in degradative enzymes and its elevated pH, combined with differences in the time scales of different physiological processes involved in tissue regeneration require the use of effective drug delivery systems. In this review, we will first discuss the pathophysiology of chronic wounds and then the materials used for engineering drug delivery systems. Different passive and active drug delivery systems used in wound care will be reviewed. In addition, the architecture of the delivery platform and its ability to modulate drug delivery are

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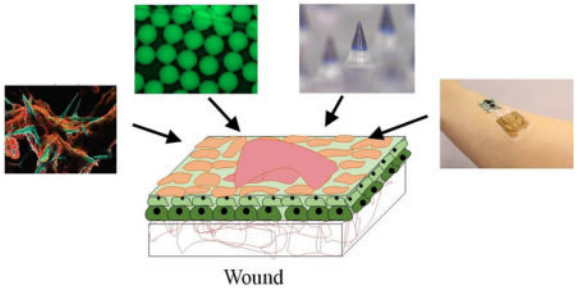
discussed. Emerging technologies and the opportunities for engineering more effective wound care devices are also highlighted.

## Graphical Abstract




## 1. Introduction

Skin is a barrier protecting internal organs from potential environmental hazards[1]. Skin possesses excellent regenerative properties and injuries or cuts can be healed through a highly orchestrated cascade of physiological events. However, in some cases, this regenerative property is impaired and wounds do not heal in a timely fashion, placing the patients at a significant health risk. Usually, wounds that do not heal in 90 days are referred to as chronic wounds. The treatment of chronic wounds and large burns is expensive and laborious as they are susceptible to infection and often require surgical treatment. Compromised wound healing exerts a massive burden on the healthcare system. In the US around 4.5 million people need treatment for chronic wounds and it is estimated that over $25 billion is spent annually on management of chronic wounds [2]. Furthermore the burden of chronic wounds is growing due to the increasing incidence of obesity and diabetes [3, 4]. In addition, around 40,000 burn victims are hospitalized every year and 4000 of them die from their injuries. Managing burn wounds is also very challenging due to the extent of the injury [5].

Wound care dates back to several millennia. The most ancient therapies were based on covering the wound with leaves and cloth and applying natural ointments in order to reduce pain, prevent infection, and keep the wound closed. Although some of these strategies are still in practice, they have shown to be insufficient for inducing healing in chronic wounds. In addition, the use of conventional wound care practices for treatment of deep cuts results in the formation of permanent scars. Thus, significant efforts have been dedicated towards developing alternate therapies that restore the regenerative properties of the native skin [6]. These activities can be broadly divided into the following groups: 1) identification of biological processes involved in wound healing and those being disrupted in chronic wounds to find therapeutics that support natural healing mechanisms; 2) development of drug delivery systems that facilitate the effective delivery of therapeutics at the right dosage and time into the wound bed; 3) synthesis of materials that can be used as a scaffold for tissue growth; 4) engineering advanced dressings that function beyond a physical barrier and can sense the wound environments and provide information of its status.

Drug delivery systems are of particular importance as the ineffective vasculature in wound bed can prevent effective delivery of drug to the healing tissue when the drug is administered systemically. In addition, the side effects of some drugs, the low half-life of biological factors, and the dynamicity of the wound environment require complex drug delivery systems that can deliver the active factors in proper dosage to the appropriate location [7]. Over the past decade, significant progress has been made in the field and many different systems and platforms have been developed.

In this manuscript, the recent progress in various areas of wound care with particular emphasis on drug delivery aspects is critically reviewed. The physiology of wound healing and the pathophysiology of chronic wounds will also be discussed. The materials used for engineering wound dressings and scaffolds for wound care are reviewed and systems designed for controlled release of drugs and factors are discussed. Micro and nano-engineered transdermal drug delivery platforms are also highlighted. A new class of dressings that are smart and can sense the wound environment and can provide information essential for active wound care will also be discussed. The opportunities in the area of drug delivery for effective treatment of wounds will be highlighted. It should be noted that the focus of this review will be on the delivery systems rather than on the delivered therapeutics.

### 1.1. Wound physiology

Wounds can be categorized into acute and chronic types [8]. Acute wounds are the outcome of traumatic or surgical events that heal predictably following a regular healing process. Burn wounds are another class of wounds that are caused by heat, chemicals, electricity, sunlight, radiation or friction [9]. Burns can be classified into superficial (I°), partial-thickness (II°) and full-thickness burns (III°). I° burns only involve the epidermis and usually heal in a week without any additional procedures. Superficial II° burns undergo re-epithelialization similar to split-thickness skin graft donor sites from dermal appendages in 2 – 3 weeks with good functional and cosmetic outcomes. Deep II° burns require weeks, even months, to re-epithelialize and are associated with prolonged pain and severe scarring. Skin grafting is needed to accelerate the wound coverage. III° burns can heal only to some extent by epithelialization and contraction, however, they usually need skin grafting [10].

Acute skin wound healing is an intricate physiological process that is governed by different cell types, growth factors, chemokines, and cytokines [1]. Traditionally, wound healing processes have been divided into four overlapping phases of hemostasis, inflammation, proliferation, and remodeling that each wound needs to go through in order to heal normally (Figure 1) [11, 12]. The body’s immediate response to injury is hemostasis that occurs at the site of the injury to stop the bleeding and minimize hemorrhage. Platelets and inflammatory cells are the first cells to arrive at the site of the injury by binding to the exposed collagen in the extracellular matrix (ECM). The platelets then secrete a number of proteins such as fibronectin, von Willebrand factor (vWF), sphingosine-1-phosphate, and thrombospondin to enhance further platelet stimulation. The release of clotting factors stimulates fibrin matrix deposition to form a stable clot which serves as a provisional matrix for cells migrating to the wound bed. Also, the aggregation of platelets induces vasoconstriction that reduces blood flow to the wound bed. Platelets trapped inside the clot also secrete other important

growth factors including transforming growth factors (TGF-α, TGF-β), platelet-derived growth factor (PDGF), insulin growth factor (IGF), interleukin 1 (IL-1) to further progress the subsequent phases of wound healing. TGF-β recruits additional cells, including neutrophils and macrophages. PDGF also helps with vascularization and recruits fibroblasts, connective tissue cells which deposit collagen and promote repair of the damaged tissue [13].

Inflammation phase occurs immediately after the injury and lasts for about 3 days. During this phase, the complement system activates and together with coagulation generates various vasoactive mediators and chemotactic factors that attract leukocytes to the injury site within the first 24–48 hr after wounding. At this stage, mast cells (a member of leukocytes) release granules filled with enzymes, histamine and other active amines which are mediators responsible for the characteristic signs of inflammation around the wound site. The release of these mediators causes surrounding vessels to become leaky and allows for the efficient movement of neutrophils from the vasculature to the injury site. Fluid accumulation at the wound site causes swelling which is one of the signs of the inflammation [14].

Neutrophils are the next predominant cells in the inflammatory phase that are activated within 24 hr after injury [10]. The major function of the neutrophils is to remove pathogens, foreign material, damaged matrix components and dead cells by the process of phagocytosis. Using different chemical signals, neutrophils are attracted to the site of injury by the process called chemotaxis and attach to endothelial cells in the nearby vessels surrounding the wound. Then, they stimulate endothelial cells to express specialized cell adhesion molecules (CAMs). CAMs function as molecular hooks to recruit more neutrophils to bind to the endothelial cell surface and squeeze through the cell junctions that have been made leaky by the mast cell mediator 4–6 [15, 16]. In about two days after wounding, monocytes and lymphocytes stimulated by cytokines, growth factors, and chemokines migrate to the wound site and differentiate into macrophages that phagocytose remaining necrotic tissue, pathogens, and debris and initiate the formation of granulation tissue [17]. Therefore, macrophages have a similar function as neutrophils with better regulation of proteolytic destruction of wound tissue through the release of protease inhibitors [18]. During the inflammatory phase macrophages also produce important growth factors (such as TGF-β, PDGF, tumor necrosis factor α, TNF-α) and cytokines (such as IL-1, IL-6) that are responsible for the proliferation of fibroblasts, smooth-muscle cells and endothelial cells as well as and ECM deposition [19]. At the end of the inflammation phase, neutrophils are phagocytosed by macrophages. The reduction in the number of inflammatory cells and factors in the wound indicate the commencement of proliferation phase [13, 20, 21].

The proliferation phase of wound healing is when the wound is “rebuilt” by fibroblast proliferation and collagen deposition to replace the provisional fibrin matrix. The proliferation phase starts around 2–3 days after the injury and continues until the wound is closed. In this phase angiogenesis, tissue granulation, re-epithelialization, and wound contraction occur [1]. Endothelial cells form new capillaries in a process called angiogenesis that is induced by several growth factors such as VEGF-A, fibroblast growth factor 2 (FGF-2), PDGF, and TGF-β. Angiogenesis is essential for granulation tissue formation during the proliferation phase. Newly formed capillaries bring oxygen and nutrients to the

growing tissue and take away waste products. The formation of granulation tissue allows the re-epithelialization to begin. The process is stimulated by inflammatory cytokines (such as IL-1 and TNF-a) that stimulate fibroblasts to produce growth factors (such as epidermal growth factor, EGF; keratinocyte growth factor, KGF; and hepatocyte growth factor, HGF) which in turn attracts keratinocytes to migrate to the wound bed [22]. Basal keratinocytes migrate from the wound edges as well as from the skin appendages to the injured area where they proliferate, differentiate and eventually form a cover over the wound. Fibroblasts which have migrated to the wound from bone marrow activate and begin synthesizing the extracellular matrix by secreting various ECM proteins (such as collagens, fibronectin, and hyaluronan). Macrophages stimulate fibroblasts by secreting PDGF and EGF [23]. The fibroblast already in the wound bed differentiates into specific fibroblasts called myofibroblasts that close the injured area by pulling the wound edges together in a process called wound contraction [1].

The last phase of wound healing is called maturation and remodeling phase. It begins a couple of weeks after wounding and can last over 1 year. During this phase, all the processes activated in the inflammation and proliferation phases terminate. Endothelial cells, macrophages, and myofibroblasts that are no longer needed undergo apoptosis or exit the wound [24]. Small capillaries aggregate into larger blood vessels and the metabolic activity of wound healing decrease. The ECM of the damaged area consists mainly of collagen and other ECM proteins. Initial deposition of type III collagen, known as reticular collagen, gradually replaced by type I collagen which is the dominant fibrillar collagen in skin. Fibroblasts secrete the lysyl enzyme oxidase, to realign collagen into an organized network which increases the tensile strength of the tissue to about 80% of normal tissue. This process is orchestrated by various matrix metalloproteinases (MMPs), which fibroblasts and other cells secrete [25, 26]. Migration of cells on ECM and remodeling and degradation of the ECM by MMPs are key elements of wound repair.

### 1.2. Pathophysiology of chronic wounds

Normally skin repair after wounding is very efficient but under certain conditions wound healing can become impaired. Abnormal wound healing results from a dysfunctional alteration in the carefully regulated biologic processes that characterize normal healing; the restoration of the tissue is either downregulated when the wounds fail to heal or upregulated that results in scarring [27]. The pathophysiology of chronic wounds is still not completely understood but it is known that instead of moving forward in the healing process they get stuck in the inflammation phase. Impaired vascularization and consequent hypoxia, the inability to progress to the healing phase, prolonged and increased inflammation, and inability of immune-cells to control bacterial infection are all critical challenges inhibiting the physiologic healing of chronic wounds [28]. The severe hypoxia creates large regions of avascular/non-viable tissue which is a hospitable environment for bacterial growth and biofilm formation. Biofilm further intensifies inflammation, inhibiting ECM deposition and tissue repair. This condition places the patients in significant danger and recurrent surgical procedures (wound debridement or even tissue amputation) are needed to avoid life-threatening complications.

Prolonged and overexpression of various interleukins and other inflammatory cytokines (such as TNF-α) prevents the healing process from advancing to the proliferation phase. Hyper inflammation also affects the expression of MMPs that play an important role in wound repair by degrading and removing damaged ECM molecules from the injured tissue. However, their excess proteolytic activity is associated with chronic wounds because they destroy growth factors, cell surface receptors, and temporary ECM essential for cell migration [29, 30]. In addition, lack of growth factors and presence of too many senescent cells in the injured area may result in the inability of these wounds to heal. Inadequate microvasculature can lead to chronic non-healing wounds that are especially common in diabetic patients [28].

Most chronic wounds do not heal through regeneration but through fibrosis forming excessive amounts of connective tissue. Fibrosis also follows chronic inflammation and elevated amounts of pro-inflammatory mediators (such as TGF-β) have been found in the wounds that heal by fibrosis. Growth factor activity is poorly regulated causing unnecessary fibroblast proliferation, neovascularization and increased collagen and fibronectin synthesis [31]. In addition, excessive and prolonged wound contraction occurs resulting in a formation of fibrotic scar tissue [32]. Pathological scars after an injury can be categorized into keloids and hypertrophic scars. Keloids are an abnormal overgrowth of the scar tissue. They extend beyond the boundaries of the original wound and do not regress spontaneously over time. Hypertrophic scars are more common and do not get as big as keloids by not expanding over the borders of the wound. They may also spontaneously regress over time [33].

### 1.3. Existing wound care systems

As described before, physiologic cutaneous wound healing involves a complex, precisely regulated set of interrelated biological pathways [20, 34–36]. Any factor leading to a variable disruption of these orchestrated phenomena can be a cause of pathologic healing in broader terms. Disrupting factors can be innate (e.g. scarring), exclusively extrinsic (e.g., infections, mechanical stress, et cetera), intrinsic (e.g., aging, diabetic condition, vascular disease, poor systemic conditions, et cetera) or mixed [20, 34–36]. Despite the extremely variable range of conditions that can impair healing, overall we can identify two main scenarios: 1) physiologic healing in a healthy patient with no comorbidities, and 2) pathologic healing in patients with local/systemic comorbidities [2, 3, 20, 29, 34–39].

In healthy patients the goal of ideal wound care therapies would be to 1) protect the wound from external agents (e.g. bacterial infections, mechanical stress), 2) accelerate closure through maintenance of wound moisture, and 3) minimize/avoid scarring. In addition to these goals, wound therapies in patients with local/systemic disorders leading to chronic non-healing wounds would include: 1) removing necrotic tissue and biofilm, 2) modulating inflammation (including edema) and unlocking the inflammatory phase of healing, and 3) boosting the reparative phase of healing (e.g. epithelial migration, granulation tissue formation through collagen deposition and ECM remodeling, angiogenesis, and tissue blood perfusion, and lymphangiogenesis) [2, 3, 20, 29, 34–40]. The TIME (tissue, infection/inflammation, moisture balance and the edge of the wound) guidelines, proposed in 2002, list some of these factors and try to include them in an integrated therapeutic strategy [41,

42]. Other elements of wound care that should be taken into consideration to maximize patients' wellness and outcomes include pain and treatment-related factors such as a decreased frequency of dressing changes, and the reduction in wound-care associated costs [2, 3, 43–45].

Advanced wound dressing should primarily aim to prevent bacterial infection by adequate sealing of the wound micro-environment from external contaminants [46]. The dressing should be able to contain bacterial (or fungal) proliferation, limit infection morbidity and possibly eradicate the pathogen [47, 48]. One of the wound care approaches that have become popular is vacuum assisted closure (VAC) of wound in which a negative pressure is generated at the interface of the wound [49]. In this approach a foam or sponge is placed on the wound and the other side of the porous material gets connected to a vacuum pump, which applies suction. VAC therapy has multiple benefits including: removal of exudates rich with pro-inflammatory cytokines and proteins, reducing the chance of infection and biofilm formation, and increasing the blood supply to the wound bed [50, 51]. Similar to the majority of other wound care products, they are passive and they effectiveness for treatment different types of chronic wounds is not clear. Application of VAC therapy for vast wounds can also be challenging.

Two substantial challenges limit the effectiveness of current wound care strategies: 1) the inability to properly detect bacterial colonization/infection (which is based on clinical inspection and confirmation by laboratory analysis) 2) the non-specificity of the topical antimicrobial/antibacterial therapies [52]. As a consequence, diagnosis of wound infection and administration of therapy are often delayed and are less effective. Misdiagnosed infected wounds are associated with prolonged healing and care, several localized and systemic comorbidities (e.g., amputations in diabetic foot ulcers), and mortality (through bacteremia and septicemia) [53]. Dressings loaded with non-specific antimicrobial drugs have only minimally addressed these challenges. Topical antibacterial/antibiotic therapy has the advantage to reduce effective doses required to kill pathogens and limit systemic effects of drugs [54]. However, unnecessary delivery of antimicrobial/antibiotic substances can be a cause of impaired healing by itself as it can deregulate the cutaneous microbiome, lead the development of antibiotic resistance, and have systemic toxicity. In order to successfully counteract a possible infection, advanced dressings need to provide tightly-regulated patient/bacteria-specific release of antimicrobial or antibiotic substances [55]. Current wound care strategies mostly rely on the concept of "one treatment fits all" and have been shown to be outdated, ineffective, and non-individualized [34, 44]. In particular, treatments for chronic wound are expensive, labor-intensive, often nonspecific, and rely on a wide range of therapies (including cleansing, debridement, oxygen therapy, antibiotics, and surgery) that are not always integrated to improve therapeutic effectiveness, optimization of medical resources, and patient compliance [56].

Maintenance of physiologic wound moisture and gas exchange is a key feature of effective wound dressings [57, 58]. Several studies have shown that a moist wound environment increases migration and proliferation of keratinocytes, promoting wound epithelialization and closure [59, 60]. It also influences the migration of endothelial cells, angiogenesis, remodeling of the ECM, and it has been associated with a less intense fibrosis [2]. Wound

moisture can be influenced by several patient-specific factors: while some wounds might present with low levels of hydration others might show excess exudates. Moisture of a wound could also vary over time. Most strategies currently available for wound care adopt a non-specific approach to increase wound moisture [61].

Chronic wounds are often characterized by the presence of high quantities of necrotic tissue which limits healing and is the ideal pabulum for bacterial colonization and growth [8]. Wound debridement can be performed using several different strategies including surgery, autolytic (endogenous), enzymes substances, or other mechanical methods [62]. Several commercially-available dressings provide some embedded debridement capacity. Incorporating substances capable of effectively removing necrotic tissue in a wound dressing allows for a less painful, continuous, cost-effective, and more physiologic debridement compared to surgery or other methods relying on expensive and invasive medical devices [63].

There are a variety of wound healing products that are currently regulated by the U.S. Food and Drug Administration for use in the United States. These products, mostly in form of dressings, can be categorized as passive, medicated, or interactive dressings [64]. Passive non-drug-eluting dressings have no direct effect on the wound except for acting as a physical barrier. Medicated dressings have been used to promote the healing process either indirectly by removing necrotic tissue, or directly by enhancing wound healing stages. The active agents contained in medicated dressings can include cleaning or debriding agents for necrotic tissue removal, growth factors, antimicrobial agents, and monoterpenes. The dressings used to deliver these agents to wounds include hydrogels, hydrocolloids, alginates, polyurethane foam films, and silicone gels [64]. SANTYL® Ointment is the sole collagenase-containing biologic debriding agent that has been FDA-approved for treatment of burns and dermal wounds [65].

Wound dressings containing drug(s) are regulated as combination products and are designated to an FDA center that retains the primary regulatory responsibilities and oversight over the product based on the product's PMOA. Wound dressings containing drugs are regulated by the Center for Devices and Radiological Health if their PMOA is that of a medical device and otherwise by the drug authorities at the Center for Drug Evaluation and Research [66]. Wound dressings containing drugs are a pre-amendment, unclassified device type that has generally been subject to a premarket review through the 510(k) pathway and cleared for marketing if they are shown to be "substantially equivalent" to a legally marketed predicate device. Wound dressings that do not meet this criterion are automatically Class III under section 513(f)(1) of the FD&C Act. For example, the FDA has mandated that dressings that serve as a replacement for full-thickness skin grafting, accelerate the normal rate of wound healing, or treat full-thickness (3$^{rd}$ degree) burns are Class III medical devices. An example of such a dressing is the Integra® Omnigraft™ Dermal Regeneration Matrix that was approved through the premarket approval (PMA).

In general, existing wound care products have significantly improved the patient care. However, they usually target only one aspect of the impaired cascade and cannot address the multifactorial nature of impaired wound healing. In addition, they are often based on the

"one product fitting everyone" concept, which significantly reduces their effectiveness. Maintaining the long term activity of fragile molecules and growth factors has been another key challenge preventing their use in commercial products.

## 2. Materials used in wound care

The materials used in the treatment of chronic wounds are used for two different purposes: 1) scaffolding materials that can host the endogenous cells and facilitate their growth and wound closure; 2) temporary dressings that cover the wound area and maintain a suitable condition supporting the healing process.

The ideal wound dressings are supposed to cover the wound, preserve the body water content, be oxygen permeable to allow oxygen access to growing tissue, and prevent the growth of environmental pathogens without interfering with the wound healing [67]. The utilized materials should be immunocompatible, non-degradable, and should not support cell ingrowth and cellular adhesion so to avoid complications during their removal. Dressing delivering drugs and biological factors should preserve the activity of the drugs and should be able to release the drugs at the desired rate. Another important function of wound dressings is exudate management. Wound exudates contain a large quantity of inflammatory cytokines and chemokines and are a suitable for bacterial growth. The effective removal of wound exudates without dehydrating the tissues is of great importance. The optimal material should guarantee gas and fluid permeability in order to absorb odors, maintain moist conditions and avoid dehydration and exudates accumulation which can result in the formation of necrotic tissue [68].

Scaffolding materials used for the treatment of chronic wounds, should facilitate the tissue regeneration, restore the tissue function, and promote a rapid healing process preventing chronic wounds [69]. The material should possess a degradation rate that matches the rate of tissue growth. In addition, neither the material nor the byproducts of the degradation process should induce immunogenicity and toxicity [69]. The scaffolding material should adhere properly to the surrounding tissues and its mechanical properties should match those of native skin to avoid the detachment and breakage over the course of healing. It should also maintain its water content or strategies should be devised to prevent material dehydration. They should have a limited swelling capacity and maintain their shape over time. These scaffolding materials can also be used as a depot of growth factors and the drug that are directly being delivered to the healing tissue. In this frame, engineered skin substitutes have been explored in order to create a 3 dimensional (3D) architecture that can mimic the ECM and reproduce the natural cell microenvironment [70]. Biomimetic materials are considered the most promising alternative for the production of these constructs. The optimal material should guarantee gas and fluid permeability in order to absorb odors, maintain moist conditions and avoid dehydration and exudates accumulation [68]. In this section, various materials used for engineering wound dressings and skin scaffolds will be discussed and their characteristics will be listed.

### 2.1. Materials in temporary dressings

Materials used for wound dressing applications vary in terms of the origin of materials, physical forms, architecture, and properties depending on the specific circumstances. Simply put, there are several different types of wound dressing products in the form of gauze, thin film, foam, hydrogels, hydrocolloids, membranes each of which is suitable for treatment of a specific wound type.

Medical gauze is the most widely used wound dressing product [71]. Gauze is made from woven or nonwoven fabrics based on natural or synthetic fibers, such as cotton yarns and polyester fibers. Gauzes can absorb exudate from the wounds and can keep the environment moist. Moreover, gauzes can be made as sterilized product and can be used in combination with other additives such as petroleum, saline, antibiotics, and antiseptics, or with other wound dressing products, which further expanded their applicability. However, when used alone, gauzes cannot provide good barrier protection against microorganisms. Also, the removal of gauze might cause a second trauma.

Thin film dressing, typically made from polyurethane, is a transparent and elastic synthetic wound dressing product [72]. The elasticity of such polymeric materials allows for comfortable movements of the affected body part. Importantly, polyurethane thin films are semi-permeable, which permits the exchange of oxygen, vapor, and carbon dioxide, but at the same time serves as a barrier to bacteria. Also, the transparency of thin film dressing allows for inspection of wound bed to assess wound healing. However, for wounds with high exudate, the use of polyurethane thin film might lead to accumulation of body fluids and maceration.

Foams made of synthetic polymers such as polyesters also have the mechanical elasticity that accommodates movement of the affected body part and can absorb more exudate than thin film dressing [73]. Moreover, foams are also able to help maintain the moisture environment around the wound bed and permit gas exchange, which are important features to facilitate wound healing. In addition, the porous structures of foams provide cushioning protection of the wounded tissue as well as good thermal isolation properties. Overall, foams are an economic and effective wound dressing that are suitable for various wounds. However, their high water uptake reduces their effectiveness as drug delivery systems. Hydrogels are crosslinked three-dimensional network structures that can be swollen with a large amount of water [74]. Hydrogel-based wound dressings can be found in amorphous or sheet forms, or as impregnated gauze [73, 75]. Since hydrogels are swollen with water or glycerin, hydrogel wound dressings can donate moisture to dry or minimally exuding wounds. Also, hydrogels can be easily applied to the wound site and can be easily removed when needed. However, the major concern of hydrogel dressings is their permeability to both gas and oxygen, which limits their use against infection. Thus, hydrogel dressing combined with antibacterial compounds has been developed. Kumar et al studied a composite wound dressings made by chitosan hydrogel loaded with ZnO nanoparticles for wound dressings (Figure 2a–c). The antibacterial activity of chitosan and ZnO particles combined with the release of zinc ions improved keratinocyte motility in the wound area and promoted epithelization and healing (Figure 2d) [76]. Another key concern for the use of

hydrogels is their rapid dehydration without a proper covering. The dehydration, however, might be reduced by incorporation of hygroscopic materials [77].

Another type of dressing is made from sodium and calcium alginate extracted from seaweed. Alginate is a class of natural polysaccharides with mannuronic and guluronic acid units [78]. Alginate has a unique capability of high absorbency of water. As a result, when applied to wounds, the dressing absorbs the exudate to form a hydrogel, which significantly limits bacteria activity. Therefore, alginate dressings are particularly useful for highly exuding wounds. Also, the calcium ions existed in the dressing not only physically crosslinked alginate to form stable physical gels, but also showed bioactivities in certain biological processes involved in wound healing [79]. In one study, the effectiveness of Kaltostat which is a nanofibrous commercially available dressing was compared with two alginate-based dressings crosslinked by the utilization of polyethylene imine and ethylenediamine [80]. The alginate dressings possessed larger pore sizes of about 100–250 μm and facilitated the air permeation (Figure 2e–g). They also better managed the wound moisture and as a result, faster wound healing was achieved in animal studies comparing to the commercial dressing.

Hydrocolloid dressings refer to colloidal materials, or gel-forming agents, typically made from gelatin, pectin, or carboxymethylcellulose [81, 82]. When topically applied to wounds, the colloidal materials absorb the exudate to form a gel state that sticks to the wounds and becomes permeable to water and oxygen. Hydrocolloid dressings under working conditions can provide thermal insulation and a moist environment, and are easy to remove due to the lack of mechanical stiffness. Therefore, hydrocolloid dressings are usually produced with a strong and impermeable film backing, which provides isolation of the wounds from bacteria and reduces the chances of infection.

Overall, any of these materials has some advantages, but none of them can be considered as the perfect dressing. Among them, hydrogel dressings that can manage the wound moisture and carry different types of drugs have attracted noticeable attention. The key problem with these dressings is fabricating dressings that fit large burns and skin defects. In addition, the dressing should be designed in a way that could form a conformal contact with the skin and does not constantly move against the healing tissue. The ease of removal is also important and hydrogels and alginate are usually easier to remove without inducing damage in the neo-tissue.

### 2.2. Biomaterials as skin regeneration scaffolds

The major goals of traditional wound dressing are to protect the wound beds and provide the favorable environment to promote wound healing. However, these products cannot replace the lost tissue, for example, severely damaged dermis [83]. To help repair chronic ulcers that are difficult to heal, cellular tissue-engineered skin substitute products have been developed. These substrates can be seeded with cells to form an engineered skin or can be implanted acellularly to recruit local cells and facilitate their growth. The presence of scaffolds with certain bioactivity can solve the challenge of continuous removal of temporarily ECM caused by excessive MMPs presence. To this end, the use of bioactive materials such as collagen, hyaluronic acid, chitosan has become the focus of current research in this area. Specifically, collagen and hyaluronic acid are the components of the ECM in the living

tissues, are fully biocompatible and biodegradable, and have demonstrated promising results *in vivo* [84].

The development of substrates with nanofibrous architectures by the electrospinning technique results in structures that can mimic the natural collagen fibers in ECM [84]. Since the collagen fibers are known to play critical roles in maintaining the integrity and strengths of the skin tissues, electrospun products can provide a scaffold with biomimicking nanofibrillar structures to promote wound healing. The high surface area of the electrospun fibers allows exudate accumulation, while the interconnected nanopores permit gas permeation. Also, the electrospinning process is compatible with various natural and synthetic polymers. It is possible to use electrospinning tofabricate composite membranes loaded with bioactive species such as antibiotics or nanoparticles to introduce additional functions [85].

Early substrates used as scaffolds for wound care include films, gels, sponges, or membranes based on natural biopolymers such as collagen, chitosan, gelatin, and hyaluronic acid, as well as on synthetic polymers including polyurethanes and polyesters. Composite scaffolds containing both natural and synthetic polymers might provide combined properties such as bioactivity, stability, and mechanical strength. These scaffolds can also be pre-seeded with autologous and allograft cells to facilitate the healing. In this case, the cells either populate and close the wound or serve as factories for production of biological factors regulating the wound environment [86]. Currently, one of the major concerns associated with cell-laden skin substitutes is the relatively high cost for long-term *in vitro* culture for maturation. To avoid these steps, the development of injectable scaffolds that can encapsulate cells, form tissue constructs in situ, and promote cell migration and organization has been recently demonstrated [87]. Such injectable hydrogels are usually adhesive to the surrounding tissues, fill the wound cavity, and provide a suitable environment for wound closure and promote healing process and tissue regeneration. *In vivo* studies have demonstrated that full-thickness skin defects treated with antibacterial injectable hydrogels showed thicker granulation tissue and higher collagen deposition compared to commercial skin substitutes, showing the excellence of the injectable systems as candidates for wound healing [88]. Current research efforts in this area are mainly focused on the tuning the adhesion strength and mechanical properties of these injectable scaffolds as well as incorporating biological factors, which can regulate the environment for expedited tissue healing.

**2.2.1. Electrospun nanofibrous matrices—**Among different scaffolding materials, fibrous substrates have gained noticeable attention for the fabrication of constructs for wound healing. It has been demonstrated that fibrous scaffolds are able to influence cell alignment, shape and function by mimicking the ECM fibrillar organization [89]. Nanofibrous scaffolds can be produced using various techniques such as self-assembly, phase separation, and electrospinning [90]. However, the electrospinning method is the most promising method to fabricate nanofibrous scaffolds [91]. This simple and efficient technique is based on an electrical field which charges a polymeric solution that is ejected from a syringe and collected on a metallic ground plate [92]. Electrospun nanofibrous scaffolds show high surface to volume ratio, interconnected pores and fiber dimensions in the range of 10–100 nanometers proving that they can properly mimic the ECM native

structure [93]. Moreover, electrospun matrices show very interesting characteristics such as oxygen-permeability, the possibility of fluid exchange without accumulation (i.e. exudates), suturability and uniform adherence in situ, making them a great candidate for wound healing purposes [94–96]. Electrospun mats of natural proteins such as gelatin and gelatin methacryloyl (GelMA) have been fabricated and implanted in wound models [97]. The presence of these nanofibrous materials significantly improves the wound healing rate by reduction of necrosis and enhancement of vascularization (Figure 3a–d) [97].

Synthetic polymers such as polycaprolactone (PCL) [93], poly(L-lactic acid) (PLLA) [98], poly(L-lactic acid-co-glycolic acid) (PLGA) [99] are mainly used for producing fibrous scaffolds for skin substitutes. Natural polymers such as gelatin [89], chitosan [100], and collagen [99] were added during the material preparation. Chandrasekaran et al. proposed a biocompatible electrospun scaffold made of poly(L-lactic acid)-co-poly(ε-caprolactone) (PLACL) combined with gelatin [89]. They demonstrate that surface plasma treatment can improve the hydrophilicity, leading to better cell proliferation and collagen deposition [89]. Similarly, chitosan-based constructs have been also investigated for wound healing and dressing applications, in lieu of their strong intermolecular hydrogen bonds, antibacterial activity, and hemostasis [101]. Chitosan-based electrospun scaffolds were demonstrated to support fibroblast viability, adhesion and proliferation *in vitro*, as well as promote wound healing in a rat model [101].

Other biomimetic compositions have also been electrospun and successfully used for the culture of skin cells [102]. Recently, the encapsulation of bioactive molecules in a synthetic polymeric nanofibrous structure has also been explored in order to improve the biocompatibility and overcome the low biological properties of synthetic polymers related to the lack of cell-recognition sites [93, 103]. In one example, co-polymers of PCL-PEG were electrospun and then soaked in rhEGF, 1-hydroxybenzole (HOBt), and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) solutions to graft EGF [104]. The results showed superior wound healing in animals receiving functionalized nanofibrous scaffolds (Figure 3e,f) [104]. Anesthetic solutions for pain relief and antibiotics, such as ampicillin [92], for infection treatment have also been integrated into the scaffold structure [92]. In one study, an angiogenic peptide (Vasoactive intestinal peptide, VIP) was encapsulated in situ as particles over PCL nanofibers. Electrospun nanofibers were first coated with mussel-inspired dopamine, creating an extremely adhesive layer over the nanofibers [105]. The angiogenic peptide (VIP) was then absorbed as a layer over PCL/DA nanofibers. The VIP coated PCL/DA was then immersed in acetone for in situ formation of VIP loaded microspheres within the PCL nanofiber structure. This encapsulation method provided a gradual VIP release over the course of 5 days and the total released amount was significantly higher compared to other samples with microspheres or those without DA component. *In vivo* application of PCL/DA-VIP nanofibers on full thickness wounds on mice significantly enhanced the wound healing with 96.5% coverage of the wound area at day 7 post surgery. Immunohistochemistry analyses also showed a significant increase in CD31 expression with PCL/DA-VIP group, showing increased angiogenesis [105].

In general, electrospun scaffolds have been shown to preserve the activity of drugs for relatively long periods of time. In addition, depending on their composition, they can

gradually release the encapsulated drug over a period of days to months. These properties combined with their ECM-like composition make them a suitable choice for scaffolding materials in skin care. However, one key problem that limits their success is their small pore size distribution (smaller than 10 μm) which significantly reduces the rate of cell infiltration and ingrowth. There have been efforts to engineer electrospun scaffolds with larger pore sizes (larger than 20 μm). However, this is an active research area to improve the controllability of electrospinning process [106].

**2.2.2. Hydrogel scaffolds—**Hydrogels are promising materials for designing scaffolds that promote wound healing [7, 74]. Their intrinsic porous and hydrophilic structure guarantees gas exchange and fluid balance, controlling water evaporation and absorbing exudate and providing moisture to the wound area. Moreover, transparency is an interesting aspect for monitoring the regeneration. It has been demonstrated that hydrogels can sufficiently mimic the ECM structure and functionality, for example by promoting cell adhesion and proliferation and directing cell migration [107]. The hydrogel composition might also influence cell growth, migration, and maturation [108, 109]. Among synthetic and naturally derived hydrogels, as the main components of ECM glycosaminoglycans (GAGs), such as hyaluronic acid and chondroitin sulfate, and collagen-based hydrogel have been studied the most. Researchers demonstrated that the use of GAGs in the hydrogel composition can lead to enhanced cell infiltration, spreading and proliferation. As reported by Kirker et al., hyaluronic acid concentration is one of the key factors for hydrogel resilience and influences cell differentiation and motility [110]. GAG-based hydrogels showed a significantly superior re-epithelialization and higher collagen deposition and organization compared to commercial products [110]. On the other hand, collagen is well known to have proper mechanical and adhesive characteristics but poor angiogenetic properties and fast degradation rate [111]. Therefore, other naturally derived biomaterials such as fibrin, chitosan, dextran and alginate have been explored. Fibrin has been considered for its angiogenic properties and fibrin-based hydrogels have been successful in promoting vascularization and cell recruitment which favors the wound healing process [112]. However, challenging control over their mechanical properties and degradation rate, the risk of immune response or infectious disease transmission, as well as slow crosslinking process limits the successful utilization of fibrin-based scaffolds in wound care [113]. Among naturally derived biomaterials, chitosan has also gained much attention because of its high hydrophilicity which promotes cell adhesion, migration, growth and differentiation. It is well known for its anticholesterolemic, antimicrobial activity and hemostasis which enhance the healing and regeneration process [107]. It has been demonstrated that chitosan-based hydrogels show bactericidal properties if the chitosan concentration is higher than 188 g/mL [107]. In order to guarantee proper angiogenesis Sun et al proposed a dextran-based hydrogel modified with amine groups to improve adhesion and integration on the wound site. The rapid degradation of the hydrogel structure permitted easy endothelial cell penetration into the wound area which favored vascularization. It is reported that the system could guide proper tissue regeneration with adequate epidermal morphology [114]. In addition to GAG-based hydrogels, protein-based scaffolds have also been widely used in the literature for promoting wound care. Collagen is the main constituent of ECM and collagen-based scaffolds have successfully supported wound healing. Currently, there are

commercially available collagen-based scaffolds that are recommended for the treatment of skin disorders. Gelatin is the denatured form of collagen and has been used as scaffolding materials for skin tissue engineering and wound care [115]. Gelatin-based hydrogels adhere to surrounding tissues and it has been demonstrated to support formation of epidermis (Figure 4a,b) [115].

In general, the hydrogel system should also favor the wound healing process and protect it against pathogens. The intrinsic structure should have the potential to support cell growth [112] and encapsulate bioactive molecules such as drugs [116] and growth factors for efficient tissue regeneration. Injectability and in situ hydrogel formation are considered the greatest advantages of the hydrogel structure. The former allows for site-targeted and minimally invasive scaffold implantation during the surgery, minimizing the patient pain and discomfort while the latter permits the obtainment of scaffolds with precise defect shape without fluting or wrinkling in the wound area. Zeng et al. proposed an injectable gelatin hydrogel which provides a suitable and stable environment for adipose derived stem cell loading and trapping maintaining stemness and viability for proper in situ cell delivery [111]. Lately, thermoresponsive hydrogels have also been gaining traction as in situ formation systems. This typology of hydrogels is very interesting mainly due to their ability of gelation at body temperature. Miguel et al investigated the role of agarose, a marine algae derived biomaterial, in thermosensitive hydrogel compositions. The agarose-based three-dimensional structure presented a rigid network with proper mechanical properties. It has been proven that the system was polymerized in situ at 37°C due to its thermal properties and supported cell adhesion and proliferation [107].

In general, hydrogels are excellent scaffolds supporting tissue ingrowth and eventually wound closure. They offer high water content and ECM mimicking microarchitecture. Their mechanical properties can be tailored to match native tissues and usually can be functionalized with various proteins. Their relative large pores in comparison to synthetic hydrophobic polymers result in the quick release of freely encapsulated compounds, which reduced their effectiveness as drug delivery tools. Another major shortcoming of hydrogels is their lack of suturability, making their implantation challenging. However, recent advances in the engineering of adhesive hydrogels have somehow solved this major challenge. For example, GelMA and elastin-based adhesives have been developed that are degradable and offer up to 20 times the adhesiveness of commercial fibrin glue [117, 118]. Due to abundance of collagen and elastin in the Skin ECM, it is expected that these adhesive hydrogels promote skin regeneration. Overall, improving their drug perseverance and ability to release different drugs with suitable release profiles has remained to be addressed.

**2.2.3. Foams and spongy scaffolds—**Spongy biomaterial structures, obtained by freezing and subsequently freeze-drying of solutions, are already well explored for wound healing purposes. Their large pore size in the range of 50 μm to millimeters allows this kind of system to significantly support cell infiltration, migration and signaling [120]. Porosity and pore size distribution can be controlled by different material concentrations and/or freeze-drying parameters. Due to their high porosity, well-interconnected pores, excellent properties of absorbing fluids and oxygen permeability, sponges have been successfully applied for the treatment of different types of leg ulcers. This system has the great advantage

of maintaining physiological moist conditions and promoting granulation tissue formation [121]. Mainly naturally-derived biomaterials such as collagen, gelatin, chitosan, and alginate have been developed to produce sponges for wound healing applications. Collagen-based sponges are most commonly used because of their good mechanical and physicochemical properties which prevent wound contraction and promote fluid absorption, respectively. These sponges promote cell adhesion, function, migration, and proliferation of fibroblasts and keratinocytes cultured on their surfaces [121]. Considering the poor antibacterial properties of collagen, Ramanathan proposed a collagen sponge loaded with anti-infective bioactive molecules. Results reported good keratinocyte and fibroblast collagen deposition and growth factor expression and proper re-epithelialization 14 days post application [121]. However, the biggest disadvantages of conventional collagen, generally derived from porcine or bovine sources, are its fast degradation and the risk of human transgenic disease transmission. For these reasons, fish collagen and gelatin have lately gained interest as a potential material for wound dressings. Chandika et al. successfully studied a fish collagen-based sponge scaffold crosslinked with sodium alginate and chito-oligosaccharides for the formation of biocompatible stiff structures with lower biodegradability [122]. Gelatin provides a suitable degradation profile as well as angiogenic properties whilst avoiding the disadvantages associated with collagen. However, its porosity and water uptake characteristics appeared to be inferior compared to other naturally derived hydrogels made of hyaluronic acid, chitosan or alginate. Gelatin has also often been combined with chitosan which can potentially increase the antibacterial and hemostatic properties of the construct. However, it is reported that the growth factor injection is not adequately efficient due to its high diffusivity and the activity of the biomolecules is not maintained for a long time [123]. In order to overcome these problems, Jinno et al proposed a sponge scaffold composed of 10% acidic gelatin which guarantees the maintenance of FGF-positive charge. They optimized the FGF release rate and the gel composition demonstrating that 7 $\mu g/cm^2$ could accelerate the wound healing and vascularization [124].

In general, sponges offer larger pore sizes in comparison to the hydrogel scaffolds, which facilitate cellular ingrowth. At the same time, these large pores can potentially affect their mechanical properties and swelling ratio. Thus, the material composition should be engineered in a way that these properties could be controlled over the course of wound healing. The large pores of spongy materials have another negative effect on the quick dispersion of freely loaded drugs and growth factors. Overall, hydrogels have attracted more attention than sponges to engineer scaffolds that can promote wound healing.

**2.2.4. Composite materials—**As reported above, hydrogels constructs are commonly used as scaffolds for wound healing. However, some unfavorable properties of their intrinsic structures such as their low mechanical strength and inadequate flexibility and inability to allow for long term drug release have limited their use for wound healing applications. Several studies have shown that they do not guarantee wound site protection and they may fail when high cyclic stress is applied. In order overcome these problems, researchers have studied the possibility of incorporating ceramic, metallic and polymeric nanoparticles into both hydrogel and electrospun constructs [125, 126]. The encapsulation of nanoparticles such as zinc oxide, titanium oxide and silver particles as antibacterial agents in the hydrogel

and electrospun scaffolds has also been explored lately to improve the poor antibacterial properties of the basic structures, avoiding bacterial colonization, local and internal infections and unorganized collagen deposition [127, 128]. Titanium dioxide particles were incorporated in a chitosan hydrogel developed by Behera et al. in order to improve the mechanical and antibacterial properties of the hydrogel structure. The incorporation of the nanoparticles improved the fibroblast attachment, function, spreading and proliferation favoring the wound healing [129]. The incorporation of biodegradable polymeric nanoparticles which can load, protect and modulate the release of bioactive molecules such as growth factors, drugs and proteins have also been explored lately. In particular, PLGA-based carrier systems are the most exploited due to the lactate degradation products which they release during the degradation process. These micro and nanocarriers will be discussed in details in the following sections. Another advantage of composite systems is improving the adhesion of the engineering constructs. For example, stem rose-mimicking constructs have been generated by electrospinning of branched ZnO particles and PCL (Figure 4c–g) [119]. The generated constructs had slightly larger pore sizes than the pristine polymeric scaffolds, yet offered sufficient mechanical properties. The constructs were extremely potent against bacteria cultures, while supporting the growth of keratinocytes [119].

Overall, the composite systems based on hydrogels or electrospun scaffolds can combine the beneficial properties of the incorporated components. Thus, by combining suitable polymers and drug carriers or biologically relevant micro/nanofeatures, one can engineer scaffolds that meet both the physical and biological requirements for achieving rapid wound healing. The incorporation of drug carriers can also solve the major drawback of hydrogels, which is their insufficient drug release profile.

**2.2.5. Bi-layered scaffolds—**Chronic wounds, as well as traumatic injuries, usually affect different both dermal and subdermal layers of skin. The dermis possesses low cell density and is composed of ECM deposited and maintained by fibroblasts which support the vascular, lymphatic and nervous systems. Because of its structure, the dermal regeneration is less efficient and more complicated than epithelial regeneration [130]. For these reasons, research groups have recently focused on the development of bi-layered scaffolds which combine both the epithelial and the dermal layers [131]. It has been reported that a system which provides a dense superficial layer and a porous lower layer might be the most promising alternative for complete full-thickness skin regeneration. The epithelial layer should prevent bacterial infiltration and dehydration of the wound site. The ideal dermal layer is instead supposed to have great fluid absorption properties and should promote fibroblast penetration. In this frame, Boucard et al. proposed a novel acellular bi-layered scaffold composed of chitosan hydrogels obtained through a low energy physical crosslinking method, avoiding any additional chemical agent. The upper hydrogel layer was optimized to be rigid and dense in order to guarantee protection, gas exchange and adequate mechanical properties. A soft lower hydrogel layer was designed to be flexible and able to adapt and adhere to the wound site. A pig animal model was considered for the scaffold implantation evaluation showing collagen I and IV deposition as well as angiogenesis and migration of inflammatory cells. The scaffold promoted the dermal-epidermal interphase regeneration and the wound healing of the full-thickness skin tissue [131].

The fabrication of multi-layer constructs with suitable properties supporting the growth of different layers can further improve the rate of tissue generation. Such constructs can be fabricated using microfabrication techniques such as molding, lithography, and 3D printing. In addition, if the layers are made from different composite materials, then suitable factors and drugs can be locally released to further enhance the growth of each layer. The benefits and shortcomings of different scaffolds engineered for treatment of wounds are summarized in Table 1.

## 3. Passive drug delivery systems

The complex process of wound healing involves hemostasis, angiogenesis, and restoring the skin barrier function. The proper occurrence of these processes requires the presence of growth factors and cytokines. However, in some cases these factors are not sufficiently present or are significantly upregulated and may derail the healing process from its normal cascade or completely halt it. Therapeutic agents such as growth factors, cytokines, antibacterial agents, proteins, small molecules, and bioactive agents can improve the rate of physiological processes leading to wound healing. There are several factors that should be considered in deciding the administration route of therapeutics: 1) the dysfunction wound bed vasculature reduces the bioavailability of compounds administered orally or intravenously; 2) some of the drugs can have systemic side effects; 3) the wound environment is rich in various pro-inflammatory cytokines that can deactivate the drugs; 4) physiological processes are time consuming and the administered drugs should be present during that time.

Thus, local delivery of therapeutic agents is compelling compared to systemic delivery since it reduces the undesired side effects such as toxicity or suboptimal delivery. Advances in the field of pharmaceutics and micro/nanotechnology have enabled researchers to fabricate drug delivery system that can control the release of the drug in the wound environment or directly deliver the drug to the healing tissue or cells. Localized controlled release provides spatiotemporal control over the drug dosage at the wound site, protects the drug from metabolic deactivation, and maintains the drug concentration over a prolonged period of time. An optimal drug delivery system should sequentially and selectively release antibacterial agents, growth factors, cytokines, and other small molecules in a controlled way so that the wound would follow the necessary course of healing [132]. The sequential release of therapeutic agents is of paramount importance for chronic wound healing. Chronic wounds suffer from delayed angiogenesis, resulting in extreme hypoxia, followed by a reduction in the production of reactive oxygen species by immune cells. As a result, more pro-inflammatory cytokines are secreted to recruit more immune cells [6]. Continuous infiltration of immune cells without proper healing results in excessive production of pro-inflammatory cytokines such as MMPs, which will excessively degrade the temporary ECM deposited by cells at the injury site and will prevent tissue regeneration. To disrupt the impaired cycle of ischemia, reperfusion, and inflammation, sequential and selective release of anti-inflammatory agents followed by pro-angiogenic growth factors, epidermal growth factors, and small molecules has been suggested. In this section, various drug carriers designed for wound care and technologies used for their fabrication will be reviewed. We will also highlight their release mechanisms.

### 3.1. Controlled-release drug carriers

In drug delivery systems, the encapsulated therapeutics can be released through different mechanisms which can be broadly classified as active and passive delivery. In active delivery, the release is triggered in response to environmental stimuli (pH, temperature, enzymes, chemical reactions, redox reactions, etc.) or external stimuli (magnetic field, electric field, light, ultrasound, etc.). In contrast, passive delivery relies on the diffusion of the drug through the carrier matrix to reach the surrounding medium [133]. Inorganic porous drug carriers, such as mesoporous particles, metal-organic frameworks, ceramic or carbon-based nanotubes have been extensively studied as drug carriers since they provide proper encapsulation for poorly soluble drugs and can also protect the drugs from physiological degradation. Organic carriers such as lipid-based systems, layer-by-layer systems, and hydrogels have also been used as passive transdermal drug delivery tools as they are degradable can pass natural epidermal barrier and can be uptaken by targeted cells [134–136]. In general, carrier size, shape, porosity, degradability, and electrostatic charge can affect the rate and effectiveness of the drug release [137].

**Polymeric drug delivery systems** are formed from nondegradable or biodegradable polymers and have been widely used since these systems can be tailored through the physicochemical properties of the polymers as well as various possible encapsulation methods [138]. In polymeric systems, the release is affected by parameters such as molecular weight ($M_w$), glass transition temperature ($T_g$), crystallinity, solubility and polymer degradation rate [139, 140]. Polymer molecular weight has a direct effect on the $T_g$, viscosity, crystallinity, mechanical properties, and degradation rate. Polymers with lower molecular weight have a faster degradation rate and higher elastic modulus. This results in higher deformation and pore expansion upon deformation, leading to higher release. In contrast, polymers with higher molecular weight have lower elastic modulus and are less deformable upon degradation, limiting the drug release [141]. Polymer $T_g$ defines the temperature at which amorphous regions transition from glassy to rubbery state. At temperatures lower than the $T_g$, amorphous regions are glassy and have a limited diffusivity. Above the $T_g$, the amorphous regions have a higher mobility and a significantly higher diffusivity, leading to higher release rates. Since the permeation occurs through amorphous regions, polymer crystallinity is also a detrimental parameter, especially when working with low molecular weight polymers [142, 143]. The hydrophilic/hydrophobic ratio of the polymer also has an impact on the release. Hydrophobic polymeric particles go through surface erosion while hydrophilic polymeric particles swell and the degradation occurs within the bulk of the polymer [143, 144].

Parameters such as polymer chemical composition, molecular weight, and crystallinity degree can modify the degree of polymer solubility in aqueous system. Non-degradable polymeric particles are used to fabricate matrix-type and reservoir-type drug careers. The release mechanism of these systems is mainly diffusion controlled. In matrix-type systems, parameters such as diffusion distance, polymer degree of swelling, and drug concentration gradient determine the diffusion rate. However, in reservoir-type systems, the thickness and permeability of the polymeric particle defines the rate of drug diffusion and release [145]. Drug release from biodegradable polymeric particles occurs by two typical degradation/

erosion modes. In surface eroding systems, degradation occurs on the outer surface of the particle while in bulk erosion systems, degradation takes place homogeneously all through the polymeric particle [146, 147]. Therefore, the degradation and release can be tuned by developing blends composed of hydrophilic and hydrophobic polymers. Polyesters such as poly(glycolic acid)(PGA), poly(lacticacid) (PLA), PLGA have been rigorously studied for drug delivery applications [148, 149]. PGA is a linear polyester with the simplest aliphatic structure with a Tg around 35–40 °C and high crystallinity resulting into poor solubility in aqueous medium. PLA, composed of poly-L-lactide and poly-D-lactide monomers is hydrophobic and demonstrates different mechanical properties, Tg and degree of crystallinity based on the ratio of its monomers [150]. While PDLA is amorphous with a $T_g$ of 55 °C, PLLA is semicrystalline with a $T_g$ of 53 °C. By copolymerization of lactide and glycolide monomers with specific ratios (L:G), PLGA is obtained, which is one of the most popular materials for engineering drug carries [151, 152]. PLGA particles are mainly considered as bulk-eroding system, providing an initial burst release followed by a zero-order release. The release kinetics of PLGA systems is influenced by multiple factors such as the drug type (hydrophilic vs. hydrophobic), PLGA molecular weight, and monomer composition ratio [153, 154]. For instance PLGA with L:G of 50:50 degrades in 1–2 months. By increasing the lactide monomer ratio, degradation rate slows down, as PLGA with L:G of 75:25, and 85-15 degrade in 4–5 months, and 5–6 months respectively. Upon degradation, PLGA breaks down to its original monomers, PLA will be cleared through the tricarboxylic acid (TCA) cycle and PGA is either removed from the body or converted into other metabolites[146, 155].

Various growth factors have been encapsulated in PLGA micro or nano-particles for wound treatment. In one study, VEGF was encapsulated in 10–60 μm PLGA particles, showed an initial burst release followed by 14 days of sustained release and an increased endothelial cells migration and proliferation [156]. EGF was also encapsulated in PLGA in multiple studies. In one study, EGF was encapsulated in PLGA nanoparticles (193.5 nm) with a high efficiency (85.6%) [157]. Exhibiting a burst release (around 50%) in the first hr, complete release was achieved in 24 hr. *In vitro* studies demonstrated that upon exposure to EGF encapsulated PLGA nanoparticle, fibroblasts growth rate was increased more than 10%. *In vivo* studies on diabetic mice showed an initial decreased healing rate on day 3 for the group treated with EGF loaded PLGA nanoparticles. On day 3, the wound was still in inflammatory stage and PLGA nanoparticles also triggered an inflammatory response as foreign objects. However, the healing rate of the group treated with EGF encapsulated PLGA nanoparticles was significantly increased as compared to the control group and the group treated by soluble EGF on days 7, 17, and 21 post surgery [157].

PCL has a linear aliphatic structure with a very low $T_g$ (−60 °C) and a rather low melting point (60 °C). PCL has been extensively used a scaffold for tissue regeneration purposes and has a very slow degradation rate of about 2–3 years. When degraded, PCL breaks into hydroxycaproic monomer units which will subsequently be incorporated into the β-oxidation cycle. PCL degradation rate can be decreased by copolymerization with other polymers such as PEG, PLGA, HA, gelatin, or alginate [158]. PCL drug carriers have been generated in various forms such as spherical micro and nanoparticles as well as nanofibers, which were discussed in details in previous sections. Polyaminoacids are mostly crystalline

at room temperature and are capable of encapsulating low molecular weight drugs. The degradation of polyaminoacid-based particles can be tuned by varying the ratio of hydrophilic aminoacids within the structure [159]. Poly-L-glutamic acid and poly-L-lysine have independently been used for oral and chemotherapeutic drug delivery applications. In a recent study, Wang et al. synthesized a hydrogel composed of water-soluble ε-polylysine and γ-poly(glutamic acid) [160]. The composite hydrogel showed increased antimicrobial properties against *Escherichia coli* and *Staphylococcus aureus* [160]. Such systems can become more advanced once growth factor encapsulated particles are also embedded within the hydrogel structure. Polymeric systems offer excellent drug perseverance and enable relatively long term drug release. Since during the fabrication of polymeric drug carriers harsh and hydrophobic solvents are used, the encapsulation of fragile molecules carries the risk of deactivation. In addition, usually the loading efficiency of hydrophilic drugs in polymeric drug carriers is lower than hydrogel systems.

**Natural polymers and hydrogels** have also been frequently used for fabrication of drug carriers. Naturally occurring polysaccharides such as alginate, chitosan, dextran, hyaluronic acid, and fibrin provide high biocompatibility and are abundantly available. Therapeutic agents can be physically encapsulated within the scaffold structure or chemically grafted to the polysaccharide backbone. These polymers have also been used as particulate drug carriers for wound healing. In a study by Ribeiro et al. VEGF and EGF were both encapsulated in chitosan microparticles with 255 μm diameter [161]. Growth factor loaded chitosan microparticles were then embedded inside a dextran-based hydrogel. *In vivo* experiments on Wistar rat burn model showed that a single topical application of the composite hydrogel over the burn wound resulted in an increased healing rate compared to applying soluble FGF and EGF every 2 days [161]. Alginate particles crosslinked with calcium chloride have also been used as VEGF carriers. These particles with a diameter of 300–700 μm, were loaded with 2 and 4 μg VEGF/$cm^3$ [162]. A sustained zero-order VEGF release was achieved after day 4, until day 21 with a release rate of 50–90 ng/day and 70–120 ng/day from 2 and 4 μg VEGF/$cm^3$ microspheres, respectively. *In vivo* wound healing on Wistar rats indicated an increased capillary network formation at the epigastric groin fascia of rats treated with VEGF encapsulated alginate microspheres [162]. Hyaluronic acid (HA) is a highly hydrophilic polymer and has been extensively used as a hydrogel scaffold for wound healing applications. Nanoparticles (130–350 nm) of hyaluronate and lecithin were used to encapsulate vitamin E. These particles were next embedded in a bioadhesive film composed of sodium alginate, PEO, and *Aloe Vera* extracts. The proposed formulation provided a slow and sustained release for about 3 months *in vitro* [163].

Fibrin, a non-globular protein with high haemostatic properties has also been used as scaffold for wound healing applications [164]. Apart from those, fibrin has also been used as drug carrier for wound healing applications [164]. Antimicrobial and antifungal agents, such as ciprofloxacin and fluconazole were encapsulated in fibrin nanoparticles with a low release at pH 7.4. In contrast, upon exposure to higher alkaline pH 8.5, the release was increased. Ciproflaxin release was increased 3-fold (16% to 48%) and fluconazole release was increased more than 4-fold (8% to 37%) [165]. Fibrin-based carriers have also been used for growth factor delivery. In one study, dual release of FGF-1 and VEGF was obtained by

fabricating a scaffold composed of fibrin coated poly(ether)urethane–polydimethylsiloxane blend. After the fabrication of polymer-based scaffold, FGF-1 and VEGF were added to fibrinogen precursor. The growth factor containing fibrinogen solution was next coated over the polymeric scaffold, creating a uniform fibrin layer acting as the drug carrier. Within the first 2 days, 30% FGF-1 and 40% VEGF were released from the fibrin coated scaffold. In addition, released factors retained their bioactivity for 7 days [166]. Natural polymers are excellent choice for the encapsulation of water soluble molecule. The key limitation of these materials is their large pore sizes in comparison to polymeric systems, which results in fast release of the encapsulated drugs.

**Lipid-based drug delivery systems** are another class of drug carrier widely employed in drug delivery due to their affinity with cell membranes and ability to pass through biological barriers such as skin [167]. Among different lipid based drug carriers, liposomes are the most frequently used [168, 169]. Composed of an aqueous core surrounded with phospholipids with hydrophilic and hydrophobic heads, liposomes have gained noticeable interest for drug delivery applications since they provide the possibility of encapsulating both hydrophilic and hydrophobic moieties in their aqueous core and lipid bilayer corona [170]. Stromal cell-derived factor-1 (SDF-1) was encapsulated in the liposome core with a high encapsulation efficiency (80%). SDF-1 loaded liposomes (150 nm) were next dispersed throughout an acellular dermis, which was applied over full thickness wound in genetically diabetic mice [171]. Results showed that both control group (acellular dermis with no SDF-1) and the group receiving free SDF-1 only demonstrated similar wound closure rate with full closure on day 28. In contrast, acellular dermis embedded with SDF-1 encapsulated liposomes had a 15% higher closure rate and full wound closure was achieved 21 days post surgery and showed a significant increase in granulation tissue thickness compared to other groups [171]. The effect of growth factor encapsulation in liposomes in promoting wound healing was also highlighted by Pierre et al. rats with scald injuries [172]. Rats that received liposomes containing IGF-1 with a very low dose (0.9 μg/kg/week) had a similar effectiveness in promoting wound re-epithelialization compared to rats that received higher IGF-1 doses (5.0 μg/kg/week) and growth hormone simultaneously [172]. Some liposome-based formulations suffer from low stability associated to burst release. To further increase the encapsulation efficiency and stability of liposomes, new approaches have been suggested. For instance, Xu et al. developed a new liposomal formulation with a hydrogel core composed of silk fibroin [173]. Growth factors, such as bFGF were encapsulated in silk fibroin with high efficiency, providing a sustained release of bFGF from the designed liposome. The bioactivity of bFGF was retained even after 3 days pre-incubation of designed liposomes with wound fluids. Designed liposomes increased the wound closure rate in a mouse model with deep second-degree scald model. The increased healing rate was associated to promoted angiogenesis and enhanced cellular proliferation in the dermis and epidermis [173]. Liposomes are excellent drug carriers, which are biocompatible and could deliver drug to both intracellular and extracellular environment. However, they usually have a shorter drug release in comparison to polymeric systems and offer lower loading capacity. To overcome the limitations associated to liposomal structures, solid lipid nanoparticles and nanostructured lipid carriers have been developed. These formulations provide higher stability, and encapsulation efficiency [174]. They have also proved to be potent drug

carriers for wound healing applications [175]. Amphiphilic copolymers have also been used to generate liposome-like particles for drug delivery applications. These particles have recently been reviewed elsewhere [176].

**Inorganic materials** are also frequently used for engineering of drug carriers. Gold nanoparticles have received noticeable interest in various drug delivery applications due to their stability and anti-inflammatory properties [177]. Inorganic materials lack the proteins in natural systems and are typically considered to be less immunogenic. In wound healing, gold nanoparticles have been used for delivery of active compounds such as antioxidants and nucleic acids. Studies have shown the ability of gold nanoparticles to transiently open the stratum corneum and as a consequence increase the absorption of antioxidant and anti-inflammatory components added to the mixture to accelerate wound healing [178]. Another study, by Lee et al. made use of gold nanoparticles in combination with phytochemicals to increase particle stability without cytotoxic side effects that are often encountered when chemical stabilizers are used [179]. Similar to the previously mentioned work, these phytochemicals also possess anti-inflammatory and antioxidative properties. Even though phytochemicals can easily oxidize, in this system the gold nanoparticles prevent the phytochemicals from being oxidized and the application of these particles showed *in vivo* biocompatibility, blood vessel formation and anti-inflammatory effects in mice burn wound models [179].

Mesoporous silica is another class of drug delivery vehicles that have received significant attention [180]. These particles possess excellent drug loading capacity and the electrostatic interaction between the solid matrix and the encapsulated compounds can significantly increase the release time [180, 181]. Mesoporous particles are one of the few drug carriers that can offer almost linear release profile [182]. Because of their biocompatibility, mesoporous silica has been considered for various biomedical application [183]. In particular, mesoporous silica drug carriers both in the form of particles and needles have been used for treatment of wounds and have demonstrated promising results.

Carbon-based materials such as carbon nanotubes (CNTs) and graphene have also been studied as drug delivery tools. Both materials have good affinity against active compounds such as nucleic acids. There are examples of carbon-based systems used in treatment of chronic wounds [184]. However, their use in biomedical engineering has been controversial as they are not bioresorbable and have the potential of inducing chronic toxicity. Detailed reviews on carbon-based materials for drug delivery applications can be found elsewhere [185, 186].

Overall, the selection of proper material for engineering the drug carrier is crucial. The charge and their water solubility play a role in selection of the drug carrier. The stability of the drug carrier as well as the potential effects of wound environment on the targeted drug and its stability is also important to be considered. In addition to material composition, the shape, size, and microstructure of the drug carriers also can be used to tailor the release profile. Thus, understanding of techniques that can be used for shaping different drug carriers is important. In the following section we will discuss these techniques.

### 3.2 Tools for fabrication of drug carriers

Chronic wounds are usually caused by multiple causes and different biological processes are impaired. For this reason, there is a need to boost all relevant processes involved in tissue regeneration. However, some of the biological processes do not overlap and have different durations, requiring releasing factors at different rates. Thus, noticeable attention has been paid to identification of method to encapsulate multiple compounds and keep their release profiles different. Factors that can affect the release profile include material composition, carrier microstructure, carrier shape and geometry, distance from the encapsulated drug to the carrier surface [187, 188]. Thus, tools that are used for the fabrication of these drug carriers are important in terms of their reproducibility and robustness. For example, particle size plays an important role in the release kinetic and effectiveness of drug delivery [189]. Thus, methods that result in the formation of carrier with high polydispersity are generally less effective in achieving the targeted temporal profile. In addition, nanoparticles with diameter less than 10 nm can be filtered out through kidneys, while larger particles are susceptible to phagocytosis.

The simplest way for fabrication of drug carriers is emulsifying or double emulsifying (Figure 5a) [190]. In this approach, two immiscible fluids are mixed together and as a result spherical droplets of one liquid are formed in the second one. This mixture can be further emulsified to form double emulsions [191]. Emulsification is the most common method for the fabrication of polymeric and lipid-based drug carriers. This approach has also been frequently used for the fabrication of hydrogel based drug carrier. The particle size can be controlled by changing the solutions viscosity and the mixing speed. Nanodroplets can be fabricated by the utilization of ultrasonic probes. Despite the robustness of emulsification, the formed particles are usually polydisperse. In addition, the formed particles are usually spherical. Molding is another method that can be used for particle fabrication. The molds can be fabricated using micro and nanofabrication tools. Molding can be used for the fabrication of both polymeric particles and hydrogels. The formed particles are usually monodisperse, which is a major advantage for achieving predictable drug release. In addition, molding can be performed under sterile and not harsh conditions and thus the stability of the drugs can be preserved. One major limitation of molding is the shape of the formed particles. Fabrication of spherical particles is challenging, but sheet-like, rod-shaped, and planar-constructs can be robustly fabricated. The size of formed particles is also in general larger than those fabricated by emulsification.

One of the most attractive tools for engineering drug carriers is microfluidic platforms [192]. Microfluidic platform have the ability of fabricating multicompartmental droplets (Figure 5e–f) [193, 194]. Droplet based microfluidic systems work similar to emulsifying systems, with the exception that particles are formed by flow-induced shear stress. Thus, formed particles are reproducible and uniform with predictable release profile. Microfluidic systems enable the fabrication of double emulsion droplets and have been used for fabrication of both polymeric and hydrogel drug carriers. Lipid-based particles have also been fabricated. The formed particles using droplet microfluidic systems are usually microsized and are larger than those can be achieved with regular emulsification. Microfluidic fabrication of particles has been reviewed elsewhere in details [188]. The key challenge with microfluidic

drug carrier fabrication is the low throughput and the limitation of size and geometry. Electrospraying and self assembly are other approaches that have also been used for engineering of drug carriers. Detailed information about the fabrication of drug carriers using these systems can be found elsewhere [195, 196].

Achieving different release profile for various compounds is desired in wound healing. This can be achieved through 1) the use of multiple drug carriers with different sizes or compositions; 2) the use of multi-layer multicompartmental drug carriers. In one example, double emulsion systems were used to fabricate PLGA based drug carriers in which PDGF-BB were encapsulated inside PLGA containing chlorhexidine (CHX), which has antibacterial activity. This enabled them to release one hydrophilic and one hydrophobic drug with different release profiles. Wounds receiving dual treatments showed reduced infection and enhanced healing (Figure 5a–d) [190]. In another example, PDGF-BB were encapsulated in PLGA nanoparticles and then the mixture of the fabricated particles and chitosan/poly(ethylene oxide) mixed with VEGF were electrospun to form nanofibrous scaffolds in which VEGF was released fast and PDGF-BB was released gradually [197]. The sequential delivery of the growth factors resulted in enhanced wound healing in diabetic animals.

The ability to release drugs with different profiles is required to promote healing of complex non-healing wounds. The emergence of micro- and nano-technologies has facilitated the fabrication of uniformly sized and structured drug carriers with predictable release profile. However, one key limitation of these fabrication methods is their low throughput and their scalability.

### 3.3. Passive transdermal delivery systems

An important factor affecting the outcome of localized drug delivery is the selection of a suitable point of delivery. Chronic wounds are covered with a layer of non-viable tissue, which separates the outside environment from the underneath tissue [198]. Thus, if drugs and factors are delivered topically, they should first pass through the dead tissue filled with pro-inflammatory cytokines to access the cells that are supposed to receive the therapy [199]. As a result, a significant amount of drugs or factors may get deactivated before reaching the growing tissue. In addition, the significant exudate production in chronic wounds can further reduce the rate of penetration of drugs administered topically. The most traditional way of drug delivery across the skin, hypodermic injections, is quite unfavorable as it is painful, requires professional assistance and can transmit diseases when the hypodermic needles get in contact with different patients.

Thus, there has been a significant push to develop tools that can deliver drugs transdermally. These tools range from micro/nanocarriers that could pass through the skin barrier and stratum corneum or microneedles that could painlessly poke through the barrier and deliver drugs to the viable tissue underneath. Among different drug carriers, lipid-based particles in the form of liposomes and polymeric particles have been widely used. In case of wound therapy, the skin barrier is breached and thus such drug carriers might not be as necessary as compared to the treatment of other skin disorders. Microneedles are arrays of short needles that were initially developed for painless delivery of therapeutics transdermally [200]. They

are sufficiently small in size to pass the stratum corneum but not hit the nerves underneath [201]. These microneedles can be categorized into four groups (Figure 6a): i) solid microneedles disrupting the epidermis barrier and enabling the penetration of topically administered drugs [202], ii) microneedles coated with drugs that can penetrate the tissue and deliver their payload in there [203], iii) dissolvable microneedles that penetrate the tissue and stay there and release their payload gradually as they degrade (Figure 6b) [204–206], and iv) hollow microneedles that penetrate the tissue and facilitate the active delivery of drugs into the region of interest [207].

Since the first transdermal drug delivery product, a three-day patch that released scopolamine for the treatment of motion sickness, was approved for commercialization on the United States market in 1979, many more transdermal drug delivery products have hit the market [208]. Since then microneedle arrays have been used for a wide range of biomedical application including the delivery of insulin, vaccines, and pain medications. However, there has been little interest in them for the treatment of chronic wounds and burns. In one example, Takeda et al. developed microneedles using chondroitin sulfate as the base material loaded with basic fibroblast growth factor (bFGF), a growth factor that is released during the early stages of wound healing and triggers endothelial cells to exert behavior typical for wound healing processes [209]. The needle arrays were tested on rat models with wounds inflicted using a surgical scalpel. ELISA assays on bFGF levels in the tissue showed initially elevated concentrations that slowly declined over time [209]. Caffarel et al. developed a dissolving microneedle system incorporating a photosensitizing compound that has antimicrobial effects to treat infected wounds [210]. This mechanism making use of a photosensitizing drug, also termed photodynamic antimicrobial chemotherapy (PACT) aims to produce highly reactive radicals in the tissue upon irradiation of the photosensitizing drug. Continuing the trend of the use of microneedles for antimicrobial treatment, Park et al. designed antibacterial microneedles loaded with green tea extracts. Green tea includes polyphenols which have shown to be potent antibacterial and anti-inflammatory agents. More specifically, the catechins present in green tea extracts exhibit inhibitory effects on various bacteria. To deliver the extract to the wound area, dissolvable microneedles made of hyaluronic acid were developed [210].

One interesting application of microneedles for the treatment of skin injuries has been proposed by the development of microneedle arrays with swellable tips (Figure 6c,d) [211]. The system was designed in a way such that once upon penetration of the skin, the needles would swell and lock themselves in place. These needles were used for improving the adhesion of skin flaps frequently used for the treatment of burns and chronic wounds. In a follow up study, these needles were loaded with insulin and were used for transdermal and long term delivery (Figure 6e,f) [212]. The array proved to be successful in reducing blood glucose levels in diabetic rodents.

In general, microneedles are an interesting tool that can be fabricated from polymers that are known for their excellent drug protection and the gradual release of their payload. In these cases the drug can be released over the time for completion of physiological processes. These microneedles can be made as composites of different materials and they can also be

developed in a multi-layered way to enable drugs required for late stage wound healing to be released at a later time.

### 3.4. Systems for intracellular delivery

With recent progresses in the field of biology and genetics, recent years have seen many successful examples in which the cells have been programmed to achieve a desired phenotype. Chronic wounds result from dysfunctional cell populations. For example in diabetic patients, endothelial cells are less responsive and usually take longer to form functional vasculature in the wound bed [213, 214]. In addition, in wound healing, macrophage phenotype plays an important role in the tissue regeneration. At the inflammation phase, M1 macrophage polarization (the pro-inflammatory phenotype) results in the removal of debris and pathogens. During the proliferation phase, the phenotype will be polarized toward the anti-inflammatory M2 phenotype [215]. However, in chronic wound this change of phenotype does not occur and results in continuous inflammation. Thus, noticeable attention has been dedicated to transfer genes, plasmids, and active molecules directly into the cells and different tools have been developed for this purpose. These drug delivery systems are usually active, but there are some passive systems which will also be discussed here.

Passive systems usually should possess features smaller than cells that enable them to be internalized. Liposomes and nanoparticles have been frequently used for silencing or activating genes that are important for wound healing. In one example, 13 nm gold nanoparticles decorated with nucleic acid (SNA) were used to downregulate ganglioside-monosialic acid 3 synthase (GM3), which is over expressed in diabetic wounds [216]. The use of these nanovectors had a superior effectiveness on the downregulation of GM3. Upon the treatment of diabetic wound models, superior healing was observed in comparison to free siRNA delivery (Figure 7a–c) [216]. However, the delivery effectiveness of these nanoparticles in heavily exuding wounds can be compromised. Thus, other effective ways which are less prone to being washed away would be more robust and can be applied to different types of wounds. Recently, nanoneedles have emerged as a useful tool that can penetrate cell membrane and delivery plasmids directly in them [217, 218]. In one example, mesoporous silicon nanoneedles were engineered and were successfully tested for delivery of a number of plasmids to cells both *in vitro* and *in vivo* [218]. In animal studies, VEGF-165 gene was delivered using the nanoneedle array to the cells and the results shows a significant enhancement in vascularization in comparison the animals receiving the same gene via hypodermic injection (Figure 7d–g) [218].

The area of cell reprogramming is emerging and it is expected to play a pivotal role in the future of medicine. Along with the advancement in the field drug delivery tools are needed to more effectively deliver the therapeutics into the cells without exerting unwanted damage to cells or their phenotype. Although the current tools have shown promising outcomes, these systems are either hard to fabricate or are prone to dislocation from the targeted site.

### 3.5. Kinetics of controlled release

The goal of drug delivery systems such as micro- and nano-sized particles, gels, and fibers is to increase the drug bioavailability and achieve a sustained biodistribution. Naturally-derived and synthetic macromolecules have been used to entrap drugs and provide a controlled release. The release rate is defined by at least one of the following mechanism: (1) diffusion-based release, (2) degradation-based release, and (3) affinity-based release, and. Zero-order release kinetics is usually preferred since a steady drug concentration is maintained between the minimum effective concentration (MEC) and maximum toxic concentration (MTC) [219]. Although a zero-order release profile is desired, most drug delivery systems show a thriphasic release profile. The initial phase shows a rapid release of drug from the reservoir and is referred to as the burst release. This occurs due to the diffusion and migration of drugs to the surface of drug carrier during the fabrication process or during storage. In phase 2, the release is mostly governed by the diffusion of drug through the polymeric matrix or through the pores of the drug carrier. For biodegradable drug carriers, hydrolysis and degradation of the matrix is also initiated at this phase. In phase 3, a faster release is observed due to erosion of the drug carrier [154, 220, 221]. Parameters such as matrix chemical structure, molecular weight, swelling degree, and porosity, as well as drug-carrier interactions, and drug-drug interactions can affect the release profile [222]. Upon exposure to water, the pores and channels of the reservoir become filled with water. Driven by chemical potential gradient and osmotic pressure, drug molecules diffuse through these water-filled pores and randomly move towards the releasing medium. Apart from diffusion through the pores, drug molecules can diffuse through the polymeric matrix and can also be released due to the erosion of the carrier matrix [223]. Polymeric biodegradable materials have been widely used as drug carriers. These polymers have labile bonds such as esters, amides, and anhydrides in their backbone which will break by hydrolysis or enzymatic degradation resulting in erosion of the drug carrier. Degradation occurs either from the surface or the bulk of the polymeric matrix. As water penetrates through the matrix of the drug carrier, hydrolysis takes place resulting in pore formation and enlargement which will ultimately alter the kinetics of drug release. Affinity-based systems rely on transient interactions between the drug and polymeric matrix [224].

Originally inspired by the controlled release mechanisms observed in the extracellular matrix, affinity-based drug delivery systems use transient interactions between the drug (small molecules, proteins or DNA) and the polymeric matrix. The strength of these affinity interactions is defined by dissociation constant ($K_D$). This value is proportional to the rates of components association and complex dissociation as well as the equilibrium concentration of the components ($C_{drug}$, $C_{matrix}$, and $C_{complex}$). Therefore, the $K_D$ can be calculated as $K_D[M] = \frac{C_{matrix} * C_{drug}}{C_{complex}} = \frac{dissociation\ rate}{association\ rate}$. Designed polymeric matrices can create strong transient interactions with therapeutic agents with a strength range of $10^{-4}$ to $10^{-9}$ M, resulting into a slow diffusion-based release of drug from polymeric matrix, reducing the chance of burst release [225]. Affinity-based systems can be divided based on type of interaction between the drug and polymeric matrix. Most common systems rely on electrostatic interactions (heparin-based, heparin-mimetic or non-heparin interactions), while other novel systems rely on hydrophobic interactions (cyclodextrins interaction with small

hydrophobic molecules) or multiple interaction systems (protein-protein or aptamer-based interactions) [226]. In general, understanding the release kinetic and proper modeling of drug diffusion from these carriers can help with rational design of more effective drug delivery tools with predictable results.

Overall, passive drug delivery tools are suitable choices for enhancing the healing rate in chronic wounds. However, the unpredictability of these wounds and the fact each wound has its own signature will be a major obstacle against achieving optimal therapy using passive systems. Thus, systems that can be used for on-demand drug delivery has been developed that enable active intervention in the dysfunction healing cycle. These systems will be reviewed in the next section.

## 4. Active drug delivery systems

Controlled release drug delivery systems that allow for steady passive drug release over time already provide more efficient treatment options than traditional drug delivery methods. These traditional methods, such as hypodermic injections, often result in an elevated plasma concentration of the drug that is outside of the therapeutic window which can result in side effects and reduce the effectiveness of the treatment. The ability to passively control release enables the system to contain larger amounts of drug while maintaining a drug concentration in the blood within the limits of the therapeutic window, thus allowing the drug to be used for a longer period of time and in a more efficient manner [227].

Wounds are dynamic environments and the proper timing of administration of active compounds is important. The treatment of some pathophysiological complications, however, might only require drug release at the right time. For example, infection is a serious source of complications associated with chronic wounds. Administration of antibiotics as prophylactic therapy has been suggested to prevent infection. However, the excessive use of antibiotics negatively affects the healing process and can result in formation of antibiotic resistant strains. The emergence of antibiotic resistant strains so called “superbugs” is one of the biggest challenges that medicine is facing in the next few years. Current clinical practice includes the treatment of infection through systemic or topical delivery of antibiotics once infection detected by clinicians and confirmed by culture of wound swabs. Thus, for treatment of infected wounds, drug delivery systems should be designed that can release antibiotics only as needed with the correct dosage. This feature can achieved through the use of systems that can either be triggered externally or self-respond to changes in physiological conditions such as pH, temperature or other microenvironmental changes in the tissue. Such systems are called stimuli responsive and over the past two decades various stimuli-responsive drug delivery systems have been developed. Polymers are the most used material for engineering stimuli-responsive systems due to their tunable character allowing for precise control over mechanical and physicochemical characteristics of the material and sharp changes in material properties in response to stimuli [228].

On-demand and stimuli-responsive systems have many advantages compared to passive release systems. As a result of their ability for spatial, temporal and dosage control over the drug release, these systems require a lower drug loading whilst also decreasing the adverse

effects to the patient. This makes drug delivery therapies more efficient, cheaper and safer [229]. In this part we will review both self-responding and externally controlled systems.

### 4.1 Self-responding drug delivery systems

Developing systems that can respond to their environment and change their state has been attractive for many biomedical engineering applications and in particular for drug delivery systems. To achieve this goal, hydrogels and materials that can swell or change their state in response to environmental and external responses has been developed (Figure 8a). In the wound environment, physical and chemical properties such as temperature and pH are indicators of wound status that fluctuate by variation in the level of inflammation, oxygenation, and infection. Usually, skin temperature is in the range of 32°C to 34°C; however, it may locally increase due to inflammation. After a skin cut, the exposure of blood and body fluids temporarily increases the local pH to about 7. This value will be reduced to a slightly acidic value of 4–5 during the healing process. However, bacterial infection can change the pH [181]. It has been reported that the environment of infected wounds is either extremely acidic or slightly alkaline depending on the type of bacteria and wound condition. The level of oxygenation also affects wound pH. In chronic and non-healing wounds which contain significant necrotic tissue, for instance, the pH becomes alkaline locally. Thus, significant effort has been dedicated to the development of drug delivery systems that respond to variations of the environment temperature and pH.

Thermo-responsive polymers have been widely used for engineering self-responding drug delivery systems. Thermo-responsive polymers can be divided into two classes based on the way they respond to heat: lower critical solution temperature (LCST) polymers and upper critical solution temperature (UCST) polymers. The first class of polymers exhibits desolvation upon exposure to heat, whilst the second class becomes soluble when heated [230]. These critical temperatures can be tuned and are dependent on many factors such as molecular weight, polymer concentration and, if applicable, any other materials that are added in the system such as drug formulations [231]. The critical temperature is important, it should be high enough to not get triggered in room temperature and not too high such that high temperatures that can negatively affect the healthy tissue and the activity of the encapsulated drug are required for the material's state to change. Thus, the suitable range for critical temperature is 35°C –45°C [229, 232].

Poly(N-isopropylacrylamide) (pNIPAM)-based polymers have been widely used for engineering thermo-responsive drug delivery systems. The critical temperature of pNIPAM is around 32°C, which is close to skin temperature. pNIPAM is hydrophilic below its critical temperature and becomes hydrophobic above that, where the aqueous solution containing hydrophilic drug will be pushed out of the drug carriers. Due to the low critical temperature of pristine pNIPAM, it can be used for engineering systems that can release their content once placed on the wound surface. Tran *et al.* designed such a thermo-responsive system by electrospinning pNIPAM and PCL to create nanofibers with a high surface-area-to-volume ratio [233]. After incorporation of ibuprofen into the nanofibers, their drug release was tested at 22°C and 37°C and a significant change in release profile was observed. The composite nanofibers showed a reduced burst release as well as a controlled release profile

over 4 h compared to fibers made of only pNIPAM [233]. However, the critical temperature of pNIPAM can be increased by grafting other monomers to the NIPAM chains and can reach over 37°C. In addition, it has been shown the generation of hybrid pNIPAM-based systems can increase their critical temperature. In one example, the critical temperature of hybrid particles of NIPAM-poly(ethylen diacrylate) (PEGDA) was increased to close to 37°C minimizing the passive release of antibiotics at room temperature. Other thermoresponsive drug carriers based on Pluronic F-127 and chitosan have also been successfully synthesized and tested in the literature for engineering self responding systems. In one example, curcumin and DsiRNA were loaded into Pluronic hydrogels and the effectiveness of the drug release for modulation of inflammation in diabetic wounds was demonstrated *in vitro* [234].

PH responsive materials, often ionisable polymers that are weak acids or bases, function through a change in their ionization state resulting in changes in the polymer conformational state [235]. In the case of hydrogels, a change in conformational state means a change in swelling behaviour which can be utilized to control drug release [231]. Ninan *et al.* developed a pH-sensitive hydrogels consisting of tannic acid-carboxylated agarose, in which tannic acid was used for its antibacterial properties (Figure 8b) [236]. Additionally, zinc(II) chloride was crosslinked with the hydrogel. Zinc salts stimulate cell proliferation, have antioxidative properties, and have been shown to be beneficial for wound healing through promoting the synthesis of new ECM, reducing free radical activity, and limiting the growth of bacteria. To study the responsiveness of the hydrogel, the release of tannic acid at different pH values was studied and a minimal release was shown at a pH of 7.4 as opposed to acidic conditions where controlled release was observed. Furthermore, the constructs were minimally toxic to 3T3 fibroblasts as tested *in vitro* and exerted antimicrobial effects that were comparable to gentamicin, a commercial antibiotic, as tested on *E. coli* bacteria [236].

To develop materials that respond to variation in both pH and temperature, copolymers of pH and temperature responsive materials have been developed and used for engineering drug delivery systems. For instance, Garbern et al. synthesized NIPAM and propylacrylic acid (PAA) co-polymers through reversible addition fragmentation chain transfer meant for drug delivery in regions with an acidic pH [237]. This copolymer response to pH changed in the range of 4.5 to 6 as well as temperatures ranging from 20°C to 50°C. Depending on modifications in the random copolymer as well as polymer concentrations, the transition characteristics of the hydrogel were tuned. The hydrogel exerted a controlled release of the growth factor VEGF at pH values of 5 and 6, which are relevant in wound healing applications. Interestingly, drug release rate was not only controlled by polymer dissolution, but also by electrostatic effects between the protein and the polymer's unreacted anionic groups. In a less acidic environment, fewer carboxylate groups were protonated leading to the possibility of electrostatic interactions with the VEGF, hindering protein release [237].

Another class of materials that has recently been explored as an option for responsive systems are materials that respond to the level of chemokines and cytokines in the wound bed [238, 239]. For example, the level of pro-inflammatory enzymes such as elastase and cathepsin have been demonstrated to be highly upregulated in chronic infected wounds [240,

241]. Thus, the use of protease cleavable peptides that can link suitable drugs to the polymeric backbones can result in the formation of polymers with a drug release rate that is proportional to the concentration of the targeted chemicals. In one example, hyaluronic acid capped-mesoporous particles were engineered to carry drugs [242]. The capping hyaluronic acid could be degraded by hyaluronidase-1, resulting in the release of drugs. In another example, rhEGF was conjugated to dextran to be protected against environmental conditions [243]. Upon delivery and exposure of the caged growth factor, dextran was degraded by α-amylase, exposing the protein. The protected growth factors had a better long term effect on keratinocyte growth (Figure 8c–e) [243]. Currently, such systems are widely being used as diagnostic tools for detection of hyper-inflammation and infection, but they may serve as an excellent tool for engineering self-responding materials that can modulate the level of inflammation or automatically eradicate infection. In another interesting study, thrombin-responsive microneedles were fabricated that could release heparin in response to localized upregulation of thrombin to avoid thrombosis [244]. Such technologies can be used for wound care by incorporation of drugs that can regulate the wound microenvironment.

Self-responding systems are excellent drug delivery tools that are helpful for treatment of patients with limited access to medical facilities and for diabetic patients in which any skin cut can potentially turn into a chronic wound. However, the key limitation of these systems is their loading capacity, especially for systems responding to biological cues. These materials are also usually not FDA approved for internal use and are limited to temporary dressings. Thus, there will be a gap between the delivery point and the healing tissue, which can negatively affect the therapeutic outcome. Overall, these materials can potentially revolutionize the wound care if these challenges are solved.

### 4.2 Externally triggered drug delivery systems

Another class of active drug delivery systems is those that can be triggered externally. Such systems should ideally offer zero passive release rate and the targeted drug would be only released once needed. Although such systems have numerous applications in medicine, in wound care they are mainly suitable for the delivery of antibiotics, anti-inflammatory drugs, and pain medication. In these systems, an externally triggered module drives the drug towards the skin or through that [245]. Recent advances in the area of microfabrication and flexible electronics have further enabled the development of such systems. For example, the combination of stimuli responsive drug carriers and flexible heaters has led to development of wearable devices that can release drugs on demand. In one example, Bagherifard et al. fabricated flexible heaters and casted a layer of alginate hydrogel containing pNIPAM microparticles on top of that [246]. The platform was integrated with a driver that enabled the triggering of the heater and drug delivery (Figure 9a–e) [246]. In another example, nanofibrous meshes were fabricated in which thermoresponsive drug nanocarriers were embedded into elastic nanofibrous meshes [247]. These meshes possess morphology similar to paper and have been used as a substrate for fabrication of flexible electronics. However, to avoid the triggering of the drug carriers a low temperature radio frequency sputtering was used to deposit metallic heaters from various metals including gold, silver, magnesium, and zinc (Figure 9f,g). It demonstrated that the release profile of the drugs could be controlled by the applied voltage and the generated heat. The released antibiotics were potent against

culture of different bacteria. The device could be triggered using a smartphone (Figure 9h,i) [247].

Usually skin disorders are multifactorial and different drugs at different stages of wound are required. Also, for patients who are leaving in remote areas, having a patch which is already loaded with potentially needed drugs in which they can be triggered as needed is helpful. However, releasing different drugs with independent profiles is challenging. In a recent study, Mostafalu et al. formed multicompartment fibers with a core thread heater coated by a layer of alginate-based hydrogel [248]. Thermoresponsive microparticles of pNIPAM-PEGDA were fabricated using a microfluidic systems and incorporated into the hydrogel coating. The fibers were then woven into a patch and each fiber was connected to a controller that enabled addressing them independently (Figure 10a,b). It was shown that the fibers could be triggered one by one or together and the number of triggered fibers would result in the release of specific quantity of the drug (Figure 10c–e). The system was effective for preventing bacterial growth. Also, the release of VEGF from the engineered patches helped with improved vascularization and wound healing both *in vitro* and in diabetic animal models (Figure 10f,g) [248].

One interesting example of active delivery for wound care is topical oxygen delivery [249]. It is known that the tissue oxygenation can significantly improve the rate of wound healing. Currently hyperbaric oxygen therapy (HBOT) and topical oxygen therapy (TOT) are being practiced for treatment of diabetic and chronic wounds [250, 251]. However, oxygen therapy usually requires the presence of sophisticated devices and which are not portable. In addition, these systems carry the risk of oxygen poisoning in patients. To address these challenges, recently a wearable dressing was developed by Ochoa et al. in which hydrophobic porous substrates were coated with catalyst particles and were bonded to a PDMS layer containing microchannels [252]. A manual pump was used for pushing $H_2O_2$ through the channels. In contact with catalyst particles, $H_2O_2$ was broken into water and oxygen. Only oxygen could permeate through the hydrophobic membrane towards skin (Figure 10h,i) [252].

An alternative to thermoresponsive drug carriers for engineering externally triggered systems is the iontophoretic drug delivery platforms [253]. In these systems, charged drug molecules or drug carriers are placed between two electrodes and are moved along the electrical field to penetrate the skin (Figure 11a). These systems have been previously used for transdermal delivery of drugs. For example, in an example, sweat generating drugs were delivered to enhance the rate of sweat generation in human subjects [254]. These systems can also be applied to wound care as they enable precise control over drug delivery. Iontophoretic delivery of nitric oxide was compared with its subcutaneous delivery for wound healing after skin flap surgery [255]. The results indicated superiority of the iontophoretic delivery in improving flap survival.

In the past decade, the use of jet injections has gained attention for transdermal delivery of therapeutics. Jet injectors generate high-speed fluid streams to penetrate the skin and deliver compounds to deeper layers of the skin (Figure 11b). Jet injectors have already seen use in a clinical setting in the fields of skin remodeling and rejuvenation and are being explored for

use in wound healing [256, 257]. Kobus et al. showcased the capability of the AirGent, a microjet injection device that is used to deliver compounds into the skin in a minimally invasive manner, to induce wound healing [256]. Kwon et al. used a similar injector called the INNOJECTOR™ to investigate the process of skin rejuvenation through HA injection. They discovered that the microtrauma which stimulated surrounding tissue to an increase in collagen synthesis was caused by the activation of vimentin, a protein that plays a role in wound healing [258].

Different approaches such as gene transfer using jet injectors are also receiving attention. Gene therapy generally relies on the use of viral vectors or nanoparticles, which possess safety issues and are limited in efficiency. The use of needles for gene transfer into rats has previously been established, however jet injectors showed a 100 fold higher efficiency. Kunugiza et al. used the Shima Jet, a jet injector that has already seen use in humans, to co-inject HGF and prostacyclin synthase (PGIS). Treatment of mice models using this approach resulted in promoted wound healing (Figure 11c–e) [259].

One important area of active delivery systems is the use of externally triggered microneedle-based platform. In one study, microfabricated tapered microneedles were used for insulin injection. The successful of these systems led to effective control in blood sugar level. These microneedles can be integrated with other actuation mechanisms such as ultrasonication devices, piezoelectric systems, and micropumps for active drug delivery [260].

Overall, the active delivery of drugs for wound care is a relatively new and less explored area, which has significant potential for changing the current wound care practice. Identifying mechanism that can eliminate the unwanted drug release is important, but realization of such platforms would significantly reduce the pain and morbidity of chronic wounds. Also, finding effective tools that allow the efficient transport of drug into deeper layers of skin and wound in a minimally invasive fashion could further improve the outcome of the utilized therapeutics.

### 4.3. Smart and automated systems

Automated drug delivery devices are mostly used to maintain the level of cytokines, drugs, and other conditions at a desirable level [261]. Current medical devices usually either have the capability of monitoring or delivery of therapeutics. In this approach, medical professionals are considered the decision makers, who can interpret the data and decide about proper course of therapy. Recent advances in electronics have enabled the packaging of systems with high processing capacity in portable and wearable formats. These electrical devices can also be connected to remote devices through internet or Bluetooth communication. Thus, the data can be easily processed on board or online and the decisions can be made automatically for proper treatment. Chronic wounds affect a large number of populations and the continuous need for hospital visit by patients to be assessed on the wound healing progress place substantial pressure on medical professionals and patients [262]. Thus, systems that can automatically monitor the wound environment as well as patients' health while being capable of therapeutic delivery have become attractive for wound care. As a result, significant attention has been paid to the development of sensors for wound care, which have been recently reviewed elsewhere.

Although various smart systems with both sensing and delivery capabilities have been reported for controlling blood sugar level or treatment of movement disorders, there are only a few examples of smart bandages. One of the challenges that have significantly affected the progress of the field has been identifying specific markers that can lead to specific diagnosis in wound care [263]. Wound pH and temperature have been related to the status of wound [264]. Elevated temperature is an indication of inflammation and elevated or significantly acidic pH can be an indication of non-healing wounds which are usually contaminated with pathogens [264]. In two different studies, automated bandages were developed that were equipped with either electrochemical or colorimetric pH sensors as well as drug delivery modules (Figure 12) [77, 265]. Mostafalu et al. were the first to engineer an integrated multilayer bandage in which an array of electrochemical pH sensors were embedded within a hydrogel layer carrying thermoresponsive drug carriers casted on a flexible heater [265]. The sensors and heater were connected to a microcontroller that could also communicate with smartphones. Critical pH values were set on the controller and once the pH was outside the acceptable range the heater was triggered to release antibiotics (Figure 12a,b) [265].

Overall, this area is developing and it is expected that more advanced automated devices to be engineered. Along with advances in wound biology, more specific markers and wearable sensors for their detection should be identified to enable specific diagnostics and treatment. The integration of multi-drug delivery systems such as the one published by Mostafalu et al. [248] with these automated bandages is essential as there is usually not a single drug needed to inducing healing or alleviating the symptoms in patients.

## 5. Concluding remarks and future directions

The field of wound healing has been growing rapidly and a large number of groups are investigating various aspects of wound pathogenesis and providing mechanistic insights about the healing process. In addition, advances in biology and pharmaceutical sciences have resulted in the production new active molecules that improve the tissue regeneration rate and expedite the halted physiologic processes. Along with these advances, better and more reliable drug delivery systems should be designed and tested to improve the bioavailability of these therapeutics at the site of injury. One key area that requires substantial improvement is in the design of drug carriers that address the multifactorial nature of chronic wound occurrence and support the sequence of physiologic processes essential for proper wound healing.

Reducing the distance from the delivery point to the growing cells is also of great importance. For this reason, better transdermal delivery systems that can bypass the necrotic tissue without the need for surgical debridement is essential. Microneedle arrays are excellent tools for this purpose, but their penetration depth, release profile, and release mechanism should be optimized to ensure effective healing.

As medicine moves toward the one solution for all to personalized therapies, the area of wound care will undergo fundamental changes. Each type of wound has its own signature and the sequence of events leading to disruption of healing cycle is different in each case. Thus, developing smart systems that automatically respond to the abnormal changes could

significantly advance the field. This goal can be achieved through two approaches: 1) development of advanced smart materials that can respond to the wound environment and release therapeutics that can mend the dysfunctional processes; 2) engineer automated systems that can sense the wound environment, analyze the data, and deliver therapeutics automatically or after consultation with medical professionals. In the first approach, finding ways to enhance the loading capacity of these systems as well as preserving the activity and properties of the incorporated drugs is of great importance. The latter approach requires combining advances in biosensing, flexible electronics, and wearable devices. Better sensing modalities that are stable in wound exudate rich with various chemokines should be generated. In addition, delivery systems that can ensure on-demand delivery of the targeted drugs or even drug carriers are off great importance. Through these efforts, we can begin to tackle the significant health and financial burden associated with chronic wounds.

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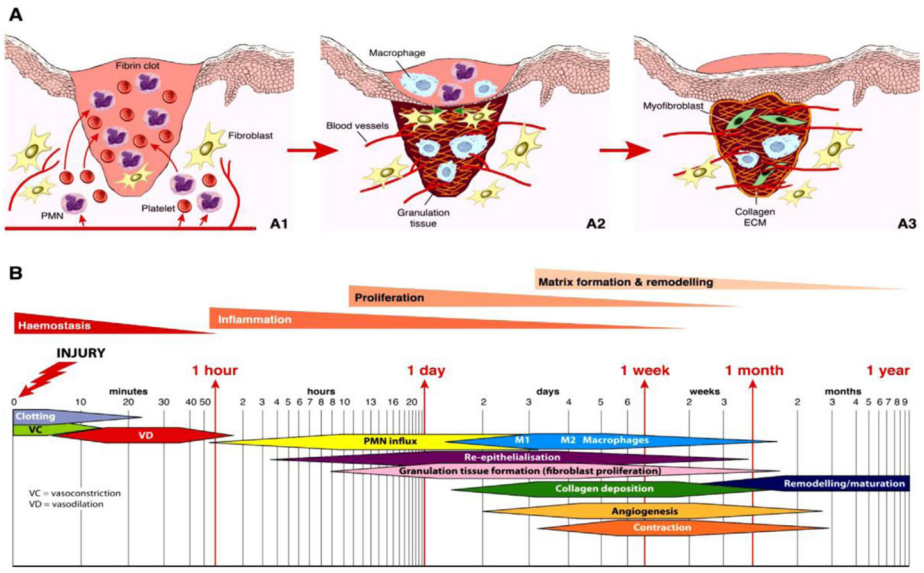


**Figure 1.**

Schematic representation of four stages of wound healing and their time scale. Figure is reproduced with permission from references [11].

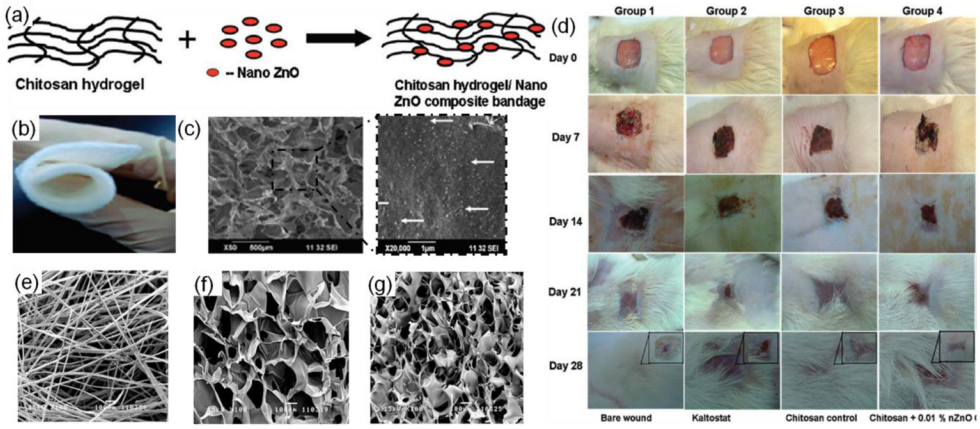


**Figure 2.**

Materials for wound dressings. (a,b) Fabrication of ZnO incorporated chitosan dressing. (c) SEM images showing the microstructure and the ZnO nanoparticles. (d) The effectiveness of the chitosan-based dressings with commercial dressings (Kaltostat) and negative control, confirming the superiority of the engineered dressings. (e) SEM image of Kaltostat commercially available dressing. (f,g) Two different alginate-based dressings fabricated by EDC-activated crosslinking of alginate with polyethylene imine (f) and ethylenediamine (g). Figures are reproduced with permission from references [76] and [80].

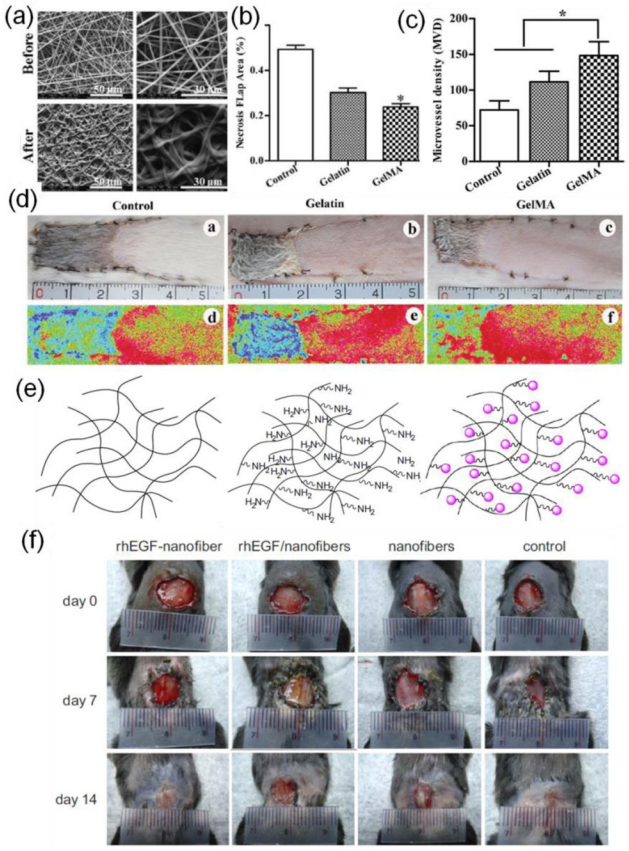


**Figure 3.**

Electrospun scaffolds for the treatment of chronic wounds. (a) The microstructure of electrospun GelMA scaffolds before and after 24 h incubation in PBS. (b, c) The effect of incorporation of GelMA nanofibers and gelatin constructs on the flap necrosis and vascularization. (d) Images of implanted electrospun nanofibrous membranes and the adjacent skin flap. Parts d-f is showing the color laser Doppler detection of skin flaps perfusion (7 days post surgery), confirming the better therapeutic outcome of GelMA nanofiber. (e) Schematic demonstration of the EGF loading into nanofibrous scaffolds. Images showing the effectiveness of inducing wound healing in the diabetic animal receiving nanofibrous scaffolds loaded with EGF. Figures are reproduced with permission from references [97], [104].

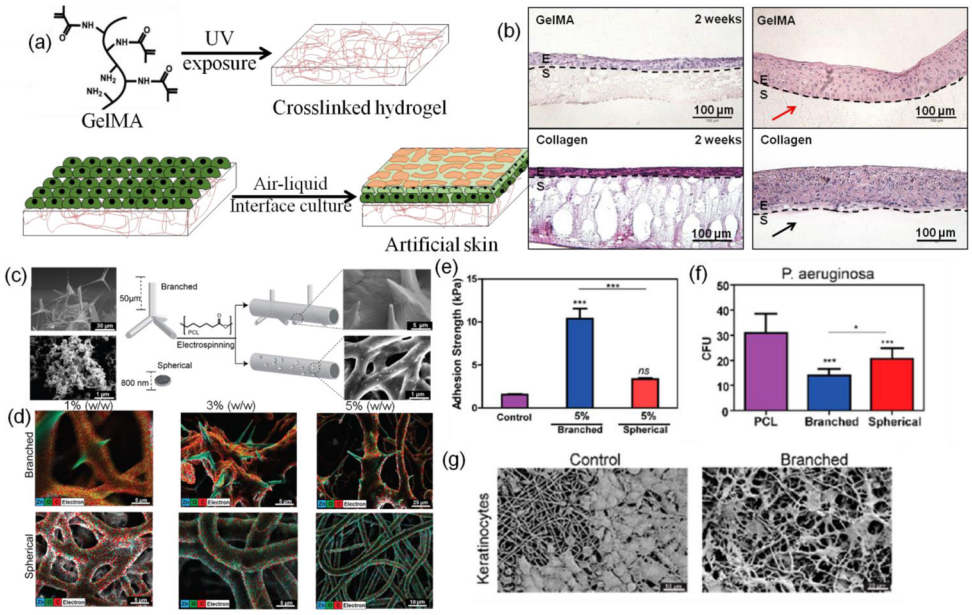


**Figure 4.**

(a) Schematic showing the use of GelMA hydrogel for epidermal regeneration. (b) The comparison of the stratified epidermis formation on both collagen and GelMA-based scaffolds, showing the comparable effectiveness of GelMA hydrogels. (c) The fabrication of composite nanofibers of ZnO and PCL. The incorporation of branched microparticles resulted in the formation of rose-mimicking structures with nano features. (d) The effect of nanospikes on enhancing the adhesion strength of the rose-mimicking nanofibrous scaffolds to surrounding tissues. (e) The better effectiveness of composite rose-mimicking scaffolds in inhibiting bacterial growth. (f) The larger pores in the composite scaffolds facilitated keratinocytes penetration. Figures are reproduced with permission from references [115] and [119].

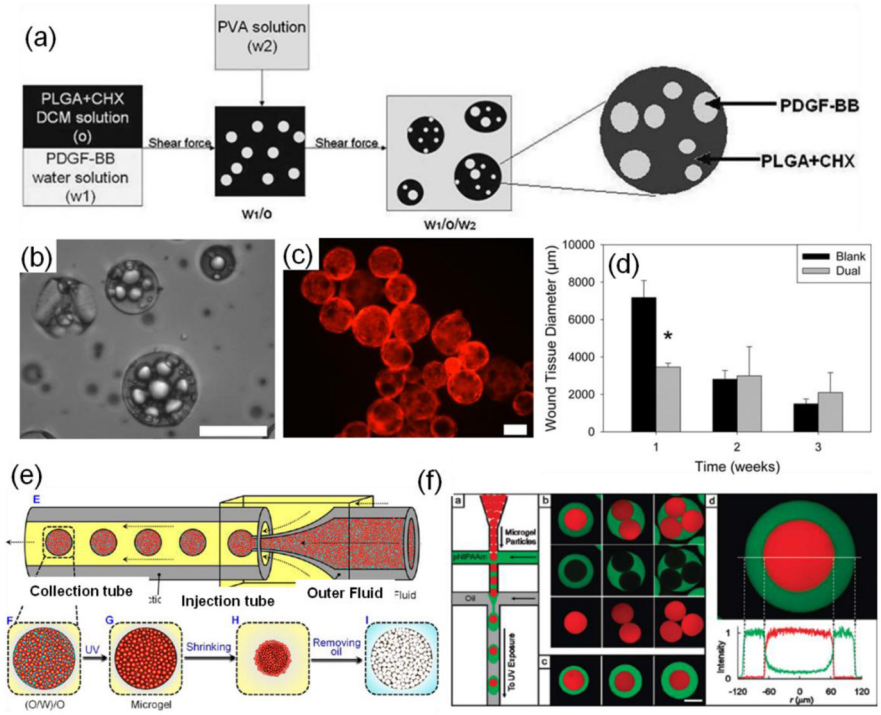


**Figure 5.**

Techniques for fabrication of drug delivery tools. (a) The process of fabricating PLGA-based drug carriers through double emulsion process. (b, c) Micrographs of the fabricated particles containing CHX and PDGF-BB. (d) The effect of dual drug delivery on wound healing rate. (e) Droplet-based microfluidic platform for fabrication of porous microgels. (f) Fabrication of multi-compartment drug carriers using microfluidic systems. Figures are reproduced with permission from references [190], [194], and [193].

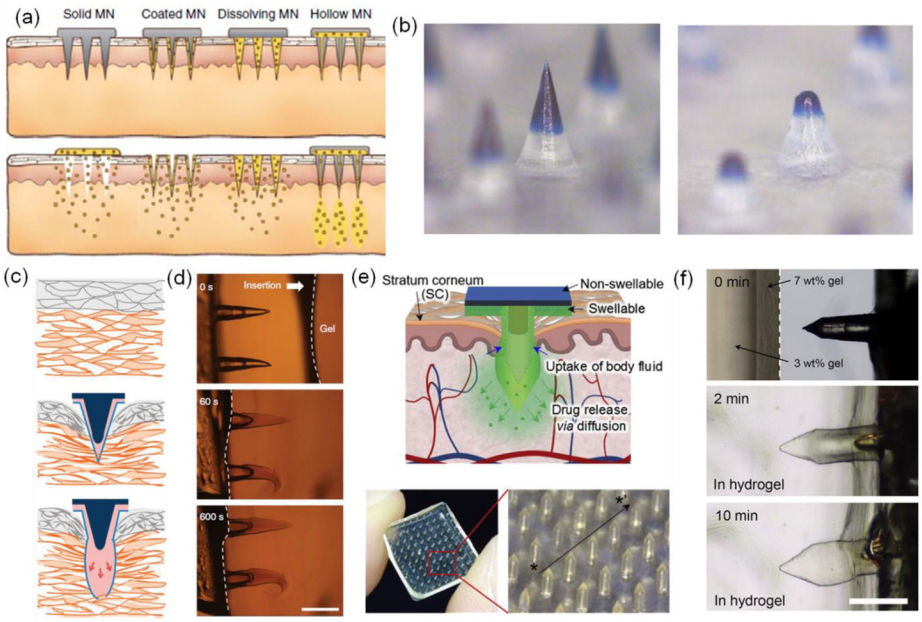


**Figure 6.**

Microneedle arrays as transdermal drug delivery tools in skin care. (a) Schematic showing different types of microneedles used for transdermal drug delivery. (b) Bi-layer microneedles with dissolvable tips carrying insulin before and after implantation. (c,d) Microneedles with swellable tips used for better adhesion of skin flaps to the surrounding tissues. (e,f) Swellable microneedles used as self-locking drug delivery tools. Figures are reproduced with permission from references [207], [204], [211], and [212].

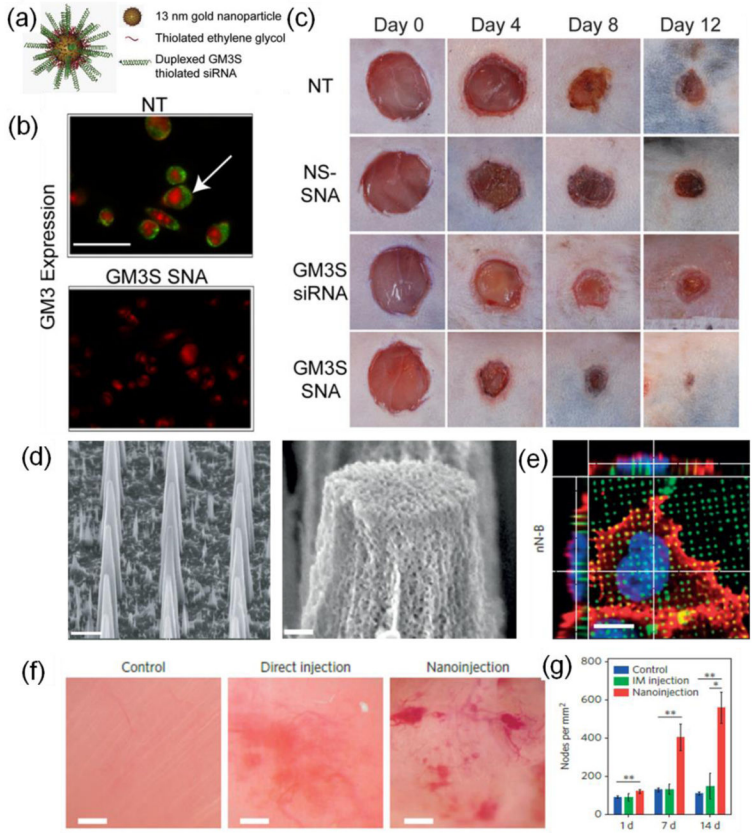


**Figure 7.**

Intracellular delivery tools. (a) Schematic of the gold nanoparticle decorated with nucleic acids (SNA). (b) The downregulation of GM3S in cells treated with SNA. (c) The effect of SNA on healing of exuditing wounds in diabetic animals. (d) SEM images of mesoporous silicon nanoneedles. (e) Confocal image of cells over the nanoneedle arrays. (f,g) Effect of VEGF-165 gene delivery on vascularization *in vivo*. Figures are reproduced with permission from references [216] and [218].

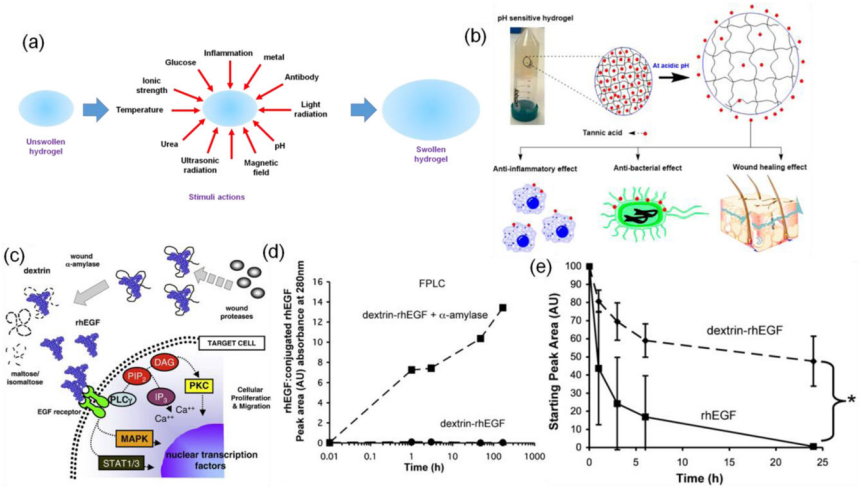


**Figure 8.**

Stimuli responsive self responding drug delivery systems. (a) Stimuli responsible for swelling of hydrogels for controlling drug delivery. (b) pH responsive hydrogels of agarose/ tannic acid crosslinked with zinc ions for the automatic release of tannic acid as an antibacterial and anti-inflammatory drug. (c) The mechanism of action dextrin–rhEGF conjugates in the wound. (d) Effect of α-amylase on the activity of rhEGF. (e) Stability of free rhEGF and dextrin-rhEGF in presence of neutrophil elastase. Figures are reproduced with permission from references [236] and [243].

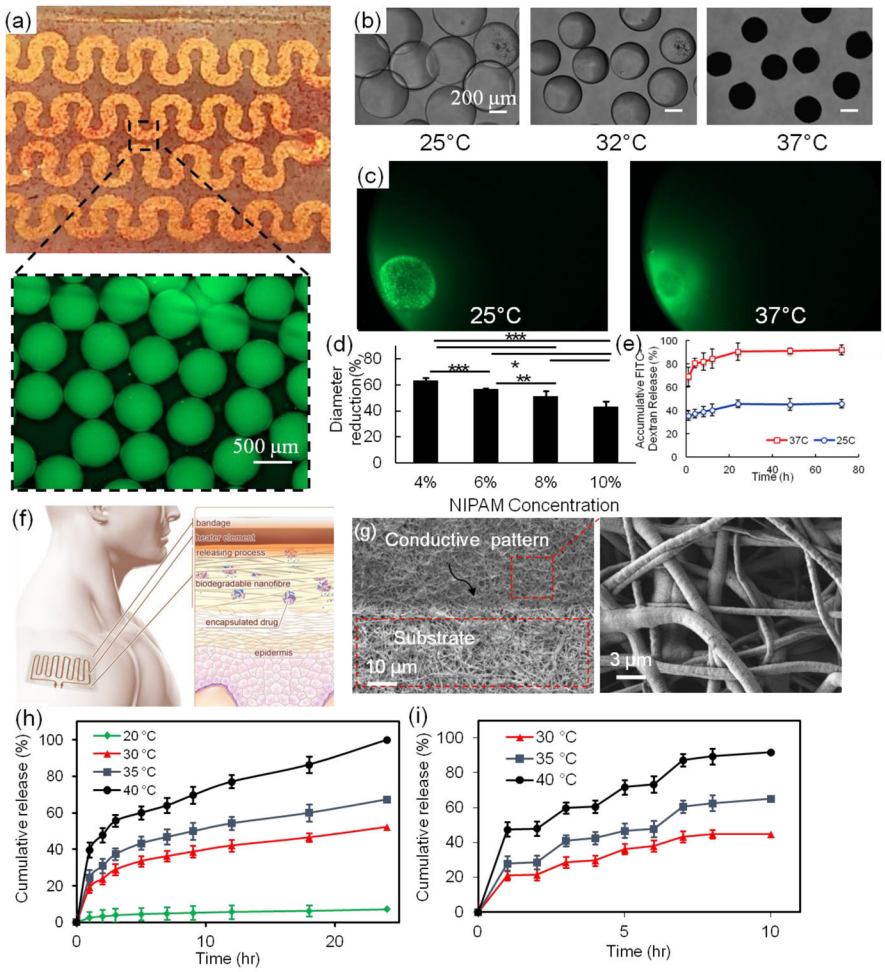


**Figure 9.**

Externally triggered thermoresponsive drug delivery platforms for wound care. (a) A photograph and micrograph of thermoresponsive drug carriers encapsulated in an alginate layer casted on a flexible heater. (b,c) The effect of temperature on the response of the engineered thermoresponsive particles and the release of encapsulated compounds (c). (d) The effect of polymer concentration of the changes of the diameter of thermoresponsive particles. (e) The release profile of FTIC-dextran as a model molecule. (f,g) Nanofibrous meshes in which thermoresponsive nanocarriers were embedded within the nanofibers. A flexible heater was directly sputterd on the nanofibrous mesh. (h,i) Cumulative release of cefazolin from the engineered nanofibrous platform in response of continuous (h) and cyclic (i) application of heat. Figures are reproduced with permission from references [246] and [247].

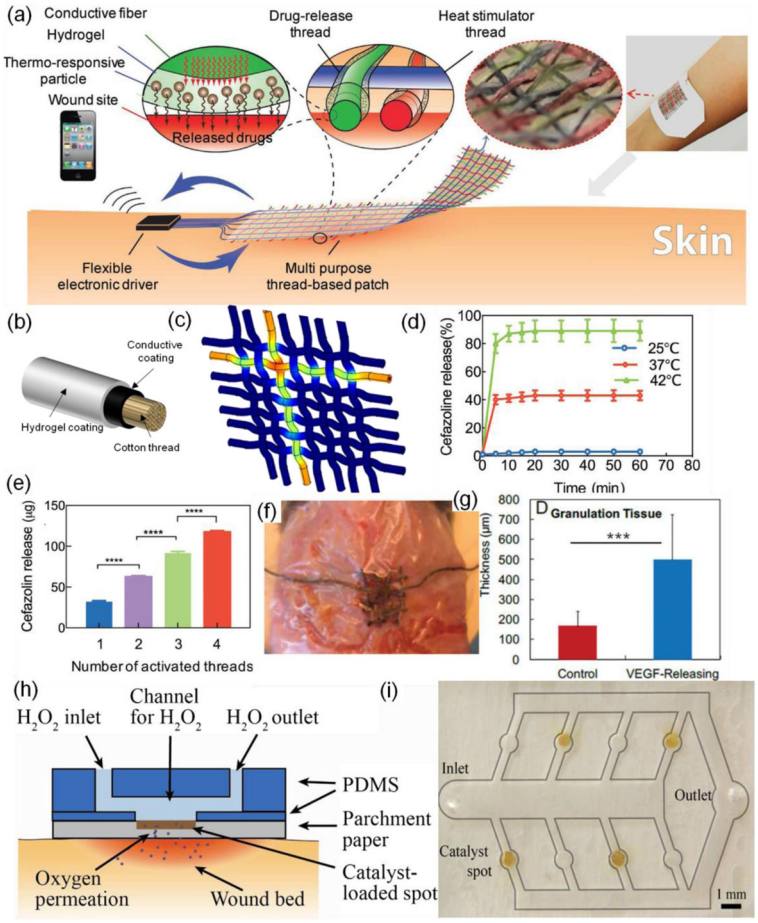


**Figure 10.**

Active delivery of different drugs and oxygen to wounds. (a) Schematics of a thread-based patch for the transdermal drug delivery in which each fiber was comprised of a core heater coated by a layer of hydrogel carrying thermoresponsive particles. The fibers were individually addressed. (b) Schematic of the engineered multi-compartment fibers in which cotton thread was coated with a conductive ink as a core, and covered with drug-loaded hydrogel. (c) Numerical simulation showing the temperature distribution when two fibers are triggered. (d) The release profile of cefazolin from the fibers at different temperatures. (e) The effect of number of activated fibers on cefazolin release from a textile patch. (f) An optical image of the patch on the wound model. (g) The effect of VEGF delivery from the patch on granulation tissue deposition. (h) Side view schematic of oxygen-releasing platform. (i) An image of a typical patch with multiple oxygen generation points. Figures are reproduced with permission from references [248] and [252].

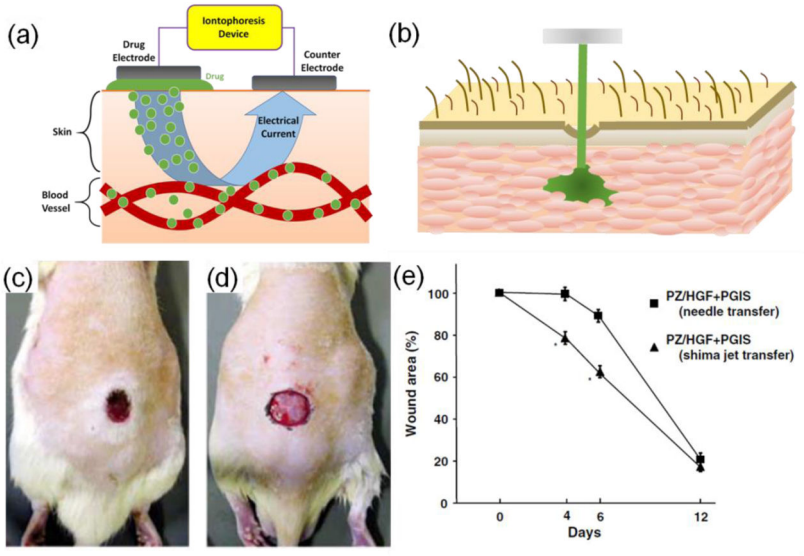


**Figure 11.**

Transdermal delivery of drugs using iontophoresis and liquid jet injectors. (a) Schematic showing the mechanism of operation iontophoretic drug delivery. (b) Schematic demonstrating the use of liquid jet injectors for delivery of drugs into skin. (c,d) The comparison of wound healing in wounded animals receiving prednisolone/HFG using jet injector (c) versus the control without receiving any therapies (d) 7 days post surgery. (e) The comparison of wound healing between groups receiving prednisolone/HFG using jet injector or regular hypodermic needles. The data showed better effectiveness of the jet injector in inducing wound healing. Figures are reproduced with permission from reference [259].

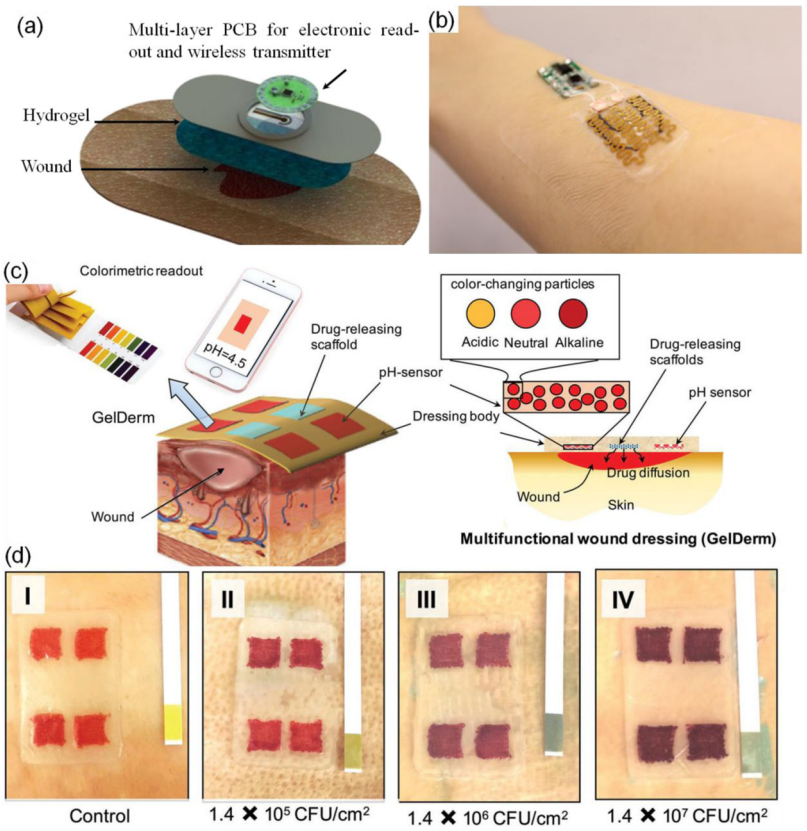


**Figure 12.**

Smart and automated bandages for treatment of chronic wounds. (a) Schematic of multi-layer dressing with both sensing and drug delivery. The onboard electronics can process the data and trigger the drug delivery if needed. (b) A photograph of the wearable bandage with both sensing and drug delivery capabilities. (c) Schematic of a 3D printed bandage with colorimetric pH sensor and drug delivery capability. (d) Effect of bacterial culture on the color of the engineered bandage. Figures are reproduced with permission from references [265] and [77].

**Table 1**

Advantages and disadvantages of various scaffolds developed for the treatment of cutaneous wounds.

| Fabrication method | Materials | Pros | Cons |
|---|---|---|---|
| Medical Gauze (e.g. textile fabricated) | Natural/synthetic fibers (e.g. cotton yarns or polyester fibers) | • Can absorb exudate from the wound<br>• Can keep the environment moist<br>• Can be sterilized<br>• Can be used in combination with other additives such as antibiotics | • Do not provide good barrier protection against microorganisms<br>• Removal of the gauze might cause a second trauma |
| Thin film dressing | Polyurethane | • Elasticity allows comfortable movement of the affected body part<br>• Semi-permeability allows exchange of gases, but still serves as a barrier to bacteria<br>• Transparency allows for visual inspection of the wound bed | • Body fluid accumulation and maceration can occur when used on wounds with high exudate |
| Foams/spongy materials | Natural or synthetic polymers (e.g. polyesters, collagen, gelatin, chitosan, alginate) | • Elasticity allows comfortable movement of the affected body part<br>• Can absorb more exudate than thin film dressings<br>• Allows gas exchange<br>• Can maintain moisturised environment around the wound bed<br>• Porous structure provides cushioning<br>• Good thermal isolation properties<br>• Porous structure supports cellular ingrowth | • High water uptake reduces effectiveness as a drug delivery system<br>• Large pores limit use as a drug delivery tool |
| Hydrogels | Natural or synthetic polymers (e.g. chitosan, fibrin alginate, hyaluronic acid, dextran) | • Can donate moisture to dry or minimally exuding wounds<br>• Can absorb exudate from the wound<br>• Can be easily applied and removed<br>• Can be injectable and form a hydrogel in situ<br>• Can mimic ECM structure and functionality | • Limited gas and oxygen permeability limits its use against infection, requires antibacterial compounds<br>• Rapid dehydration without proper covering<br>• Relatively large pores limit use as a drug delivery tool |

| Fabrication method | Materials | Pros | Cons |
|---|---|---|---|
| | | | • Generally posess poor suturability |
| Hydrocolloid dressings | Colloidal or gel-forming agents (e.g. gelatin or pectin based, carboxymethylcellulose) | • When topically applied, absorb exudate, stick to the wound and become permeable to water and gas<br>• Can provide thermal isolation<br>• Can provide a moist environment<br>• Easy to remove | • Not suitable for infected wounds, as there is poor water vapour exchange with the surroundings |
| Electrospun nanofibrous matrices | Natural and synthetic polymers or polymer composites (e.g. PCL, PLLA, PLGA, PCL-PEG, PLACL, gelatin, GelMA) | • High surface to volume ratio<br>• Can mimic ECM structure<br>• Allows gas and fluid exchange<br>• Good suturability and uniform adherence<br>• Preserve drug activity relatively long<br>• Can allow gradual release of encapsulated drug<br>• Can be coated with active compounds | • Small pore size distribution reduces the rate of cell infiltration and ingrowth |
| Composite materials | Hydrogels or electrospun constructs with incorporated nanoparticle formulations made of ceramic, metallic, or polymeric materials (e.g. zinc oxide, titanium oxide, silver, PLGA, PCL, hyaluronan, alginate, etc.) | • Incorporation of particles improves potential as drug delivery tool<br>• Composite materials combine the beneficial properties of the incorporated components<br>• Wide variety of nanoparticles can be incorporated for different applications | • Fabrication becomes more complex |
| Bi-layered scaffolds | Natural and synthetic polymers (e.g. chitosan) | • Layered structure allows local drug release in each skin layer<br>• Varying functionality and structure of layers can improve full thickness skin regeneration | • Fabrication becomes more complex and costly |