Wound healing materials – a perspective for skin tissue engineering

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Skin injury and wound healing are complex biological and intricate processes that involve activation of intercellular pathways, co-ordination of tissue integrity and homeostasis. The wound can be acute and chronic depending upon the nature and depth of the injury. A wide variety of dressing materials is available to enhance the wound healing process. An ideal dressing should act as a three-dimensional template which can mimic extracellular matrix, be biologically stable, flexible and can remove wound exudate by providing a moist environment to the wound site. It should form a protective bed to cover the wound from external hazards. This article presents a review of wound dressings made of natural and synthetic polymers or a combination of both. A variety of commercial wound healing materials is discussed briefly.

Keywords: Extra cellular matrix, polymer dressings, skin injury, wound healing.

INJURY to skin is a unique challenge and treating it appropriately is a topic of ongoing research worldwide. Cost-effective dressing materials are of immense demand to heal a wound. Many complicated interactions are involved in curing a wound through different phases of wound healing system. Non-ideal wound environment disturbs the healing cascades and makes the wound site prone to microbial attack[1]. Consistent supply of oxygen, nutrients, enzymes and cells is required at the wounded region to facilitate wound healing. An ideal wound bed aims to heal wound quickly by absorbing the exudates and providing a moist environment at the wound site. It mimics the skin structure by forming three-dimensional (3-D) network on the wound, thus, helping the dermal cells to grow and regenerate to form a new skin[1,2]. This article provides an overview of the structure and functionality of skin, skin defects and wounds and recent research trends in wound healing materials. The patents, listed in Table 1, indicate the recent trend in commercialization of wound healing products and a survey of publication over the last five years is depicted in Figure 1.

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Skin structure and its functionality

Skin, the largest organ of the integumentary system, protects the body against external hazards, maintains fluid homeostasis, initiates sensory detection and promotes self-healing when injured[3]. Skin, essentially has two layers, is descriptively shown in Figure 2: (i) epidermis that forms the covering of the body surface; and (ii) dermis that covers the connective tissue. Epidermis is mainly composed of layers of highly impermeable keratinocytes that form a protective shield against external hazards and prevent water loss from the body. Dermis is an elastic and flexible tissue located under the epidermis[3,4]. It is vascularized and provides energy and nutrition to the epidermis. The surface of contact between epidermis and dermis is known as papillae. The hypodermis is a loose connective tissue that forms subcutaneous layer placed beneath the dermis. It consists of numerous amounts of flat cells and hair roots[4–6].

Collagen, elastin and ground substance form the structural components of the dermis. Collagen forms the main framework for the skin which accounts for 70% of the dry skin weight, specifically Type I and III collagen[6,7]. Owing to its high tensile strength and stiffness, collagen provides structural support to the skin. Elastin remains entangled with the collagen and helps collagen fibres to return to their original position at rest. Ground substance is the proteoglycans, a mixture of glycosaminoglycan, hyaluronic acid, keratin, heparin and chondroitin. It binds collagen and elastin together and acts as a lubricating agent during stretching and relaxing of collagen fibres[4,7].

Skin defects

The wound in skin resulting from mechanical trauma, cuts, tumours, poor blood circulation, surgical invasion, burn, etc. is an important issue in the medical field. Wound is a break, defect or discontinuity of the skin which leads to abnormal anatomic structure and function of the skin cells[8]. Wound involving tissue injury that can heal completely in a shorter time is known as acute wound, whereas tissue injury which takes time to heal, is known as chronic wound. An acute wound is simple and

Table 1. List of patents on wound dressing materials published recently in 2016

Patent name	Company name	Application no.	Publish date
Wound dressing with a bacterial adsorbing composition and moisture holding capacity	Abigo Medical Ab.	US20160367405A1	22.12.2016
Dressing for negative pressure wound treatment	Parasol Medical Llc.	US20160361478A1	15.12.2016
Wound dressing and treatment	Smith & Nephew Plc.	US20160361205A1	15.12.2016
Abdominal wound dressing	Kci Licensing, Inc.	US20160354253A1	8.12.2016
Chronic wound dressing with added antiscar compound	University of Rochester	US20160346133A1	1.12.2016
Dressings, systems and methods for treating wound on a patient's limb employing liquid control	Kci Licensing, Inc.	US20160330155A1	24.11.2016
Wound dressing	Foshan United Medical Technologies, Ltd.	US20160317353A1	3.11.2016
Silver containing wound dressing	Convatec Technologies, Inc.	US20160263274A1	15.9.2016
Chronic wound dressing with variable pore sizes	Permeaderm, Inc.	US20160262941A1	15.9.2016
Flexible hydrogel wound dressing	First Water Ltd.	US20160250273A1	24.10.2016

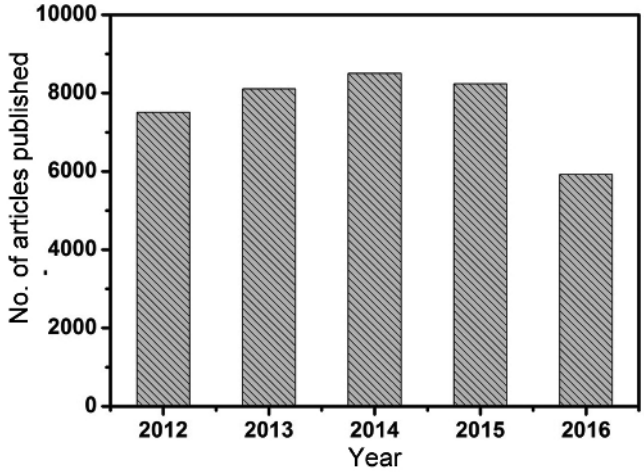

Figure 1. Research articles published in the Scopus-indexed journals in last five years for wound healing. The year 2016 does not include the updated publications in December 2016.

generally occurs due to friction between skin and external hard objects which leads to abrasion and tear of the skin. Chronic wound is the result of extensive repeated tissue insults, or due to exposure to diseases like diabetes, malignancies, etc.[8–10]. Besides, wound can also be categorized into three groups based on skin layers and regions. The wound affecting epidermis alone is known as superficial wound whereas an injury that includes epidermis and dermis along with the damage to blood vessels, sweat glands, etc. is termed partial thickness wound. Full thickness wound involves a disturbance in subcutaneous fat that lies under the epidermis and the dermis[11,12]. Such wounds are referred to as complex wounds which lead to extensive loss of skin components like skin, hair follicles and glands[13,14].

Wounds can further be classified into closed and open wounds. Close wound involves contusion, haematoma, and abrasion. Damage of soft tissue and small blood vessel without any disturbance in the anatomical structure of skin are contusion, whereas vessel rupture results in a haematoma. Abrasions are generally scrapes which lead to the damage of sensory nerves[15,16]. Defective pigmentation is observed but the wounds heal gradually with time. On the other hand, destruction of skin and subcutaneous tissue is referred to as open wound. In this case, in-depth tissue does not lose its continuity and remains healthy[17]. An open wound can be due to laceration, gunshot wound, insect bites, cutting-pricking tools, vascular neurological wound, radionecrosis, etc. All these wounds result in damage to anatomical integrity of tissue and take considerable time for healing[18].

Wounds can also be differentiated on the basis of tissue loss. Wound with tissue loss involves loss of all or some parts of tissue layers. In this case, wound area is filled with granulation tissue to procure healing. Wound without tissue loss occurs as a result of crushing of tissue and bleeding occurs in tissue based on the severity of the wound. Wounds can also be explained in terms of dry wound and moist wound[19]. The wound when kept exposed in air dries and results in the formation of scabs which slows wound healing process. Scab protects wound from environmental contamination but also forms a barrier to the regeneration of new tissue. Moisture is necessary for cell growth. Moist wound creates and maintains optimal moist condition at the wound site[20]. Moist wound treatment prevents the formation of scab by allowing epithelial cells to spread horizontally across the wound to rapidly close it. Hydrocolloid occlusive dressings reduce pain significantly, maintain moist wound environment and facilitate faster wound healing[21].

Wound healing process

Wound healing is a natural biological process. It is a combination of a series of independent processes where epidermal and dermal cells, extracellular matrix (ECM), plasma-derived proteins, growth factors, an array of cytokines all act together to restore the continuity and integrity of damaged skin to initiate replacement of lost

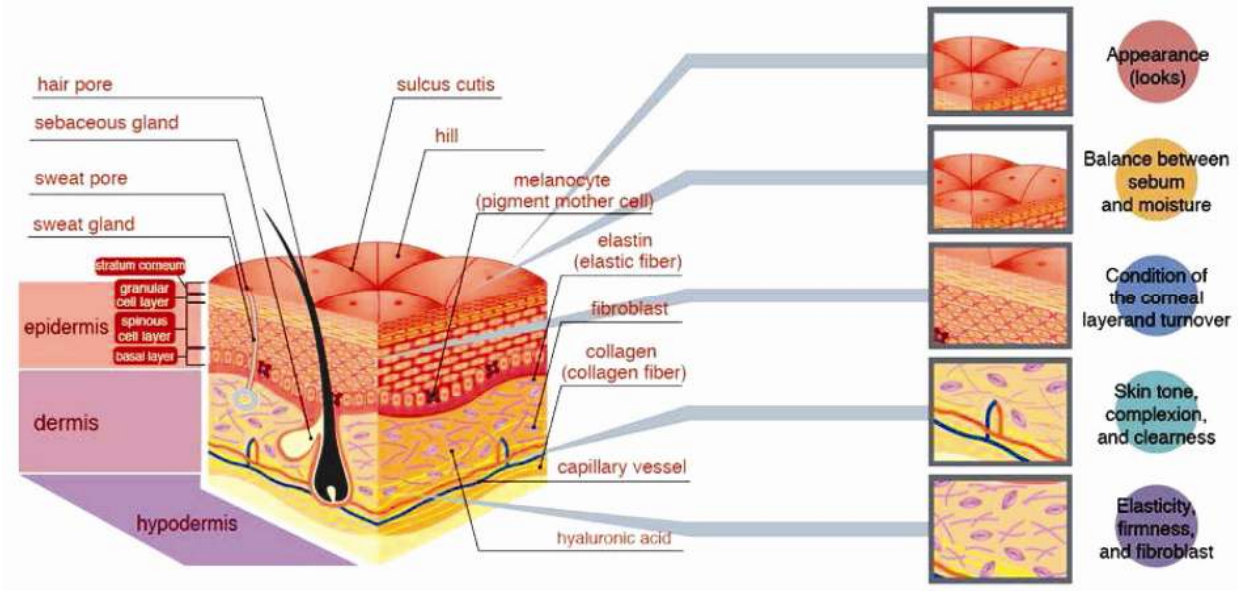

Figure 2. Repesentative image of the three layers of skin and their functionality: the outer layer of the skin is the epidermis which makes melanin giving colour to the skin. The dermis contains nerve endings, blood vessels, sebaceous gland and sweat gland. Nerve endings in dermis help in feeling sensation, tiny dermis blood vessels keep the skin cells healthy by proving oxygen and nutrients to them. It also contains collagen and elastin which are the building units of skin. The third bottom layer is the hypodermis which is mostly made of fat and helps to keep body warm and absorbs shock (adapted from online open access article on Knoji.com, 10 January 2011, by Ghaz).

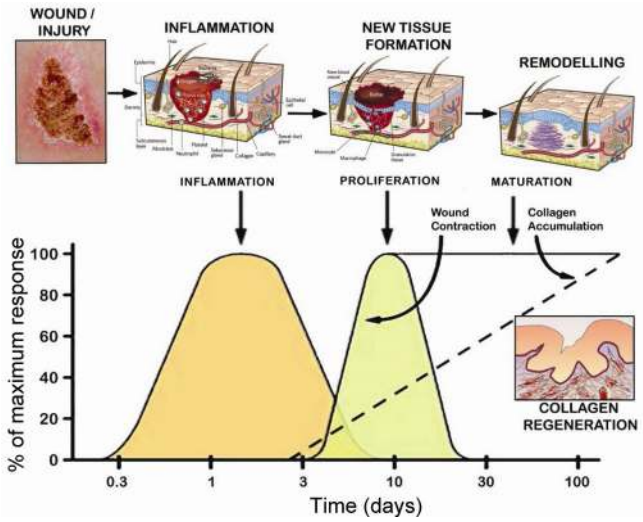

Figure 3. The phases of wound healing with respect to time and a representation of processes that takes place. The first phase is inflammation which lasts for about 1–2 days after injury. The inflammation at the wound is characterized by an ischaemic environment followed by fibrin clot and accumulation of bacteria, neutrophils and platelets in the wound. The second phase is proliferation of cells and new tissue formation which begins 3–10 days post injury. The third phase is the remodelling which lasts for longer time when collagen fibrils tend to organize leading to contraction of the wound near its surfaces. (adapted and modified from ref. 2 with permission).

tissue. The independent stages of wound healing can be coined as the classic stages of wound repair which involve overlying steps such as inflammation, new tissue formation and remodelling[1,2,21]. The various stages of wound healing and the process of new tissue formation are shown in Figure 3.

The inflammation stage begins immediately after tissue damage. It is necessary to control the rise of disturbance in blood circulation by preventing blood and physiological fluid losses[5,18]. Haemostasis is a notable phase in the inflammation stage which plays a vital role in forming platelets plug and fibrin matrix to infiltrate cells from the wound. The platelets and fibrin matrix formations are followed by the recruitment of neutrophils, degranulation of platelets and appearance of monocytes after 2–3 days of injury[2,19]. The monocytes, when differentiated into macrophages play a crucial role in co-ordinating the events responsible for repairing the wound. Cellular proliferation and migration is the second stage of wound healing system involving new tissue formation which occurs 3–8 days post tissue injury. The event starts with migration of keratinocytes on the damaged dermis and formation of new blood vessels, a process known as angiogenesis followed by its replacement by granulation tissues.

The fibroblasts stimulated by macrophages at the wound site differentiate to form myofibroblasts which contract the wound and reduce its size. Combination of fibroblast and myofibroblast helps to establish collagen-rich ECM that gives rise to the matured scar[4,18,19]. Remodelling is the third stage of wound healing which begins after the injury ceases. In this stage, endothelial cells, macrophages and myofibroblasts undergo programmed cell death, i.e. apoptosis leaving the wound site with collagen-protein rich ECM. With the advent of time, the repaired tissue is strengthened and maintained by matrix metalloproteinases (MMPs) secreted by fibroblast, macrophages and endothelial cells[2,20,21].

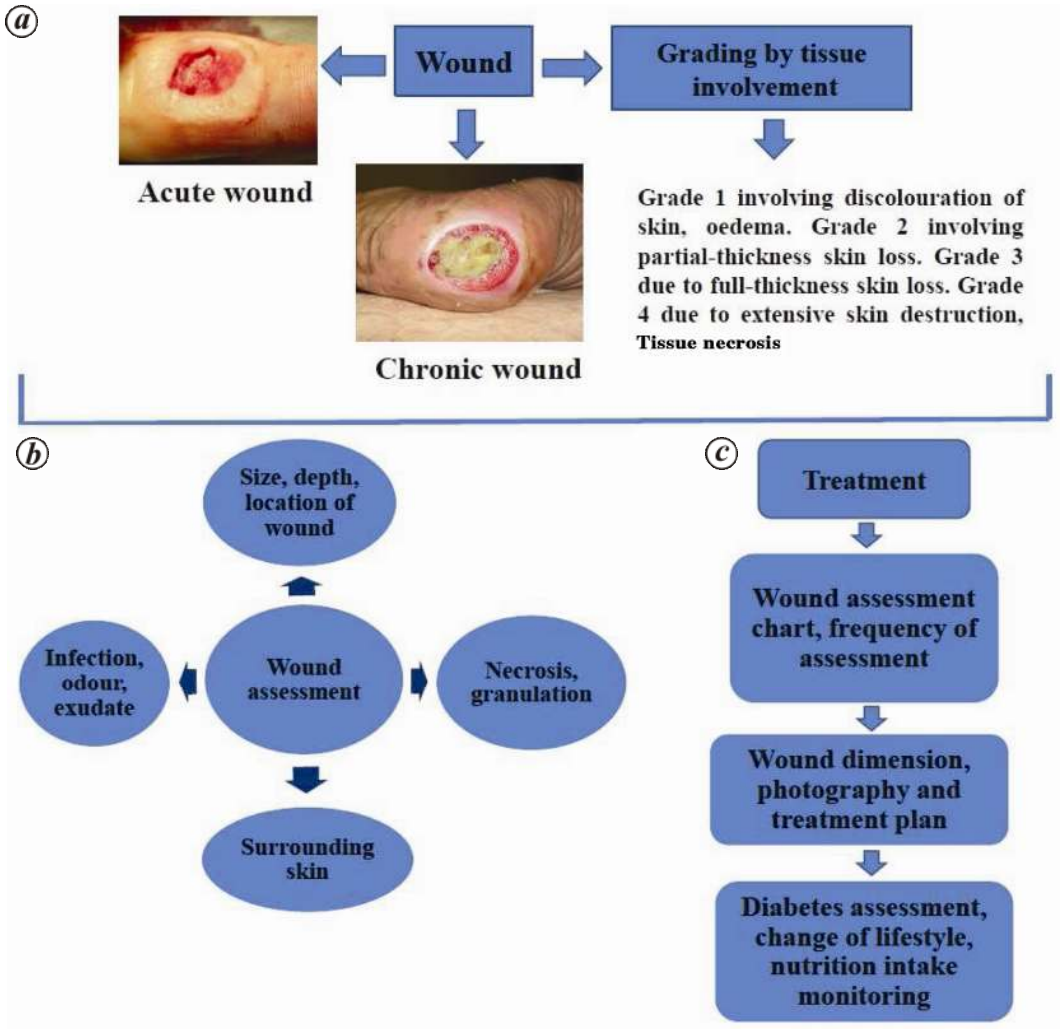

Figure 4. Schematic diagram of (***a***) different kinds of wounds: acute, chronic and wound grading by tissue involvement, (***b***) wound assessment and (***c***) treatment process (Adapted from online open access article on lienvetthuong.vn by Dinh Van Han).

Wound management

Depending upon the nature of a wound either acute or chronic (Figure 4 *a*), it is important to assess the wound within 24 h. Assessment and treatment (Figure 4 *b*, *c*) should be documented containing patient's wound size, dimension and photographs, treatment plan, diseases history and regular diet plan[22]. The most important part of wound healing treatment is the wound care dressings.

In ancient time, honey, mud, leaves, cobwebs, oil, fats and animal dung were used to stop bleeding and to absorb exudate from the wound. Wound requires moist and clean environment, hence, limits its use to some extent[22,23]. Meanwhile, permeable and non-occlusive gauze and cotton bandages are inexpensive, reliable and are highly absorbent. Force is required to remove them from the wound site which may lead to more wound trauma. Later, xenografts, allografts and autografts became the conventional natural skin replacement methods for critical wound healing purposes. There is a high risk of infection with these natural substitutes and they fail to provide suitable templates for skin cells to grow and regenerate. Besides, donor site morbidity in autograft is another factor for its limited use in healing skin wounds[23,24].

An ideal skin substitute should have the capability to act as a protective barrier between the wound and the environment, to prevent infection at the wound site, to reduce the loss of physiological fluid from the wounded region and to minimize local pain. Moreover, the basic need of skin substitute involves in restoring the structure and function of the skin. It should provide an appropriate matrix for the skin cells to grow and regenerate and form a new skin at the wound site[25,26]. It should be non-toxic, non-antigenic, biocompatible and should not get contaminated by microorganisms on the wound surface[23,26]. Recent research in skin tissue engineering depicts skin wound healing treatment which involves epidermis–dermis interaction. Such interaction designates scaffolds

that provide elasticity, strength and nutrients to support the growth of epidermis and keratinocytes on them. The tissue scaffolds act as templates to guide cells to proliferate and retain the structure and function of the damaged skin[22,25]. Healing of wound requires sufficient oxygenation. The substitute should provide room for the wound to be in contact with oxygen. Besides, it should be easily sterilized, cost-effective and must possess long shelf life. Advanced wound therapies focus on preventing ECM damage and synthesizing ECM at the wound site through various growth factors. These have been achieved with many natural and synthetic polymer dressings that are cytocompatible without any provocation of inflammatory response and support tissue regeneration[21,24–26].

Polymeric wound dressings

Natural polymers

Natural polymers are widely used to develop wound dressing materials. Varieties of scaffolds have been fabricated out of natural polymers due to their immense biocompatible and biodegradable properties. Such polymer templates provide means of imparting 3-D structures and deliver physical and chemical integrity to the cell tissue constructs.

Collagen has resemblances with the structure and composition of human skin. Hence, it is a suitable polymer to fabricate and design a wide variety of wound dressing materials. Collagen, found abundantly in mammals, is the main protein present in ECM. It has a tough triple-stranded helical structure and forms 70–80% of the dry skin weight[27]. It gives structural support to the body and regulates cellular functions like cell shape, proliferation, differentiation and cell migration[27,28]. It stimulates cellular and molecular cascades of wound healing and helps in the development of new tissue and wound debridement. Collagen dressings are derived from bovine, porcine or avian sources and are further purified to achieve as non-antigenic material[29]. On application of collagen matrix in the wound bed, drastic change is noticed within 10–14 days and improved wound is observed in the case of chronic wounds like diabetic foot ulcer or chronic venous leg ulcers. Such dressings, when in contact with wound exudate, absorb wound fluid and establish moist environment around the wound. These dressings are semi-permeable to water and oxygen. The hydrophilic nature of collagen helps it to retain fluid and pick up cells containing phagocytosed microorganisms. It plays a vital role in natural wound healing system by inducing clotting and forming matured scar at the wound site. When collagen is combined with dermal cells, growth factors and cytokines derived from the patient, it speeds up the re-epithelization of skin during wound healing. Collagen dressings are also designed as vehicles to deliver therapeutic drug on the wound surface[30]. Numerous studies have been done on collagen dressing formulations for wound and burn healing. Collagen sponges are widely used to treat deep cuts and its hydrogels have potential applications in treating cutaneous wound infections. Collagen scaffolds incorporated with fibroblasts and keratinocytes are widely used for skin grafting. It is also crosslinked with alginate to form biodegradable wound dressing material[29,30]. Glucose oxidase is incorporated in collagen matrix to enhance sustained delivery of growth factors, antibiotics, natural compounds and antimicrobial agents like silver at the wound site[28,30]. Neurotensin-loaded collagen dressings act as wound healing accelerators that stimulate fibroblasts and granulation tissue to accumulate at the wound site leading to the production of sufficient organized collagen matrix[31].

Gelatin is a protein, derived from collagen, also known as denatured collagen. Unlike collagen, it has low antigenicity and is inexpensive[31]. Gelatin is used for preparation of biocompatible and biodegradable wound dressings. It can be fabricated in the form of film or sheath for cutaneous wound repair. Gelatin film is quite effective for wound closure purposes by exhibiting re-epithelization of the epidermis and repair of ECM in the dermis. Gelatin sheaths are used to cure deep partial thickness wounds in the skin. The limitation of gelatin is its mechanical properties and is preferred to be used as a blending agent with other polymers to treat burns, diabetic and venous stasis ulcers and trauma[31,32]. Recent research suggests that gelatin is definitely an effective biomaterial for wound dressing and it has a positive biological response to facilitate cell adhesion and proliferation[33]. Gelatin/polyethylene glycol composites in the presence of dialdehyde carboxymethyl cellulose have been developed to serve as wound healing materials with low cytotoxicity[34].

Alginate is a linear unbranched polysaccharide which is composed of (1→4)-linked β-D-mannuronic acid and α-glucuronic acid residues. It is non-toxic, mucoadhesive and pH sensitive. It forms a reversible hydrogel which acts as a 3-D platform for cell transplantation and new skin formation[35]. Alginate sheaths are prepared by crosslinking alginates with polymers like gelatin, heparin and polyvinyl alcohol which directly control the degradation of alginate. Besides, calcium alginate and collagen alginate act as highly absorbent fibre dressings and provide a moist environment at the wound site. Alginate loaded by growth factors like stromal derived factor-1 improves wound healing as well[36]. Alginate dressings are porous and lack adhesive properties. Alginate, when combined with zinc and silver, offers wound dressing membranes with antibacterial properties[37]. Alginate can trigger macrophage activity and cytokine levels in the wound. Besides, simvastatin loaded alginate dressing prepared by solvent casting method is non-toxic that serves as an excellent dressing template to protect the wound and support the growth of fibroblast cells on it[38].

Study of different alginate dressings showed that they are unsuitable for healing a dry wound with hard necrotic tissues as they dehydrate the wound easily resulting in delayed healing[37,38].

Chitosan, a poly N-acetyl-glucosaminoglycan, is the deacetylated chitin derived from crustaceans like shrimps and crabs, the exoskeleton of insects, invertebrates and cell wall of fungi. It is highly biocompatible, biodegradable, non-toxic, non-immunogenic and exhibits antibacterial properties[39]. It can be easily shaped into films, gels, scaffolds, sponges and can be applied as a healing material at the wound site. It forms a suitable platform to stimulate synthesis of collagen and promotes fibroblast growth on it[39,40]. Chitosan possesses haemostatic and antibacterial properties and its unique property to heal wound makes it a suitable polymer for the fabrication of wound dressing materials.

Generally, chitosan is used in pure form or is treated with cross linkers. The pure form of chitosan fails to provide mechanical support to the cells at the burn or wounded region. Crosslinking of chitosan helps to increase its mechanical properties and hence, provides layered structure for skin tissue engineering[41]. Chitosan is crosslinked with natural polymers like collagen and gelatin to increase its stability. Chitosan gel containing epidermal growth factors and chitosan-silk-fibroin composites form excellent bandage for skin tissue regeneration. Chitosan-nano-silver films possess antibacterial properties and chitosan films along with anti-oxidants are used extensively in dermal wound healing. Such films form dense layers which enhance the functional property of the dermis by controlling the loss of physiological fluid[28,29]. Chitosan has been blended with PEG to achieve hydrogel with improved mechanical strength[42]. Chitosan accelerates fibroblast proliferation by suppressing infiltration of inflammatory cells whereas PEG enhances epithelial migration[43]. Extensive *in vivo* experiments on Wistar albino rats (Figure 5) for chitosan-based dressing materials showed progressive healing and efficiency compared to normal cotton gauze[44].

Hyaluronic acid (HA), a linear polysaccharide, is made from N-acetyl-D-glucosamine and glucuronic acid. It is widely used for treatment of severe burns and wounds. HA can be synthesized in the form of gel, sheath, mesh and film. This polymer showed great promise in animal and clinical studies of skin tissue engineering[45]. It can enhance angiogenesis and reduce intensity of chronic wound to acute wound[46]. It supports scar-free wound healing. HA when combined with other polymers forms a three-dimensional matrix which is structurally and biologically equivalent to the skin. HA, incorporated with silver-sulfadiazine in polyurethane foam, is widely used in would healing applications[45,46].

Keratin is an environment-friendly polymer which has 3-D mesh-like structure. It is composed of structural fibrous protein and is the main constituent in corneous tissues like hair, feather, wool, horns, nails and in vertebrate epithelia. It can be easily shaped in the form of hydrogel[47]. Keratin derivatives can interact with polyelectrolyte wound environment to facilitate healing process. It has high water intake capacity and can be used as dressing material at the wound site to prevent loss of biological fluid to the environment and to minimize wound exudate. The biocompatibility, soft and wet nature of keratin make it one of the promising dressing materials to treat wounds and burns. This hair-based polymer facilitates epithelialization, vascularization and reconstruction of skin tissue[47,48]. Keratin loaded with mupirocin serves dual purposes by providing compatibility for cell support and growth as well as initiates release of antibiotics in a sustained manner at the wound site[49].

Cellulose is a renewable natural polymer which is abundantly available in nature. It is the main constituent of plant and natural fibres like cotton and linen. It is environment friendly, biocompatible and degradable by bacteria and fungi present in the environment. The glucose units are joined together by 1,4-β-glucosidic linkages

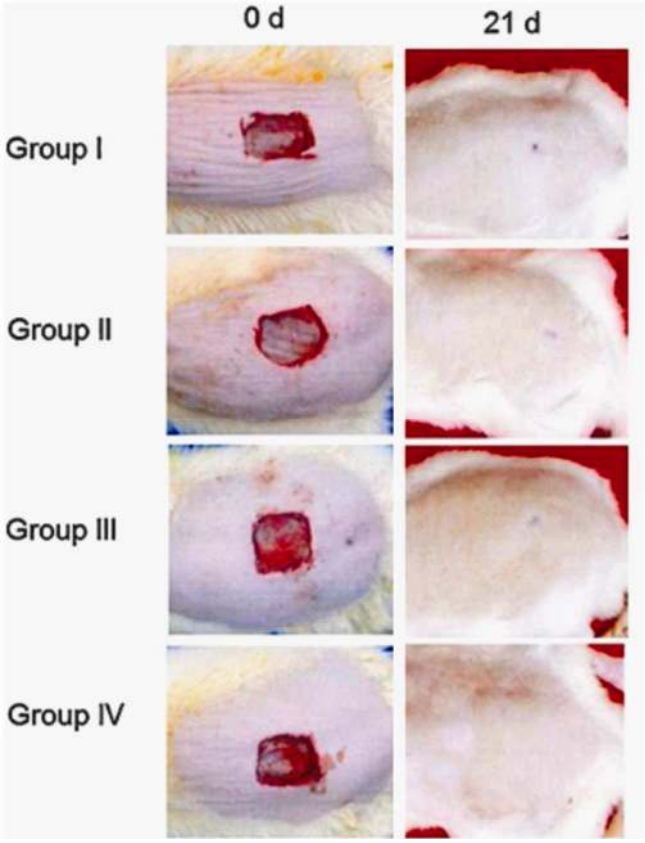

Figure 5. *In vivo* studies of chitosan based wound dressing in Wistar rat model. After 21 days, the healing is better in Group (II–IV) which had chitosan-based blend polymer dressing confirming the efficiency of chitosan based dressings that normal cotton gauze (Group I). The wound surfaces are covered totally with fibrin clot/layer initially indicating the compatibility of chitosan based dressings, in contact with the wounds and heals completely without scar. (Adapted from ref. 44 with permission).

resulting in the crystallinity of cellulose[50]. It is considered as a smart material as it has swelling capability and sensitive to external stimuli[36]. Cellulose is often crosslinked via non-toxic crosslinking agents to improve its stability and mechanical properties. The smart behaviour of cellulose makes it an efficient platform to design wound dressing templates in skin tissue engineering. Cellulose and its derivatives have been used as wound healing membranes. They offer low efficiency to absorb wound exudate and are more prone to bacterial attack[50,51]. Therefore, cellulose-based derivatives along with a combination of other natural polymers like chitosan and gelatin act as super-absorbent templates and form 'barrier substance' to protect the wound from external environment. They also maintain moisture balance in the wound bed. Cellulose-based hydrogels are transparent, hence, healing can be monitored with ease[51].

Microbial cellulose is synthesized in abundance by *Acetobacter xylinum* and its notable physical and mechanical properties and purity make it a suitable and novel material for wound healing and tissue regeneration purposes[52]. Biosynthesis of microbial cellulose is a unique process. The bacteria utilize the carbon compounds from nutrients present in the medium and lead to the polymerization of single, linear β-1, 4-glucan chains. Initially, the cellulose forms as sub-fibrils, assembles as microfibrils and finally, the polymer takes the form of a thick gelatinous matrix in static culture condition which further forms a ultrafine network of cellulose nanofibres[53]. They possess a large surface area to hold and retain a considerable quantity of water into them. Besides, they display high elasticity with appreciable wet strength and conformability. These fibres serve as an excellent barrier to protect the wound from external hazards. Such dressings are used as a temporary artificial skin to cure burns, venous leg ulcers, bedsores and diabetic foot ulcers[53,54].

Silk sericin is a biocompatible protein derived from *Bombyx mori*. It is composed of 18 amino acids and has hydroxyl, carboxyl and amino groups. It can increase cell density, cell lines and activate collagen formation at the wound site by significantly increasing the growth and proliferation of fibroblasts of the human skin[55]. Silk sericin has been successfully studied in biomedical applications for wound healing and drug delivery purposes due to its biocompatibility, biodegradability and nontoxicity to humans. Silk has been extensively used with polyglycolic acid network to enhance physico-chemical, mechanical, swelling and biological properties of the hydrogel[56,57]. Recombinant spider silk protein can be treated as wound dressing material to cover deep second-degree burn wounds[58].

Hydrocolloid dressings

Hydrocolloids constitute colloidal material (gel)-like carboxymethyl cellulose, alginate, and elastomers or adhesives used extensively as wound management products[35,51]. They can be fabricated in the form of films or sheets and are mainly used for treating light exuding wounds like minor burns, traumatic sores and injuries[52]. Hydrocolloids are susceptible to swell when coming in contact with wound exudate and form a gel to cover the wound. Removal of such dressings is painless. Aquacel^{TM} and Granuflex^{TM} (Conva Tec, Hounslow, UK) are efficient hydrocolloids and their performance is superior to tulle gauze in acute inflammatory response[23]. Hydrocolloid dressings possess occlusive outer covering which prevents water vapour transmission and reduces oxygen supply to the wound for faster healing[52–54].

Synthetic polymers

Synthetic polymers are cost-effective and reliable materials which can be tailored in a different fashion in the form of fibres, mats, mesh, films, sheaths and scaffolds to treat skin defects and wounds. Synthetic polymers are mostly used as cross-linking or blending agents and are incorporated into natural polymers to make the latter mechanically stable. Such natural/synthetic polymer blends act as temporary matrices to carry epidermal/dermal cells to cure full thickness wound.

Poly(lactide-co-glycolide) (PLGA) is a copolymer of polylactic acid (PLA) and polyglycolic acid (PGA). It is an FDA-approved biodegradable polymer with immense potentials in skin tissue engineering. It is physically strong, biocompatible and can be fabricated into desired shape and size. Skin substitutes prepared from PLGA are in great demand due to their controlled degradation and tuneable mechanical properties[59]. Polymer degradation synchronizes with the rate of epithelization; hence, achieves successful repair in a scheduled time frame. Moreover, PLGA/PLA mesh when cultured with human fibroblasts gives rise to a template to treat diabetes foot ulcer. The limitation of PLGA lies in its hydrophobicity and it fails to act as an appropriate platform for cell adherence. PLGA can be fabricated in the form of knitted mesh to support uniform cell distribution. PLGA entangled with collagen serves as an excellent 3-D mesh for homogenous distribution of cells and ECM synthesis of dermal fibroblasts in skin tissue engineering[60]. Hybrid electrospun scaffold from PLGA and natural polymer like silk has synergic effect on wound healing. PLGA controls the morphology of healing materials and showcases tremendous potential in wound healing therapy and ulcer management[54,59,60].

Polyethylene glycol (PEG) is an ether based polymer and hydrophilic in nature. It is an oligomer or polymer of ethylene oxide. The non-immunogenic, biocompatible and flexible nature of PEG make it a suitable synthetic dressing material for wound healing. The low toxic PEG macromers are well bonded with growth factor like EGF

and can be delivered at the wound site[61]. The mechanical stability of PEG can be enhanced by blending PEG with chitosan and PLGA. Blending also increases thermal stability and crystallinity of the particular polymer[62]. Such PEG-based dressings have been widely used to treat a diabetic wound by promoting and inducing growth of skin cells and collagen deposition. It also reduces scar formation[63]. The injectable hybrid hydrogel dressing system is developed from PEG-based hyper branched multiacrylated co-polymer and hyaluronic acid in combination with adipose-derived stem cells to support the viability of cells *in vitro* and *in vivo*. It prevents wound contraction and enhances angiogenesis by acting as temporary hydrogel for wound healing purpose[64].

Poly(vinyl alcohol) (PVA) is a semi-crystalline copolymer of vinyl acetate and vinyl alcohol. It is non-carcinogenic, biocompatible, hydrophilic in nature and can absorb a huge amount of water. It can be tailored to the desired shape and size like fibres, sponges and films[65]. PVA possesses low mechanical strength but this lacuna can be overcome by blending PVA with chitosan and hyaluronic acid. PVA can be crosslinked with glutaraldehyde or succinyl chloride to increase its flexibility. PVA blended with collagen enhances the quality of granulation tissue and improves the strength and flexibility of cells at the wound site[66,67]. PVA is the desired material for skin tissue engineering, drug delivery purposes and diabetic wound treatment[68].

Polyurethane (PU) is a polymer whose organic units are joined by carbamate (urethane) links. It is an excellent semi-permeable wound dressing material that protects the wound and surrounding cells from external environment. It is impermeable to bacteria, biological fluid and water. Moreover, it is permeable to gas, and maintains the desired moist environment at the wound site. To overcome the limitation of adherence of PU, collagen or collagen-based peptides are coated on the PU mesh to support the adherence of cells on it and improve tissue biocompatibility[69]. Foam dressings can be designed to form a film with adhesive borders. Lyofoam (Conva Tec) and Allevyn (Smith and Nephew) are well-established foam dressings with additional wound contact layers to avoid adherence with scab or dry wound. They are highly absorbent and the unique porous structure of the dressings makes them suitable for treating partial or full thickness wound. Foam is superior to gauze in reducing pain and comforts in healing wound in patients[69–71].

Polycaprolactone (PCL) is a synthetic polyester obtained by susceptible autocatalysed bulk hydrolysis and slow degradation of linear aliphatic polyester. It possesses perfect biocompatibility, biodegradability and bioresorbability with unique mechanical properties. It is a non-toxic low-cost polymer[72]. It is FDA approved and can be processed easily into different shapes and forms[73]. Electrospun PCL fibres act as suitable templates to treat acute and chronic wounds. They mimic the fibrous structure of ECM. The limitation of PCL material lies in its poor antimicrobial properties. Therefore, silver nanoparticles are incorporated into PCL matrix to ensure its resistance to microbial invasion[48]. In addition, the template has sufficient wound exudates uptake and water retention capacities. PCL-collagen matrix serves as an excellent template that triggers integrin-β1 signalling pathway to regulate the growth of fibroblasts and initiates wound healing[73,74].

Hydrogels

Hydrogels are synthetic polymers that are usually made from polymethyl methacrylates and polyvinyl pyrrolidine. They are insoluble and the crosslinked polymeric components present help to entrap water physically. Such unique suitable hydrophilic materials can absorb and retain a significant amount of water when placed at the wound site[34,50]. Hydrogel dressings are used along with gauze covering to hold them appropriately on the wound. They are considered as ideal dressings as they clean, rehydrate dry and necrotic tissues and initiate autolytic debridement. It has been reported that they promote moist healing and are used to treat venous leg ulcers[37,74]. Purilon™ (Coloplast) and Nu-gel™ (Johnson and Johnson) are widely recognized hydrogels for wound healing purposes. The water retaining property of hydrogels restricts them from absorbing sufficient amount of wound exudate which results in fluid accumulation. They support bacterial proliferation and develop a foul smell in the infected wound. Such dressings possess low mechanical strength and quite difficult to handle[75].

Due to poor cellular adherence of synthetic polymers, limited clinical success is achieved. Hence, they are blended with natural polymers to form composites that balance the advantages of each material. Further investigations and research are needed to understand the concept of biology and materials science involved in developing successful substitutes for skin regeneration and repair.

Commercial dressings

Commercial dressings are the engineered skin substitutes which are fabricated by modifying synthetic and bioactive natural polymers. They are manufactured by using advanced techniques and are cultured with skin cells to give rise to appropriate dressings to heal the wound. The presence of smart polymer in natural and semicrystalline form helps the dressings to mimic physiological responses during different phases of wound healing. An acellular dermal graft made of normal human dermis after the removal of cellular materials from it is coined as AlloDerm™ (LifeCell Corporation). It serves as an excellent template for the skin cells to grow and regenerate and form a new skin at the wound site[76]. Template cultured

Table 2. Common wound healing products available in the market for skin tissue regeneration with the details of its specific applications

Product name	Company name	Characteristics	Applications
Alloderm	Lifecell Corporation	Normal human dermis with all cellular material removed	Acellular dermal graft used for new skin regeneration at wound site
MySkin	Altrika, Sheffield	Cultured autograft composed of living keratinocytes, cultured from biopsy specimen of patient's own skin	Partial thickness burn, skin graft for diabetic neuropathic and pressure ulcer
Apligraft	Organogenesis	Bovine Type I collagen entangled with dermal fibroblast suspension	Epidermal and dermal graft
Integra	Integra LifeSciences Corporation	Temporary acellular silicone epidermal substitute placed over dermal scaffold, consists of collagen and growth factors	Partial and full thickness burn, diabetic, venous and pressure ulcers
BioSeed-S	BioTissue Technologies	Autologous keratinocytes embedded in fibrin glue	Venous leg ulcers
Dermagraft	Advanced BioHealing	Living allogenic fibroblasts from neonatal skin embedded on biodegradable polyglactin mesh	Diabetic foot ulcer, epidermolysis bullosa
Hyalograft 3-D	Fidia Advanced Biopolymers	Esterified hyaluronic acid matrix with autologous fibroblasts	Full and partial thickness wound, scleroderma
Laserskin	Fidia Advanced Biopolymers	Human keratinocytes on a laser microperforated membrane of benzyle hyaluronate	Acellular dermal graft
Aquacel	Conva Tec	Thin film, sheet or composite dressing composed mainly of alginates	Light and moderate exuding wounds like pressure sores, minor burns and traumatic injuries
Tegasorb	3M Healthcare	Hydrocolloid dressing in the form of thin film or sheet	Exuding wound such as minor burns and traumatic injuries
Flexigel	Smith and Nephew	Hydrogel flexible sheet	Non-healing wound of lower breast region and soft tissues
Cia Care	Smith and Nephew	Silicone sheet	Hypertrophic scar
Regranex	Healthpoint Biotherapeutics	Platelets derived growth factors containing hydrogel	Sacral decubitus ulcer
Biobrane	Dow Hickham/Bertek Pharmaceuticals	Silicone, nylon mesh, collagen	Biosynthetic substitute for regeneration of new skin
Epicel	Genzyme Corporation	Cultured autograft made of living keratinocyte, contains no dermal component	Deep dermal and full thickness burn

with autologous human keratinocytes is named as Myskin™ (Celltran Limited) which supports epidermal cells to proliferate and differentiate to a new skin. Apligraft™ (Organogenesis) is a good dressing available in the market. Bovine type I collagen along with dermal fibroblast gives rise to such epidermal and dermal skin substitute. Integra™ (Integra LifeScience) is brought in the market as artificial skin composed of collagen-chondroitin-6-sulphate matrix coated with silicone membrane[76,77]. Biosynthetic skin replacement material named as Biobrane™ (Dow Hickham) formed of silicone, nylon and collagen mesh is highly appreciated to treat chronic wounds[78]. BioSeed™ (BioTissue Technologies) made from fibrin sealant cultured with autologous human keratinocytes serves as epidermal skin substitute to treat severe wounds and burns. Dermagraft™ (Advanced Tissue Sciences) is a skin substitute cultured with human fibroblasts on biodegradable PLGA[79]. Hyalograft 3-D™ and Laserskin™ (Fidia Advanced Biopolymers) are skin substitutes developed with human fibroblasts and keratinocytes respectively on laser-microperforated benzyl hyaluronate membranes. A hydrocolloid dressing, Tegasorb™ (3M Healthcare) is a thin hydrocolloid dressing which provides sufficient moisture and conformability to the wound site and its transparency allows wound observation[80,81]. Commercial dressings possess mechanical properties and anatomical structures that ideally mimic normal dermis. Growth factors and genetic materials are also delivered to the wound site through these dressings[82]. Widely used wound dressing materials that are marketed globally are listed in Table 2.

The representative images of some of them are shown in Figure 6. Commercial dressings can also be obtained in the form of antimicrobial dressings that are incorporated

Table 3. Comparison between polymer materials and commercially available dressings in terms of composition, biological efficacy and cost-effectiveness

Dressings		Composition	Biological efficacy	Cost-effectiveness
Polymer materials	Films	Chitosan, gelatin, cellulose	Fabricated for acute, partial and full thickness wound with low exudates. Perfect for graft donor site, minor burns and to cover surgical incision	Relatively inexpensive
	Foams	Gel film coated foam or polyurethane	Designed for chronic and partial thickness and deep cavity wounds	Relatively inexpensive
	Hydrogels	Cellulose derivatives, hyaluronic acid	Mainly for acute and chronic wounds with moderate exudates. Perfect for chronic ulcers and superficial burns	Relatively inexpensive
	Hydrocolloids	Cellulose derivatives, elastomer and alginates	Designed for acute, chronic, partial and full thickness wound and can be applied on burns and dermabrasions	Moderately inexpensive
	Alginates	Sodium alginate, calcium alginate, polysaccharides	Fabricated for post-operative wounds. Suitable for wounds with moderate exudates, chronic ulcers and as skin grafts	Moderately inexpensive
	Integra	Bovine collagen and shark cartilage; two layered, cell-free membranes	Mainly for partial and full thickness wound	Expensive
Commercial dressings	Dermagraft	Neonatal fibroblast on mesh of polyglactin	Mainly for diabetic foot ulcer and to treat burns	Expensive
	Apligraft	Cultured human foreskin and bovine collagen Type-I	For diabetic venous ulcer and has short-shelf life	High cost, $1000 per circle
	Alloderm	Composed of human dermal matrix	Mainly for partial and full thickness wound and diabetic and venous stasis ulcers, meant for temporary measure and can be applied directly on the wound	Expensive, cost ranges from $50 to $500

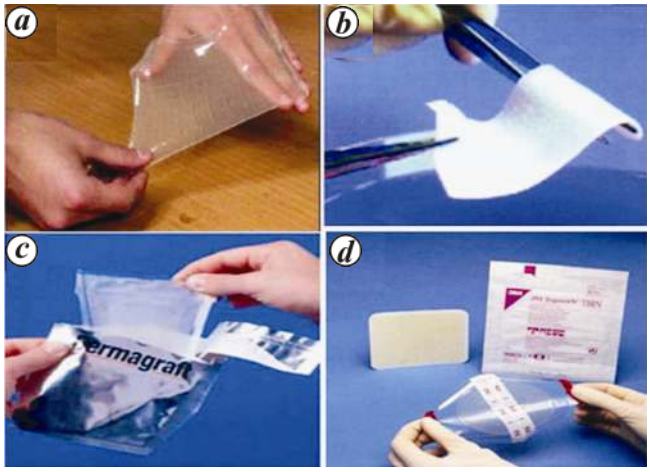

Figure 6. Glimpse of some commercial wound healing materials. ***a***, Polymeric hydrogel sheet wound dressing: It is flexible, can be cut into different shapes to fit around wound and does not require secondary dressing (adapted from Ref. 78 with permission). ***b***, Alloderm (LifeCell Corporation): Regenerated tissue matrix, human dermis processed by removing cells and essential biological components are preserved (adapted from Ref. 1 with permission). ***c***, Dermagraft (Advanced Tissue Sciences): It is non-immunogenic neonatal fibroblasts that are cultured on PLGA mesh. It is widely used to treat diabetic foot ulcer (adapted from Ref. 1 with permission). ***d***, Tegasorb (3M Healthcare): It is a hydrocolloid dressing which deals with the management of chronic wounds like pressure sores and leg ulcers. It creates optimal moist wound healing environment around the wound (adapted from ref. 78 with permission).

with antibiotics and anti-bacterial agents to combat infections for surgical, accidental wounds and for diabetic foot and venous leg ulcers. Antibiotics delivered from paraffin ointments, dialkyl carbamoyl chloride incorporated Cutisorb^{R} cotton wool dressings, and silver impregnated modern dressings are widely available antimicrobial bandages to treat dermal depth burns and wounds[83]. Actisorb^{TM} silver antimicrobial binding dressing 220, an activated charcoal dressing with silver enclosed in non-adherent nylon sheet traps foul odour from wound site and forms a protective barrier around the wound to prevent bacterial invasion, hence, reduces infection[84].

The shortcomings of commercial dressings are its high cost, antigenicity and risk of infection[85,86]. It is also challenging to harvest patient's own cells in the dressing to aid wound healing. Although commercial dressings show improvement in physicochemical and mechanical properties, wound contraction and scarring are still matters of serious concern. Investigation on other natural and synthetic polymers to develop novel wound dressings with improved features and performance is currently on in various laboratories to overcome or minimize such problems. Polymer materials and commercial dressings are compared in terms of composition, biological efficacy and cost-effectiveness (Table 3).

Conclusions

Skin tissue engineering is an advancing field and polymer dressings have benefited patients since 1990s (ref. 87). Natural or synthetic polymers or a combination of both as wound dressing materials have been demonstrated to treat a variety of wound conditions in skin tissue engineering. Other than forming a protective shield between wound and external environment, polymer dressings also serve as cellular skin accompanied by biological components to stimulate re-epithelization and granulation in skin[87,88].

Natural polymer-based materials have been investigated extensively and significant success is achieved by commercializing them for treating acute and chronic wounds. However, several problems are associated with these polymers including high cost, contraction, delayed vascularization and scarring. It is expected that blending of two or more polymers or improvement in fabrication techniques may overcome these problems to eliminate the risk of failure of such skin grafts[89,90]. The shortcomings of natural and synthetic polymers can be overcome by preparing new composite dressing templates with appreciable mechanical, physico-chemical properties and appropriate biocompatibility. The risk of disease transmission can also be eliminated by selectively combining wound healing and immune response through biodegradable polymer composite scaffolds. Solvent casting, phase separation and electrospinning techniques are widely adopted to produce a variety of polymer scaffolds that can mimic the collagenous structure of the native dermis[88].

However, bioengineers, cell biologists and clinicians are facing challenges towards further development of ideal wound dressing template with ongoing interaction and collaborations. Stem cell therapy, a new technology, is a new milestone and strategy with the characteristics of self-renewal and multi-lineage differentiation[90,91]. Such unique features of stem cell technology make it a desirable protocol in treating human diseases with regenerative medicine approaches[92]. Identification and location of stem cells in skin have already been achieved and ongoing research proved the potential contribution of stem cells in the reconstitution of skin at the wound site. Epidermal keratinocytes have a poor regenerative capacity which can be overcome by utilizing self-renewing keratinocyte stem cells[93,94]. In the next decade, stem cell therapy will be a breakthrough in skin tissue engineering to generate skin substitutes that will completely mimic structures and function of the native skin.

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