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To cite this article: Azizeh Rahmani Del Bakhshayesh, Nasim Annabi, Rovshan Khalilov, Abolfazl Akbarzadeh, Mohammad Samiei, Effat Alizadeh, Mohammadreza Alizadeh-Ghods, Soodabeh Davaran & Azadeh Montaseri (2018) Recent advances on biomedical applications of scaffolds in wound healing and dermal tissue engineering, *Artificial Cells, Nanomedicine, and Biotechnology*, 46:4, 691-705, DOI: [10.1080/21691401.2017.1349778](https://doi.org/10.1080/21691401.2017.1349778)

To link to this article: <https://doi.org/10.1080/21691401.2017.1349778>



Published online: 12 Jul 2017.



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Recent advances on biomedical applications of scaffolds in wound healing and dermal tissue engineering

Azizeh Rahmani Del Bakhshayesh^{a,b}, Nasim Annabi^{c,d,e}, Rovshan Khalilov^f, Abolfazl Akbarzadeh^g, Mohammad Samiei^{a,h}, Effat Alizadehⁱ, Mohammadreza Alizadeh-Ghodsⁱ, Soodabeh Davaranⁱ and Azadeh Montaseri^j

^aDepartment of Medical Nanotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran; ^bStudent Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran; ^cBiomaterials Innovation Research Center, Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, USA; ^dHarvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, USA; ^eDepartment of Chemical Engineering, Northeastern University, Boston, MA, USA; ^fInstitute of Radiation Problems, National Academy of Sciences of Azerbaijan, Baku, Azerbaijan; ^gStem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; ^hDepartment of Endodontics, Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran; ⁱDrug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; ^jDepartment of Anatomical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

ABSTRACT

The tissue engineering field has developed in response to the shortcomings related to the replacement of the tissues lost to disease or trauma: donor tissue rejection, chronic inflammation and donor tissue shortages. The driving force behind the tissue engineering is to avoid the mentioned issues by creating the biological substitutes capable of replacing the damaged tissue. This is done by combining the scaffolds, cells and signals in order to create the living, physiological, three-dimensional tissues. A wide variety of skin substitutes are used in the treatment of full-thickness injuries. Substitutes made from skin can harbour the latent viruses, and artificial skin grafts can heal with the extensive scarring, failing to regenerate structures such as glands, nerves and hair follicles. New and practical skin scaffold materials remain to be developed. The current article describes the important information about wound healing scaffolds. The scaffold types which were used in these fields were classified according to the accepted guideline of the biological medicine. Moreover, the present article gave the brief overview on the fundamentals of the tissue engineering, biodegradable polymer properties and their application in skin wound healing. Also, the present review discusses the type of the tissue engineered skin substitutes and modern wound dressings which promote the wound healing.

ARTICLE HISTORY

Received 15 May 2017
Revised 28 June 2017
Accepted 28 June 2017

KEYWORDS

Tissue engineering; scaffold; regenerate structures; biodegradable polymers; wound healing

Introduction

Diseases and disorders led to devastating consequences and organ failures which portray a life-threatening state. Two main approaches which were used to replace or repair the damaged or lost tissue and organs are autografting or allografting. Limitations on autografts, such as donor site morbidity and limited availability, are considered as the drawbacks of these approaches, and although allografts are not limited in supply, they show potential to provoke a strong response from the immune system and pose the transmission of disease risk, too [1,2].

It is important to consider that through the present time, tissue engineering, as an outstanding method for the repair/regeneration of damaged tissue, has been considered as an approach with the potential to transcend the limitations of both autologous and allogenic tissue repair [3].

Biomaterials, as the 3D synthetic frameworks in tissue engineering, are commonly referred to as scaffolds, matrices or constructs and provide an opportunity for the cell

attachment, proliferation and ingrowth ultimately leading to form the new tissue (Figure 1).

Materials used for fabricating the scaffold can be classified as the synthetic or natural and degradable or nondegradable, depending on the proposed usage. The properties of the polymers were influenced by some factors, including composition, structure and arrangement of their constituents [4].

Both synthetic polymers and biological-based polymers, as the biodegradable polymeric biomaterials, have been investigated extensively [5,6]. The mentioned synthetic polymers included the suitable flexibility since the structure and composition could be tailored to the specific needs [7]. Some innovative methods were established for the fabrication of the biomaterial-based three-dimensional scaffolds [8–10]. The scaffolds with the high surface area to volume ratio helped the adhesion, proliferation, migration and differentiation of the cells, all of which were deemed as the extremely desired features for tissue engineering [11,12]. The present article was intended to illustrate the various polymers, natural and synthetic, which were used to produce the scaffolds in the field

of skin tissue engineering. It covers the most commonly different hybrid scaffolds which were used for skin tissue engineering and wound healing. Also, through the present review, an attempt has been made to consolidate the different tissue-engineered skin substitutes and types of the wound dressings.

Biological polymers employed for skin tissue engineering

A large variety of skin substitutes were used in treating the full-thickness injuries. Substitutes derived from the skin might harbour the dormant viruses, and artificial skin grafts could heal with the hideous scarring, failing to the regenerate glands, nerves and hair follicles [13]. Several three-dimensional porous scaffolds fabricated from the various kinds of biodegradable materials have been developed and used for many fields of the tissue engineering [14–20]. The present part of the review summarizes the various properties of the biological polymers which were used in the skin tissue engineering.

Collagen

Collagen could be obtained from the animal tissues, and it could also be made by the recombinant methods [21]. It was characterized by the high mechanical strength, adequate

biocompatibility, low antigenicity and innate ability of being cross-linked, and tailored for its mechanical, degradation and water uptake features [22,23]. Drawbacks of the collagen comprised difficulty in processing and sterilization and also hard to regulate the extent and rate of degradability [24]. Collagen as the major protein factor of the extracellular matrix (ECM) strongly supported the connective tissues such as skin, tendons, bones, cartilage, blood vessels and ligaments [25–29]. Scaffold features could be varied by using the various concentrations of collagen [30]. For instance, bilayered collagen gels, which were seeded with the human fibroblasts in the lower part and human keratinocytes in the upper layer, as the “dermal” matrix of an artificial skin product have been commercialized under the name of Apligraf® [31]. Moreover, Biomend® was a collagen membrane that commonly used in the periodontal tissue regeneration [32]. Chin et al. have reported an approach to build anatomically accurate, multicomponent skin substitutes in a cost-effective way [33]. Glycosaminoglycans (GAGs), meanwhile, served a wide variety of functions such as linking collagen structures and binding growth factors [34]. Integra is a bilaminar membrane consisting of a bovine collagen-based dermal analogue of glycosaminoglycans and chondroitin-6-sulphate and a temporary epidermal substitute layer of semipermeable silicone. It is the most widely used dermal substitute for burning the reconstruction. Glycosaminoglycan composition in this acellular dermal substitute was designed to control the rate of degradation [35,36]. In one of the studies about the Integra’s effectiveness in the treatment of the full-thickness and partial thickness injuries, Heimbach et al. used the Integra to treat 216 burn patients and assessed its safety and effectiveness [37]. The results illustrated which Integra was a valuable, effective and safe treatment modality for managing challenging patients with the extensive burns.

Fibrin

Fibrin as the natural wound healing matrix, forms after injury and fibrinogen as a precursor of fibrin, could be obtained from the pooled plasma [38]. Fibrin scaffolds skin to collagen

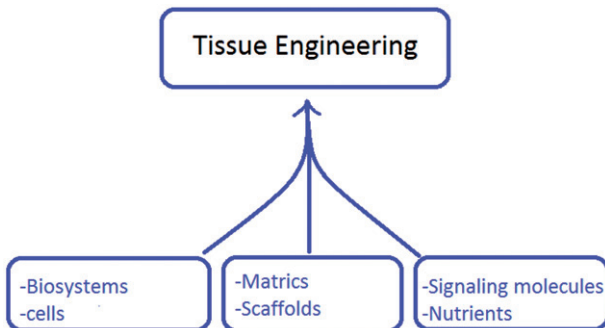


Figure 1. The tissue engineering triad.

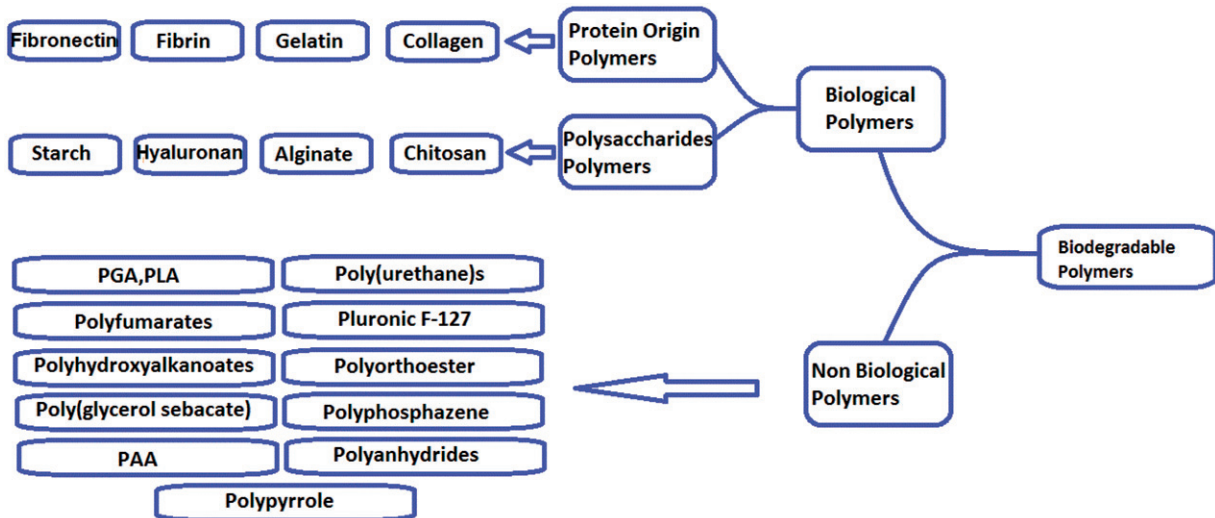


Figure 2. Flow chart for the classification of the biodegradable polymer.

contained some specific sites for the cell adhesion and the scaffold features varied depending on the concentration of fibrin used [39,40].

Fairly, rapid degradation is the most encountered drawback in the shape-specific scaffolds. Furthermore, fibrin could also be covalently modified to further change its properties [41]. Fibrin is a versatile biological-based polymer which reveals an excellent potential in the tissue regeneration and wound healing because it, alone or in combination with other factors, has been considered as a biological scaffold for the stem or primary cells to regenerate bone, ligament,

tendons, liver, cardiac tissue, cartilage, nervous tissue, ocular tissue and skin [42].

Fibronectin

Fibronectin, derived from bovine or human plasma, is a glycoprotein with a high molecular weight, which can bind collagen, fibrin and heparin. Fibronectin could be found in its soluble form in blood and participates in the wound healing procedure [43]. It can be aggregated to form mats, which could be applied as the scaffolds for the repair and regeneration of the neural tissue [44,45] (Figure 2).

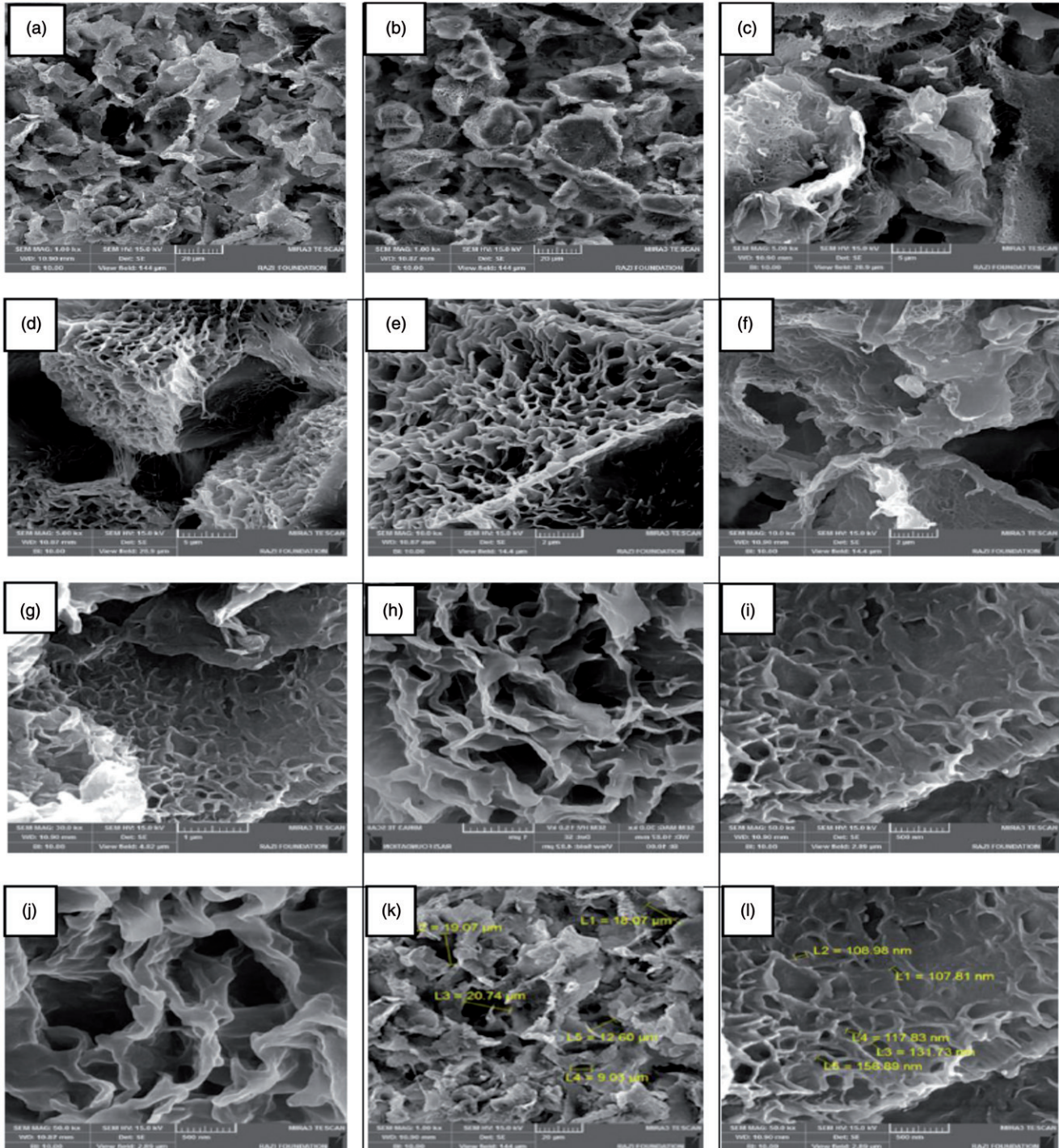


Figure 3. The porous scaffold of polycaprolactone fabricated by the freeze-drying method.

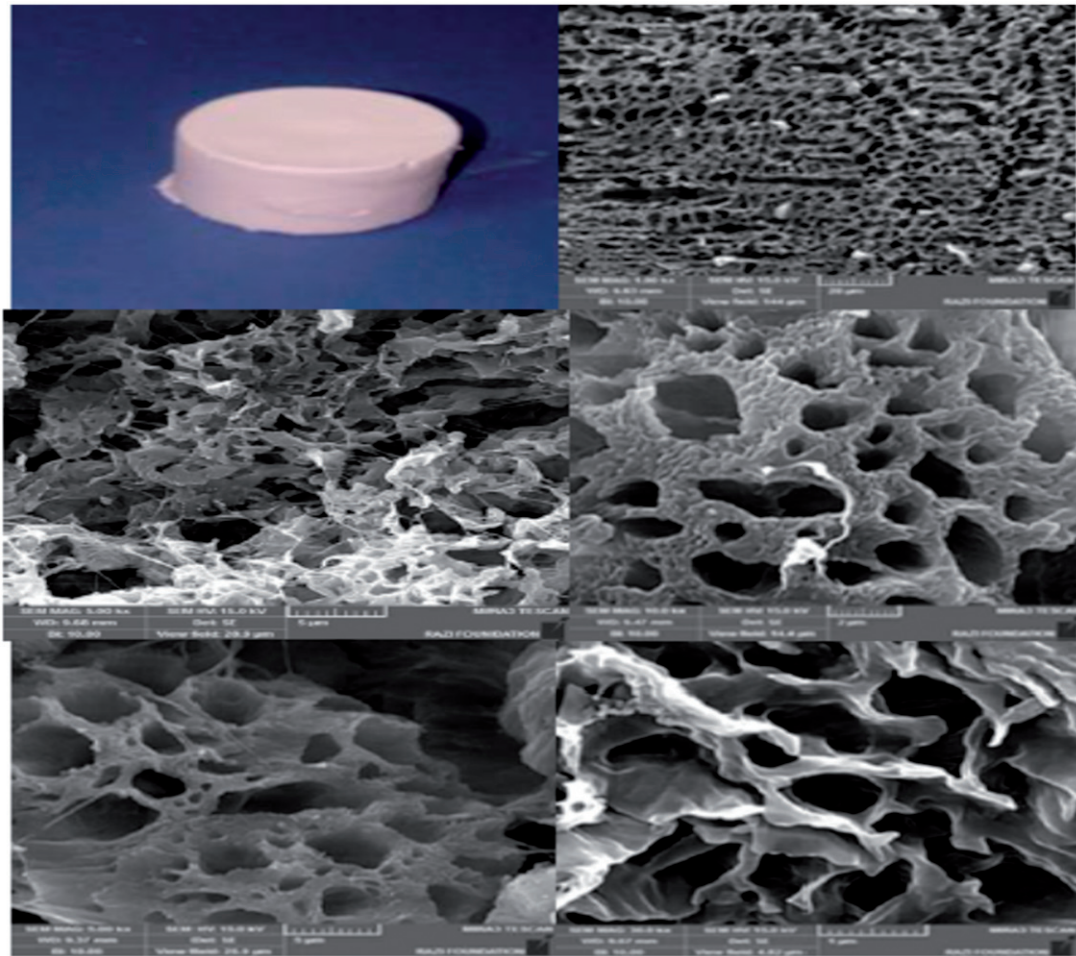


Figure 4. The hybrid porous scaffolds of the PCL/PLLA/collagen I were fabricated by the freeze-drying method.

Gelatine

Gelatine, as a natural polymer, is derived from collagen [42]. Under the specific circumstances, such as temperature, solvent or pH, gelatine macromolecules showed the adequate flexibility to come up to a great variety of the conformations. This made it feasible to vary also all the gelatine characteristics dependent on its molecular structure [44]. Regarding the presence of both acidic and basic function at groups in gelatine macromolecules, it reveals largely the number of the structural variety than other synthetic polymers [45]. Li et al. studied the gelatine with collagen, elastin and recombinant human tropoelastin in an experiment in which human embryonic palatal mesenchymal cells were seeded on all four scaffolds, and permitted to culture for 6 days. Gelatine helped cells to attach, migrate and proliferate for the duration of the test [46]. Moreover, Huang et al. presented a bilayered gelatine chondroitin 6 sulphate–hyaluronic acid membrane with a different pore size. Chondroitin-6-sulfate and hyaluronic acid were combined within the gelatine membrane to mimic the skin composition and generated a suitable microenvironment for cell proliferation, differentiation and migration [31].

Elastin

Elastin is an insoluble and hydrophobic protein which is utilized extensively in organs where shape and energy recovery

are critical factors [47]. Sell et al. produced electrospun 6 mm ID seamless tubes for testing the graft compliance. Dynamic compliance measurements created standards that ranged from 1.2 to 5.6%/100 mmHg for a set of three different mean arterial pressures, with the 50:50 ratios thoroughly mimicking the compliance of the natural femoral artery [48]. Also, Jelena Rnjak-Kovacina et al. produced the composite scaffolds of collagen and tropoelastin by the electrospun technology for the dermal tissue engineering. This composite approach illustrated that the tropoelastin electrospinning system tended to modification and allowed for a range of anymore mechanical or biological properties to be engineered into the dermal substitute scaffolds [49].

Chitosan

Chitosan has been the most plentiful polysaccharide found in environment, especially in the shell of crustacean, cuticles of insects and cell walls of fungi [50]. Molecule of chitosan has amino and hydroxyl groups, and therefore, it can be modified chemically providing a chemical versatility and metabolized by the certain human enzymes [51]. Chitosan can act as an ideal wound dressing as it exhibits a positive charge, film-forming capacity, mild gelation characteristics and a strong tissue adhesive property with an enhanced blood coagulation [52]. It supports the wound healing by increasing the

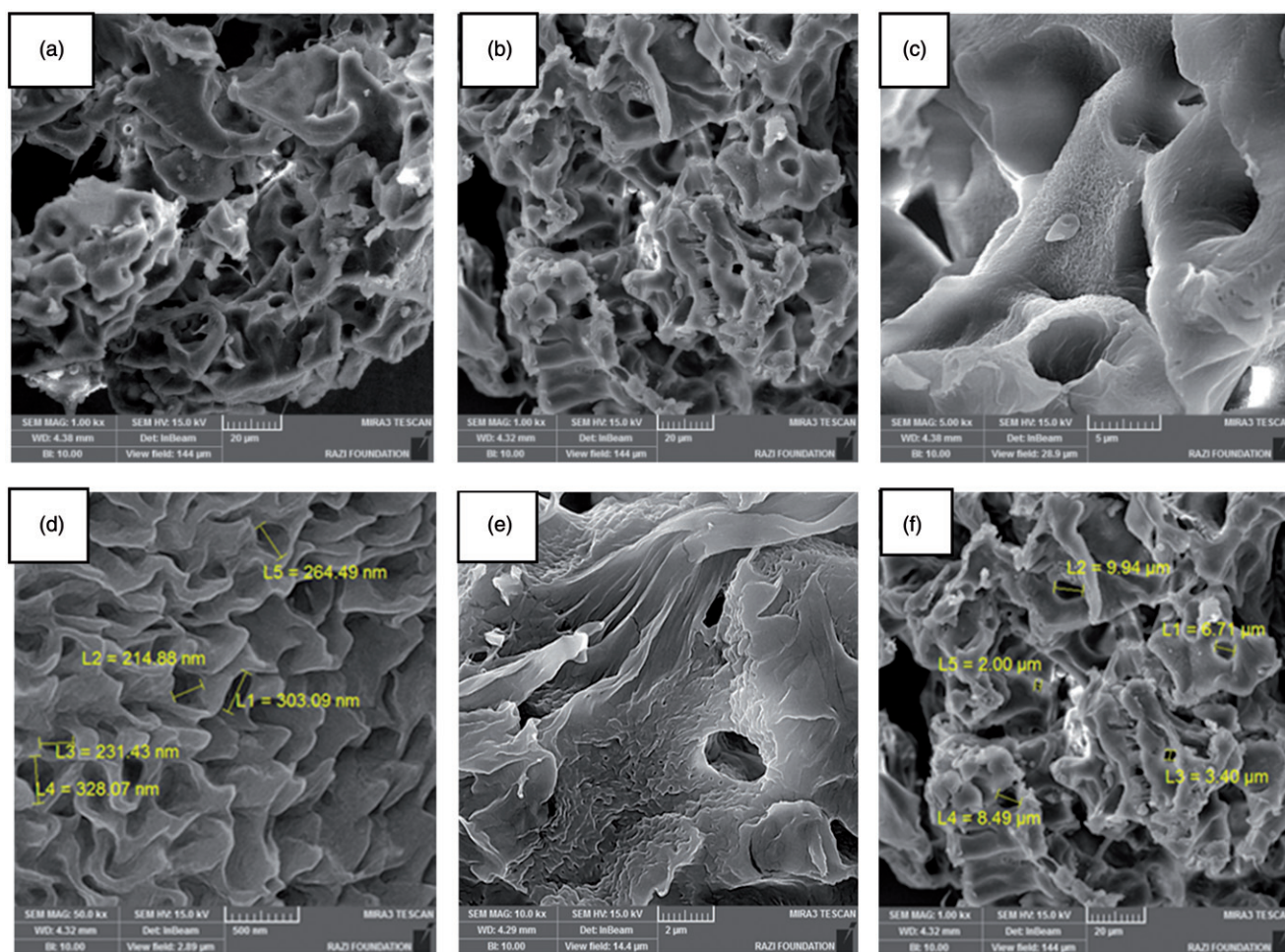


Figure 5. The hybrid porous scaffold of the PCL/collagen I was fabricated by the freeze-drying method.

functions of inflammatory cells such as polymorph nuclear leukocytes, macrophages and fibroblasts [53–55]. Chitosan has a potential use in skin repair and regeneration subsequent to injuries or burns because it could be cross-linked with the silica particles (SiO_2) which used as a porogen agent and the extractions from the developed membranes demonstrated no cytotoxicity against L-929 cells 24 h after the culture. In addition, the macroporous membrane exhibited the excellent cellular adhesion and proliferation after 24 and 48 h of culturing [56]. Chitin-based materials had also demonstrated their potential in keeping and exciting the cell phenotypes used in culturing the melanocytes, corneal keratinocytes and skin keratinocytes [57,58].

Keratin

Keratin is the main structural fibrous protein involved in hair, nails and skin [59]. Cell adhesion sequences named RGD and LDV which are contained within the keratin protein might help the cell adhesion and growth on the keratin substrates [60]. The immune response is reduced significantly when keratin is extracted from the human hair. In addition to the good biocompatibility, keratin source enjoyed the advantages of the readily available and less expensive [61]. Additional detail investigations would raise the potential of the keratin as a beneficial biomaterial for using in skin tissue engineering

[62]. In the past decade, keratin-based research for the wound healing, drug delivery, tissue engineering, cosmetics and medical devices has been the most popular subjects [4].

Alginate

Alginate was a natural polysaccharide illustrating very good biocompatibility and biodegradability, having many different applications in the field of biomedicine [63]. Dressing was used to open wounds for centuries [64]. It could prevent the wounds from more injury and bacterial infection [65]. Alginate-based wound dressings such as sponges, hydrogels and electrospun mats were auspicious materials for the wound healing that had many advantages including haemostatic capability and gel-forming ability upon absorption of wound exudates [66,67]. Alginate was found to have many important features appropriate for a wound dressing such as good water absorptivity, conformability, optimal water vapour transmission rate and mild antiseptic properties coupled with the nontoxicity and biodegradability [68]. It was recommended that the certain alginate dressings such as Kaltostat[®] could improve the wound healing by stimulating the monocytes to produce the raised levels of cytokines such as interleukin-6 and tumour necrosis factor- α [69]. It has been also reported that an *in situ* forming hydrogel wound dressing could be prepared from gelatine and oxidized alginate in the

presence of the small concentrations of borax [70]. Moreover, concerning advantages of the alginate and water-soluble chitosan, a composite polysaccharide sponge was fabricated, resulting in an anti-adhesive and antimicrobial wound dressing [71]. Also, alginates were extensively used for the tissue engineering scaffold fabrication [72–74]. For example, the alginate microspheres [75] or combination of the alginate, chitosan and chit oligosaccharides (alginate–chitosan–cos) and alginate chitosan, chit oligosaccharides with collagen (alginate–chitosan–cos–collagen) scaffold was used for the skin substitute and was illustrated that these scaffolds were improved the biocompatible nature that mimicked the functional environment of skin [76–78].

Hyaluronic acid (hyaluronan)

Hyaluronic acid (HA) was a naturally derived, nonimmunogenic, nonadhesive glycosaminoglycan which played an important role in the various wound healing processes such as angiogenesis [79]. Also, it promoted early inflammation which was the critical for initiating wound healing [79]. Furthermore, hyaluronan presents unique advantages such as easy to produce and modify, hydrophilic, nonadhesive and naturally biodegradable. Because of these excellent specifications, HA found a number of usages in medicine and cosmetics; for example, the product Hyalgan manufactured by Fidia (Abano Terme, Italy) in the 1960s was applied topically for the treatment of burns and skin ulcers [80]. In addition to the abovementioned biological polymers, other natural polymers, such as C-phycoerythrin (C-pe), also have been used in dermal wound healing [81].

Nonbiological polymers employed for skin tissue engineering

Biological polymers could be considered as the first biodegradable biomaterials used clinically [6]. Thereafter, the synthetic polymers were highly useful in the biomedical field since their properties (e.g. porosity, degradation time and mechanical characteristics) could be tailored for the specific applications [82]. The current part of the article was discussed many synthetic polymer applications in the skin tissue engineering and wound healing.

POE

Poly(hydroxyortho esters) such as polyglycolic acid (PGA), polylactic acid (PLA) and their copolymers were applied for tissue engineering [83]. Artificial skin frequently comprises animal material, such as collagen, which could contain the infectious substances [24]. Biodegradable hydrogels were usually not physically robust enough to mimic to the epidermis. Polymer-based system frequently was used in skin scaffold synthesis and was described as a polyester-based lactic acid (PLA) and glycolic acid (PGA) [84]. Nonetheless, these polyesters were revealed to degrade to their acidic components causing a high local acidity that might destroy proteins [66]. The rapid degradation of this polymer could frequently hamper processing of the present material after exposure to

aqueous media. To overcome these issues, the use of the PLA/PGA combinations was introduced. Blending of the poly-4-hydroxybutyrate with PLA and its copolymers was proven to increase the toughness and lower stiffness than PLA polymers or copolymers alone [85]. Poly(D, L-lactic-co-glycolic acid) (PLGA), meanwhile an important amorphous biodegradable polyester, has been employed as the skeletal material since it enjoys the similar properties to those of the normal tissues [86]. However, PLGA undergoes plastic deformation and failure when exposed to the long-term cyclic strain limiting use in the elastomeric tissue engineering [87]. Three-dimensional (3D) scaffolds made from the synthetic and naturally derived biodegradable polymers such as PGA, PLA, PLGA and collagen have been commonly applied in the tissue engineering of the cartilage, bone, ligament and skin [88].

PLA and PGA were striking objectives in the tissue engineering field for many reasons. They tended to “degrade” slowly, making them an attractive tool for using the internal fixation [89]. “Degradation” in this manner is used to denote the mass loss because of resorption or dissolution of the biomaterial, precipitated or accompanied by the molecular weight decrease, structural variations and decline in the strength and stiffness [90]. These materials offered a steady transfer of loads to the healing tissues [91,92]. Deependra Singh and Manju Rawat Singh optimized PLGA microspheres of gentamicin (GM) and serratiopeptidase (STP) have been incorporated into the PVA–gelatine slurry and casted into the films to prepare the multiphase hydrogel for the complete wound management. Their results suggested an accelerated re-epithelialization with the minimum disturbance of the wound bed [93]. In the other work, Muthukumar Amirthalingam et al. fabricated the novel biocompatible PLGA–curcumin microparticle-embedded chitosan scaffold for wound healing application. Their results indicated that the existent scaffold could be used as a drug delivery system to treat the severe and chronic wounds [94].

Polyethylene glycol

Polyethylene glycol (PEG), also recognized as polyethylene oxide (PEO) or polyoxyethylene (POE), was the most commercially important polyether, which referred to an oligomer or polymer of the ethylene oxide resisting protein adsorption and cell adhesion [95]. These properties helped minimize the immune response following implantation [96]. Moreover, the mentioned polymer could also be helpful to seal the cell membranes after injury, making it useful material for limiting cell death [97]. Hydrophilic PEG hydrogels could be prepared through a range of cross-linking schemes to make the scaffolds with varying degradation as well as release rates [98]. Further chemistry could be used to modify these gels to add the sites for cell adhesion or extracellular matrix (ECM) molecules to help cells to infiltrate into these scaffolds, extending their potential applications [30]. Porous gelatine–poly(ethylene glycol) (PEG) was made by using the combination of freeze gelation and freeze extraction methods for the skin cells (fibroblast cells); finally, the high growth level of those cells and biocompatibility over the synthesized scaffold was seen [99].

Poly- β -hydroxybutyrate

Poly- β -hydroxybutyrate (PHB) was considered as a linear head-to-tail homopolymer of (R)- β -hydroxybutyric acid which made the crystalline cytoplasmic granules in the large variety of bacteria [100,101]. The mentioned material was biodegradable and biocompatible microbial produced the polyester which, following implantation, degrades slowly at the body temperature and forms a nontoxic metabolite which was secreted in urine [102]. PHB has been formerly used as a wound scaffolding device designed to support and protect a wound against more damage while promoting healing by encouraging the cellular growth on and within the device from the wound surface [103]. Also, nanofibres were prepared by electrospinning from the blends of the polyvinyl alcohol and polyhydroxy butyrate and were potential scaffold material for the tissue engineering of skin [104]. Saeed Heidari Keshel et al. has reported that the graft of the collagen-coated nanofibrous PHBV scaffold loaded with USSC (unrestricted somatic stem cells) showed the better results during the healing process of the skin defects in the rat model, so it was efficient skin grafts for the treatment of the acute full-thickness skin wounds [105].

Poly(vinyl alcohol)

Due to poly(vinyl alcohol) (PVA) favourable properties such as nontoxicity, biocompatibility and biodegradability, it was used for a wide variety of the biomedical applications such as bone implants [106] and artificial organs such as skin [107]. Because PVA has well-known fibre forming characteristics, many nanofibres of the blends of PVA and chitosan were produced by electrospinning for the tissue engineering and wound healing application [108–110]. Also, nanofibres of PVA and polyhydroxy butyrate were used for the tissue engineering of skin [104].

Polycaprolactone

Polycaprolactone (PCL) was somewhat inexpensive, extremely elastic polyester which revealed a lack of toxicity with the good mechanical properties and a slow degradation time (1–2 years) [111–113]. Before coating electrospun PCL with the soluble collagen, the material was also found to show the suitable cellular interaction [114]. Li et al. proved the potential of PCL as a scaffolding material for the cell-based multiphasic tissue engineering by seeding the human mesenchymal stem cells (hMSCs) on the scaffold prepared from polycaprolactone [115]. Also, Hoda Bahrami et al. have reported the graft of nanofibrous PCL scaffolds loaded with the USSC (unrestricted somatic stem cells) showed the better results during the healing process of the skin defects in rat models [116]. Moreover, PCL/collagen I scaffolds prepared using a layer-by-layer approach provided a favourable environment for the fibroblast survival and proliferation which were useful for skin regeneration because that method allowed to produce a composite scaffold consisting of both dermal and epidermal skin layers [117,118].

Surface modification

Currently, a wide variety of synthetic biodegradable polymers were used as the tissue engineering scaffolding materials. The disadvantage of these scaffolds was their lack of biological recognition on the material surface. Moreover, hydrophobic polymers did not provide the good environment for the cell–material interactions [119]. Consequently, the surface modification of the polymeric scaffolds should have been considered as an active research area [120,121]. Various methods were being utilized to improve the surface such as incubation time, pH value and pre-treatment using aqueous solution [122].

Huizhi Chen et al. fabricated the 3D fibrous scaffolds of PLGA by liquid-collecting electrospinning for chronic wound repair. Then, the surface modification with the native ECM component aims at providing the biological recognition for the cell growth. This work showed the significant progressive proliferation of the human dermal fibroblasts (HDFs) successfully infiltrated into the scaffolds immobilized with the collagen type I [123].

Hybridization of synthetic biodegradable polymers with collagen for skin

The aforementioned two kinds of the biodegradable polymers had their respective advantages and disadvantages. The synthetic biodegradable polymers were easily produced into the desired shapes with somewhat good mechanical strength [88]. Their degradation periods could also be manipulated by controlling the crystallinity, molecular weight and copolymer ratio [82]. Despite these apparent advantages, the scaffolds derived from the synthetic polymers lack cell recognition signals, and their hydrophobic property hinders smooth cell seeding [124]. In contrast, naturally derived collagen had the potential advantages of the specific cell interactions and hydrophilicity; however, the scaffolds which were constructed completely from collagen had poor mechanical strength. Consequently, those two kinds of biodegradable polymers were hybridized to combine the advantageous properties of both constituents [125–131].

The wettability of a polymer scaffold was deemed essential for the homogeneous and sufficient cell seeding in three dimensions [4,132]. Since biodegradable synthetic polymers were relatively hydrophobic, it is difficult to deliver a cell suspension in a way that evenly distributes the transplanted cells throughout their porous scaffolds [133,134]. Hybridization with collagen could enhance the wettability of the synthetic sponges with water, which facilitates cell seeding [135]. It was reported that the hybrid sponges of the synthetic polymers and collagen possessed almost the same high degree of mechanical strength as those of the synthetic polymers much higher than that of the collagen sponges alone [136].

It was also reported that to prepare the hybrid sponges of synthetic polymers and collagen, the sponges of synthetic polymers were immersed in a collagen solution under a vacuum to fill the sponge pores with a collagen solution. Subsequently, the synthetic polymer sponges containing the collagen solution were frozen and freeze-dried to let the

formation of collagen microsponges in the sponge pores [136]. The collagen microsponges can be further cross-linked by treatment with glutaraldehyde [136,137]. Following washing with deionized water and freeze-dried, the hybrid sponges of synthetic polymers and collagen were formed [136] (Figure 3–5).

Samples of hybrid scaffolds for skin tissue engineering

This part of review summarizes the various hybrids of the synthetic polymers and biological polymer applications in the skin tissue engineering and wound healing.

PLLA–collagen

Open skin wound needs to be repaired rapidly to prevent the infection [138]. Using artificial skin substitutes for repairing avoids the complications of the grafts, but a perfect material for a scaffold which is strong and allows the regeneration of the skin tissue has to be found [35]. Some existing scaffolds are made from collagen or gelatine, which are appropriate for promoting the tissue regeneration, but they are not mechanically strong [139]. Others, which are made from biodegradable synthetic materials such as poly(L-lactic acid) (PLLA), are stronger, but not so suitable for the tissue growth [140,141]. Guoping Chen et al. at the National Institute for Materials Science, Japan, have made a hybrid scaffold that has all the essential properties. This team had also created “funnel-like” scaffolds with pores which were interconnected under the surface allowing cells to grow into the scaffold. Now, they have formed these funnel-like collagens or gelatine “sponges” on a PLLA mesh to create the hybrid scaffolds [142]. Their results indicated that the funnel-like hybrid scaffolds could be used for the skin tissue regeneration.

Poly(ethylene oxide)–chitosan. Poly(ethylene oxide) (PEO) is also a biocompatible polymer which has been applied as the cartilage tissue repair [143] and wound dressing [144]. Many nanofibres of the blends of PEO and chitosan have also been produced by electrospinning [145–150]. For instance, Klossner et al. [145] made the defect-free nanofibres with the average diameters ranging from 62 ± 9 to 129 ± 16 nm by electrospinning the blended solutions of the chitosan and PEO in acetic acid. Their investigation revealed that as the total polymer concentration (chitosan + PEO) increased, the number of beads declined, and as chitosan concentration increased, fibre diameter reduced [151].

Carboxyethyl chitosan/PVA. Zhou et al. [152] reported the biocompatible carboxyethyl chitosan (CECS)/PVA nanofibres preparation made by electrospinning of aqueous CECS/PVA solution. The fibroblasts (L929) as the reference cell lines were used for analyzing the impact of using the electrospun by using the mentioned materials for the skin regenerations in *in vitro* environment. Indirect cytotoxicity assessment of the fibre mats revealed that the CECS/PVA electrospun mat was nontoxic to the L929 cell. Cell culture results showed that the fibrous mats were good in helping the cell attachment and proliferation. This new electrospun matrix would

be used as the potential wound dressing for the skin regeneration [152].

Chitosan/collagen/PEO. It was reported that the chitosan/collagen/PEO nanofibrous membrane fabricated by electrospinning and then cross-linked by glutaraldehyde vapour had potential as a wound dressing for the skin regeneration [153]. This membrane revealed no cytotoxicity towards the growth of 3T3 fibroblasts and had good *in vitro* biocompatibility. From animal studies, it has been understood that the membrane was better than gauze and commercial collagen sponge wound dressing in wound healing rate [153].

AgNPs/chitosan/PEO. A wound dressing material composed of silver nanoparticles (AgNPs) and chitosan has been invented by using a nanometer and self-assembly technology [154], and it could significantly improve the rate of wound healing. To develop a better wound dressing, proper uniform AgNPs/chitosan/PEO ultrafine fibres were effectively prepared [155]. Assessing the antimicrobial activities of the electrospun AgNPs/chitosan/PEO fibrous membrane against *Escherichia coli* revealed that the AgNPs in the ultrafine fibres meaningfully enhanced the inactivation of bacteria. The fibrous membrane was better than other wound dressing containing AgNPs in wound healing rate. Furthermore, the higher antibacterial activity was observed in the electrospun nonwoven mats of AgNPs/PVA/CS blends than in those of PVA/CS blends [156]. The electrospinning meshes are mentioned as the excellent wound dressing.

PCL–collagen. The PCL scaffolds deal with its appropriate biostability and mechanical qualities which ensure its long-term presence and elasticity [157]. One study in particular has reported the use of PCL for the skin grafts as a mix of collagen and PCL in a composite film [158]. The aim was to monitor the degradation of the collagen in a cultured environment and monitored the cell adhesion over some days. The mentioned study followed the behaviour of the various variations of the mixture of PCL and collagen. The resorption rate of the about-one-year determined PCL altered it to the promises for the use for developing the skin grafts for burn victims [158].

Pullulan–collagen. Pullulan–collagen composite hydrogel is another porous scaffold that is capable of the skin regeneration in the cutaneous wounds. Pullulan-based hydrogel is particularly integrated in the dermal wounds [159].

Collagen–elastin. Collagen with the other natural scaffolds can be made from the several origins (traditional and salmon-derived). This scaffolding material was applied for seeding the fibroblast cells and better healing of the skin incisional injuries in animal models [160]. Marine-based collagen–elastin scaffold is a better substitute for the bovine collagen–elastin scaffold as it inhibited the transmission of the prion disease [161].

Nanofibrous scaffold–growth factor. Nanofibrous scaffold may be impregnated with the dual growth factors in the mesh-type structure [162,163]. Applications of the growth factors with the nanofibrous scaffolds are very distinguished through the recent studies [164]. Coating the dermal wounds with this mesh-type scaffolding tissue was associated with the quick releasing of VEGF and slow releasing of PDGF-BB [163]. These growth factors helped the full-thickness wound healing [163].

Smart ultrashort aliphatic peptide hydrogel

Smart ultrashort aliphatic peptide hydrogel with the properties of noncytotoxic and nonimmunogen is another scaffold that has a main tendency to the helical fibre development [165]. The mentioned scaffold promotes the epithelial and dermal regeneration with high closure rate of skin wound and burn repair. This scaffold is used without seeding the growth agents [165].

Natural scaffold and wound infection

Using the natural scaffold for the treatment of wound infection was another wound healing problem. Gelatine/copper faujasite (CAF) composite scaffold was able to improve the wound oxygen supply and accelerate the cellular proliferation [166]. Gelatine is a good natural scaffold for its biodegradability, low immunogenicity and biocompatibility and could be applied for the better viability of NIH3T3 fibroblast cells [167]. *In vivo* study of gelatine/copper composite revealed the skin regeneration in 20 days after incisional wound creation [166]. Silver ion-releasing poly(L-lactic acid) scaffold showed the wound repair maintaining the excellent viability of the fibroblast and keratinocyte cells. In this scaffold, silver ions were released from a polymeric binder [167]. Another antibacterial scaffold which improved fibronectin and type I collagen expression was the new bilayer 3D activated carbon fibre with the suitable release of the incorporated gentamicin from its poly(γ -glutamic acid)/gelatine membrane [168]. The excellent features of this bilayer novel scaffold were wound healing and antibacterial properties [168].

Acellular porcine or Xe-Derma scaffold

Acellular porcine or Xe-Derma scaffold might be a different scaffold which had an main healing effect on the human skin wound and burn tissue [169,170]. Keratinocytes confluences occurring in 7–10 days and *in vitro* differentiation of the cultured epidermal cells to the normal epidermal cells were the greatest achieved with the Xe-Derma scaffold coating [170]. Furthermore, porcine acellular dermal matrix (ADM) scaffold was applied with the numerous proportions of the human and rat keratinocytes for the full-thickness skin wound healing in the animal models [171]. These scaffold tissues had frequent healing and regenerative function.

Tissue-engineered skin substitutes and wound dressings for biomedical applications

Two types of tissue-engineered substitutes available are human skin and dermal equivalent (HSE), one is cell-containing matrix which mimics the layer of skin composed of keratinocytes and fibroblast on the collagen matrix and second one is the acellular matrix which contains only the dermal elements with the fibroblast on the collagen matrix [172]. Major mechanism of these substitutes is to stimulate and secrete the wound growth factor by which the epithelialization is achieved. They are able to release the growth factors and cytokines incorporated in dressings because bioengineered is capable of adapting to their environment [173,174]. Bioengineered dressings are appropriate for the venous leg ulcer [175] and diabetic foot ulcer [176]. For example, Apligraf consists of keratinocytes and fibroblast-seeded collagen for the venous ulcers is a FDA-approved skin equivalent substitute [175]. Some skin substitutes commercially available include IntegraTM artificial skin composed of collagen/chondroitin 6 sulphate matrix overlaid with a thin silicone sheet [177] and AllodermTM composed of the normal human fibroblasts with all cellular materials removed [178]. Also, other substitutes are LaserskinTM [179], BioseedTM [180], BiobraneTM [181] and Hyalograf3-DTM [182].

The other products that have clinical usage and promote wound healing are modern wound dressings. They are usually based on the synthetic polymers and are focused to keep the wound from dehydration and promote healing, so they have been developed to facilitate the function of the wound rather than just to cover it. Based on the type and cause of wound, various products are available in the market, but they are classified as passive, interactive and bioactive products, generally [183–185].

- a. Passive products, such as gauze and tulle dressings, are nonocclusive used to cover the wound to restore its function underneath [186].
- b. Interactive dressings, which are available in the forms of films, foams, hydrogels and hydrocolloids, are semi-occlusive or occlusive. The mentioned dressings act as a barrier against penetration of the bacteria in the wound environment [187]. Semi-permeable film dressings are constructed from the transparent and adherent polyurethane that permits transmission of the water vapour, O₂ and CO₂ from the wound so that it provides the autolytic debridement of the eschar and impermeable to bacteria [188]. These dressings are recommended for epithelializing wound, superficial wound and shallow wound with the low exudates, and examples of these dressings are OpsiteTM, TegadermTM and BioclusiveTM [189,190]. Semipermeable foam dressings are produced from the hydrophobic and hydrophilic foam with adhesive borders [191], e.g., LyofoamTM, AllevynTM and TielleTM [192,193]. Hydrogel dressings are insoluble hydrophilic materials made from the synthetic polymers such as poly(methacrylates) and polyvinylpyrrolidone [194]. These types of dressings are used for the dry chronic wounds, necrotic wounds, pressure ulcers and

burn wounds [195]. Some examples of hydrogels are NugelTM, IntrasiteTM, AquaformTM polymers, sheet dressings, impregnated gauze and water-based gels [196,197]. Hydrocolloid dressings are made from the combination of the gel forming agents such as carboxymethyl cellulose, gelatine and pectin with other materials such as elastomers and adhesives [198]. These dressings are among the most widely used interactive dressings and consist of two layers, inner colloidal layer and outer water-impermeable layer [43]. GranuflexTM, ComfeelTM and TegaserbTM are some hydrocolloid dressings commercially available [199,200]. Alginate dressings are produced from the sodium and calcium salts comprising mannuronic and guluronic acid units [201,202], e.g., SorbsanTM, KaltostatTM and AlgisiteTM [200,203].

- c. Bioactive wound dressings, which are known for their biocompatibility, biodegradability and nontoxic nature, are the last type of the modern wound dressings [204] and are derived generally from the natural tissues or artificial sources which play the serious role in healing process such as collagen [205], hyaluronic acid [206], chitosan [207,208], alginate and elastin. These materials are used alone or in combination depending on the nature and type of wound. In order to enhance the wound healing process, the polymers of these materials are sometimes incorporated with the growth factors and antimicrobials, too [43,209].

Conclusions

In sum, the tissue engineering is one of the most exciting interdisciplinary and cross-disciplinary research areas and is growing exponentially through the time. Scaffold materials and fabrication technologies play an essential role in tissue engineering. Currently, the numerous tissue scaffolds have been engineered in the field of wound healing. These nanostructures were vigorously examined *in vitro* and *in vivo* studies. The mentioned nanostructures were used for the traumatic wounds in the animal studies and investigations. Using these new scaffold tissues through the animal models was very prominent than in real patients. In this regard, safe applications of the nontoxic and nonmutagenic scaffolds need to be changed for the better compliance with the wound healing in patients. In the traumatic wounds, contractile cells (myofibroblasts) were responsible for a prominent decrease in the wound size. It is necessary to mention that the porous collagen helps skin wound healing and produces new dermal tissue with passing the wound contraction mechanism. The new porous collagen scaffold could be used in the traumatic skin wound for the better regeneration of the dermis; that is, developing tissue engineered the skin substitutes and dressing materials addressing the major interfering factors of the normal healing process will help the patients and wound care practitioners largely.

Acknowledgements

The authors thank the Department of Medical Nanotechnology, Faculty of Advanced Medical Science of Tabriz University for all

supports provided. The present work was funded by 2017 Drug Applied Research Center, Tabriz University of Medical Sciences Grant.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The present work was funded by 2017 Drug Applied Research Center, Tabriz University of Medical Sciences Grant.

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