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SCAFFOLDS - AN ADVANCED DRUG CARRIER FOR WOUND HEALING: A REVIEW

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ABSTRACT

A Wound remains a challenging problem in everyday pathology due to the complex healing process. The defects found in the traditional wound dressing potentiates to development of modern dressing for tissue regeneration. Scaffolds are carriers that are used to deliver cells, drugs or growth factors on the wound site. It provides a suitable environment for cell and tissue growth and have mechanical properties innate to the original tissue. They also have wider application in repairing bone, cartilage, nerves, blood vessels, and skin. This review provides detailed summary on properties and biomaterial selection for fabrication of scaffold. This article provides and overview on the fabrication of scaffold along with surface modification techniques. In addition, the details of marketed scaffolds have been provided. Finally, future outcome of these scaffolds is presented.

KEYWORDS: Scaffolds, wound healing, skin tissue engineering, 3D printing, biomaterials, electrospinning.

INTRODUCTION

Skin is the largest body organ functioning as a barrier to harmful external factors and prevents the entry of pathogens into the body.[1] A wound is a type of injury to the skin caused when there is a cut, torn, or punctured (an open wound), where blunt force trauma causes a contusion (a closed wound).[2] The process of wound healing is complex process, depends on several highly regulated factors working in concert to restore injured skin towards repaired function. However, it can go through numerous steps along the pathway during chronic disease conditions such as diabetes.[3] Skin tissue engineering is a promising strategy

in wound healing for treating skin loss. The traditional methods include autografts and allografts.[1] The limitation of these methods is pain, scarring, infection, slow healing in the donor site and a large amount of skin loss.[4] For the regeneration of tissue on the wounds, the use of biomaterials is encouraged. Biomaterials, as the 3D framework in tissue engineering, are commonly referred to as scaffolds or matrices. It provides an advantage for cell attachment, a proliferation of new tissue.[5] In this review, we intend to provide detailed illustrations about the properties of scaffold, fabrication techniques, biomaterials preferred, and various scaffolds available for wound healing.

THE HEALING PROCESS

Wound healing takes place in all tissue and organs of the body. The tissue repair process is initiated by a tissue injury, which is united into 4- independent phases. It includes 1) Coagulation and Hemostasis phase 2) Inflammatory phase 3) Proliferative phase 4) Remodeling phase.[8]

Phase -1 Coagulation and hemostasis

This phase begins immediately after an injury. The key aim of this mechanism is to protect the vascular system despite injury and so the function of vital organs remains protected. The long-term aim is to provide a matrix for invading cells.[6] It consists of a sequence of complex reactions mainly hemostasis and clot formation.[7] Once blood spills onto the injury site, the components of blood and platelets come into contact with the exposed collagen and other extracellular matrix components and trigger the release of clotting factors and the formation of blood clot. The clot consists of fibrin aggregated with platelets.[8] The cytoplasm of platelets consists of Platelet-derived growth factor (PDGF), Transforming growth factor – β (TGF – β), Epidermal Growth factor, and Insulin-like growth factor. These factors promote the wound healing pathway by activating and altering neutrophils and later macrophages, endothelial cells, and fibroblast.[9]

Phase – 2 Inflammatory phase

This phase creates an immune barrier against invading microorganism.[10] The lesioned blood vessels contract and leaked blood coagulates to maintain its integrity.[11] This phase act as two separate events 1. An early inflammatory phase 2. A late inflammatory phase.

Early inflammatory phase

It starts at the early phase of coagulation. The activation of molecular events leads to infiltration of the wound site by neutrophils. The neutrophils initiate phagocytosis to destroy bacteria, foreign particles, and damaged tissues on the wound site.[12] They begin to attract to the wound site within 24 – 36 hours of injury by TGF -β, complement components such as formyl methionyl peptides produced by bacteria, and platelet products.[13] Neutrophil activity reduces once all the contaminating bacteria have been removed. At the end of the task, neutrophils must be eliminated from the wound to progress to the next phase of healing.[14]

Late inflammatory phase

This phase starts after 48 – 72h of injury and so macrophages appear at the wound and continue the process of phagocytosis. The macrophages work together with platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) to stimulate the formation of granulation tissue.[15]

Phase – 3 Proliferative phase

The proliferative phase aims to diminish the lesioned tissue area by contraction and fibroblast establishes a viable epithelial barrier to activate keratinocytes. This phase involves closure of lesion and consist of subphase includes angiogenesis, fibroplasia, and reepithelization. This process begins within the first 48h in the microenvironment of the lesion and extends up to the 14th day after the onset of the lesion.[16] In 5 – 7 days of injury, fibroblast migrates into the wound and forms new collagen subtypes I & III. In normal wound recovery, kind III collagen predominates but it is changed by using kind I collagen.[17]

Phase – 4 Remodeling phase

The final phase of healing involves the development of new epithelium and final scar tissue formation. It begins two to three weeks after the onset of the lesion and can last for one year or more.[18] This phase undergoes remodeling of collagen from type III to type I. After the 3rd week, the wound undergoes a transforming condition that could remain for years after preliminary injury. The remodeling of an acute wound is controlled to maintain a balance between degradation and synthesis of new tissue leading to normal healing.[19]

In all the above processes cited, the healing of the wound is delayed by exogenous and endogenous factors. More specifically, systemic disorders such as diabetes,

immunosuppression, venous stasis as well as external agents such as the corticotherapy use and chronic smoking can act as barrier to early wound closure.[20]

SCAFFOLD AS A WOUND DRESSER

The critical part of the wound healing process is wound care dressing. Natural or synthetic bands, cotton wool, gauze, plasters are conventionally used on the wound to prevent contamination. These dressing may require frequent changes to avoid damage to healthy tissue. The wounds with thick exudate, make dressing moistened and tightly adheres to the wound which is painful while removing. Since these dressing fails to provide a moist environment to the wound and they have been replaced by modern tissue engineering.[21] The key challenges for tissue engineering are to provide space for regeneration of tissue and should maintain the right extracellular environment.[22] In tissue engineering, a porous scaffold functions as the template in cell adhesion, extension, proliferation, and differentiation. Scaffolds potentiate the growth of target tissue by mimic the physiological needs for regeneration of tissue. An ideal scaffold should possess a high absorbing capacity, proper ventilation, biocompatibility, and antibacterial properties to protect the injury from infections and dehydration.[23] The rate of tissue formation equilibrates with the rate of degradation of tissue; thereby scaffolds provide structural integrity while cells regenerate the natural matrix around the wound.[24] Various elements and factors such as ions, nanoparticles, growth factors can be incorporated into the scaffold to enhance wound healing properties.[25]

Properties of Scaffold That Aids In Wound Healing

The properties of the scaffold are classified as i) Mechanical properties ii) Physiochemical properties iii) Biological properties

Mechanical properties

The scaffold should have similar mechanical properties as native tissue to support proliferation, migration and also to protect blood vessels, lymphatic system, and nerve bundles in the unaffected area.[26] The parameters such as tensile strength, Young’s module and break down point are assessed to determine the mechanical properties of the scaffold. According to the literature, the tensile strength between 5 and 40 MPa, Young's module between 4.5 and 25 MPa, and the breakdown point between 35 and 120% are found to be appropriate for wound dressing.[27] Many studies have found that synthetic polymers such as poly (lactic-co-glycolic acid), polycaprolactone (PCL) have good mechanical properties.

They can be blended with natural polymers such as chitosan, gelatin to improve biocompatibility along with mechanical properties.[28]

Physiochemical properties

Pore size

Pore size determines the space to incorporate the cells into the scaffold. An open, wide, and interconnected pore network with 200 – 500nm size is ideal for the scaffold to interact with host tissue.[29]

Porosity

Porous scaffolds should possess 60 to 90% porosity so it can provide sufficient space for oxygenation, nutrient exchange, and cell seeding.[30] The increase of porosity can lead to a decrease of mechanical properties, a balance must be maintained between them.[31]

Wettability

The hydrophilicity of scaffolds may affect cell attachment, proliferation, and differentiation. The wettability is usually determined by measuring the contact angle at the surface of the scaffold. The water contact angle should between 30 - 70° to adhere and expand cell growth.[32]

Biodegradability

Biodegradability is a critical parameter to be considered during the fabrication of scaffolds. The degradation rate of the scaffold should be proportional to the release of incorporated drug/ cell and the healing rate of injured skin.[33] The use of chemical crosslinkers such as glutaraldehyde may affect the biodegradability of the scaffold so crosslinking time and type of cross-linkers should be optimized based on severity and type of wound.

Loading capacity and release kinetics of scaffold

This property defines the amount of drug/ cell that can be loaded on to scaffold and they should possess maximum loading capacity so that drug/ cell can be released continuously for a longer time. The controlled release of drug from a scaffold can deliver the appropriate dose at a given period at desired cells. The drug/ cells must be homogeneously dispersed throughout the scaffold to avoid burst effect.[34]

Water absorption capacity

The excessive accumulation of wound exudate can lead to the degradation of extra cellular matrix cells and excessive pain in patients. An ideal scaffold should prevent dehydration of the wound and remove the excessive wound exudate. The water absorption capacity should of 100 to 800% to prevent the accumulation of fluids and enhance new extracellular matrix cells.[35]

BIOLOGICAL PROPERTIES

Biocompatability

Biocompatible material should have the ability to act as a host response and it should not provoke any immunological reaction that may affect tissue regeneration.[36] The fabricated scaffold should be nontoxic and degradable so it can be easily replaced by new tissue. If they are found to be toxic and biologically inactive, they interact with native tissue; lead to rejection of scaffold, and results in localized tissue death.[37]

Skin adsorption

Once the scaffold is placed on the wound, it gets exposed to protein in the body's fluids. Albumin is a protein present at higher concentration in serum; they get accumulated immediately at the injury site. Later, albumin is replaced by fibronectin and vitronectin in the healing pathway.[38] The albumin adsorption should be 250 – 400 µg/ml/day to determine the ability of the scaffold to adsorb protein.[39]

SCAFFOLD FABRICATION TECHNIQUES

The fabrication of 3D scaffolds involves a wide variety of techniques. The conventional methods include Solvent casting/ particulate leaching, Gas foaming, Freeze-drying, and phase separation. The modern technique involves electrospinning and 3D printing techniques. These can be applied as single technique or in combination. However, the limits of the conventional techniques to fabricate complex scaffold and fails to have precise size control and repeatability. Nowadays 3D printing using computer-aided design (CAD) technique has been widely followed as they can have control over macro and microporosity.

Solvent casting/ particulate leaching

Solvent casting/ particulate leaching is a simple technique that creates a scaffold with even porosity and pore size. It involves dissolving a polymer in a suitable organic solvent and followed by the addition of porogens e.g.: sodium chloride, glucose, citric acid to create a

polymer–porogen network. This mixture is poured onto a mold and then the solvent evaporates polymer gets hard. The hardened polymer is washed with water to dissolve porogen and freeze-dried to yield a hard polymer scaffold with a porous network.[40] The size and shape of porogens determine the pore size of the scaffold.[41] The crucial part of this technique is selected polymer should soluble only in organic solvents and insoluble in water so that soluble salt particles can be easily leached out. The commonly used organic solvents are chloroform and methylene chloride.[42] The limitation of this technique is an alteration in membrane thickness, lower mechanical properties may alter the interconnectivity and structure of the scaffold. The residual of porogen and organic solvent can be toxic and can damage the drug/cell that is loaded onto the scaffold.[43]

Emulsification/ Freeze drying

Freeze drying is a drying process suitable for converting labile materials into solid and makes them more stable for distribution and storage. Freeze-drying consists of three steps: at a low temperature of -70 C to -80 C, the solution is freezing. The frozen sample is placed in a pressure lowered chamber, in this step ice in the material is removed by direct sublimation, and most of the unfrozen water is removed by desorption.[44] the process of fabricating freeze-dried scaffold involves dissolving the polymer in a solvent and mixed with water to form an emulsion. The mixture is poured onto a mold to frozen. The frozen emulsion is freeze-dried to remove solvent and water which creates pores in a frozen scaffold.[45] The polymers suitable for this technique are natural and synthetic polymers like silk proteins, Poly ethylene glycol, poly – L- lactic acid (PLLA), PLGA/ poly (propylene fumarate) blends.[46] The structure of the scaffold is affected by temperature, freezing rate, the difference in heat transfer during the process, and the alignment of ice crystals.[47] The limitation of this technique is the pore size and porosity are irregular, and the process is time and money-consuming.

Phase separation

The phase separation process is induced by a thermal process or nonsolvent; the use of nonsolvent may result in irregular pore structure so a thermal induction process is preferred.[48] The thermally induced phase separation involves placing the polymer solution in a temperature condition so that the polymer becomes thermodynamically unstable and separates into a multiphase system consisting of polymer – low phase and a polymer-rich phase. The polymer-rich phase solidifies to form a matrix and polymer – low phase is

converted into pores as a result of solvent removal.[49] This technique is further divided into solid-liquid phase separation and liquid-liquid phase separation.[50] This technique is preferred over 3D printing as they can provide uniform pore size and the 3D shapes are formed by combining several techniques such as solid freeform fabrication, rapid prototyping, and CAD. The limitation includes the small pore size, and use of toxic organic solvents.

Gas foaming technique

The gas foaming technique involves the formation of pores through nucleation and gas bubbles dispersed throughout a polymer. The polymer undergoes compression moldings to create solid discs within the heated mold. The discs are exposed to high-pressure carbon dioxide for 72 h at room temperature. The reduction of CO_2 pressure to atmospheric levels potentiates the solubility of a gas in polymer results in clumping of CO_2 gas and create pores. The porosity range of 93% and pore size range of 100nm can be obtained. The limitation is difficulty in controlling pore size and internetwork connection.[41]

Electrospinning

The electrospinning technique is a suitable method for preparing nanofibers (< 1000nm) or microfibers (> 1µm).[51] The instrument used for the electrospinning process consists of a syringe pump, a high voltage source, and a collector. A high voltage is passed to a capillary tube filled with the polymer solution. The polymer solution is held at the tip of the capillary tube with help of surface tension. A mutual charge repulsion caused by the electric field in the polymer solution opposes the surface tension of the polymer solution. When the intensity of the electric field increases, the mutual charge repulsion will overcome the surface tension to form a jet so the ejected polymer solution repels each other and solvent evaporates to form fibers as the jet travels to the collector.[52] The biodegradable polymers such as PLGA and polycaprolactone, poly (ethylene oxide), polyvinyl alcohol, collagen, silk protein, and other peptides.[53] This method is advantageous than other techniques as the use of organic solvents is complete and they increase the biocompatibility of scaffolds. The limitation is difficulty in cell/ drug incorporation during the process. To overcome this, the usage of sacrificial biopolymer or cryospinning is preferred as they create the desired pore size in electrospun matrices.[54]

3D Printing Technologies

A wide range of 3D printing techniques has been followed and categorized based on their technique, characteristics, printing methods. The types as follows:

Power based 3D printing

Powder-based 3D printing fabricated using a powder bed consisting of raw materials and binding powders combined using polymer glue or other thermal fusion. The newer powder-based 3D techniques are selective laser sintering (SLS) and binder jetting (BJ).[55] In SLS, particles are fused to form a solid structure using high- powered laser, and the motion of the laser is governed by an input computer aided design (CAD) file.[56] Binder jetting consists of a liquid binder that acts like glue to bind particles together forming desired structure. The crucial parameter for this technique is to choose suitable particles and the binder determines both mechanical and biological properties.[57]

Ink based 3D printing

This process involves the deposition of fluidic materials on the nozzle and releases them on a 3D platform layer by layer. It is a suitable method for direct printing of living cells or growth factors with liquefied material. The types of ink- based printing are direct ink writing (DIW) and fused deposition modeling (FDM).[58] The frequently used polymer material for ink-based printing is natural polymers such as alginate, chitosan, collagen, gelatin, and synthetic polymers such as poly lactic acid (PLA), PCL, and poly (lactic-co-glycolic acid) (PLGA).

Polymerization based 3D printing

This process involves exposing liquid photopolymer to a laser beam and gets solidified by polymer chain reaction. This process is repeated layer by layer to construct a complex 3D structure. The old version of this technique is stereolithography, which consists of low-power UV light affecting photopolymers. The newer version of polymerization-based printing is two-photon polymerization (2PP) and projection micro stereolithography (PμSL) developed for a more precise and effective direction.[59]

Sol – Gel technique

In this technique, inorganic or organic metal/ salt compounds are dissolved in a solvent that allows the formation of colloidal suspension also called sol; the sol is cast on a mold to form a wet gel. On drying the gel is converted into ceramic or glass articles. Sol- gel techniques have an advantage because of their high chemical homogeneity, low processing temperatures,

and control release of drugs. The limitations are the high cost of materials, residual fine pores, and can cause a toxic reaction due to the use of organic solution.[60]

Combination of techniques

The combination of techniques has been followed based on the requirement of a scaffold. The particulate leaching/ solvent casting technique can be combined with freeze-drying to increase the stability of scaffolds. A phase separation technique can be combined with rapid protyping technologies such as stereolithography to create a nanofibrous scaffold.[61]

POLYMER CHOICE TO DEVELOP SCAFFOLD WOUND DRESSER

Polymers are macromolecules made of repeated short units called monomers. The polymer choice plays a critical role in the fabrication of scaffolds. The polymers are classified as natural polymers and synthetic polymers. They can be incorporated either as a single or a combination of polymers.

Natural polymers

The natural polymer has good biocompatibility, biodegradability, and low antigenicity. It has innated antibacterial and hemostatic activity and so it potentiates wound healing activity. They are classified as polysaccharides and proteins. The major disadvantage of natural polymer-loaded scaffold is poor mechanical properties so they are blended or conjugated with synthetic polymers or biomolecules for their biomedical application.

Polysaccharides

Polysaccharides act as good candidate for wound healing because they share similar properties with skin ECM. They are anionic at physiological pH because of the presence of glucuronic acid units and an exception is seen in chitosan. They show high solubility in dissolution media and high network structure. The natural polysaccharides include chitosan, alginate, hyaluronic acid, etc.[62] Chitosan was obtained from shells of crab, cuticles of insects, and cell walls of fungi.[63] It potentiates wound healing as it contains positive charge, film-forming capacity, mild gelation characteristics, strong tissue adhesive property. It enhances wound healing by increasing the function of inflammatory cells such as macrophages and fibroblasts.[64] Chitosan hydrogel loaded with fibroblast growth factor promotes wound healing in a diabetic mouse model and enhances collagen synthesis.[65]

Alginate has good biocompatibility, biodegradability, gel-forming ability upon absorption of wound exudates and prevents bacterial infections.[66] The serratiopeptidase and metronidazolebased alginate microspheres accelerate re-epithelialization to promote faster wound healing.[67] Hyaluronic acid is derived from nonimmunogenic glycosaminoglycan, a natural constituent of ECM.[68] It initiates wound healing by promoting early inflammation.[69] Hyaluronic acid nanofibers based wound dressing was loaded with mesenchymal stem cells, in vivo characterization showed that it accelerates the wound healing process.[70]

Proteins

The proteins preferred for wound dressing are silk fibroin, gelatin, collagen, fibrin, elastin, fibronectin, etc.[71]

Collagen is a major protein of extracellular matrix (ECM), naturally can be obtained from animal tissues and commercially manufactured by recombinant methods.[72] It has the advantage of high mechanical strength, good biocompatibility, innate property, and good water absorption capacity.[73] The commercialized collagen scaffolds are Apligraf® and Biomend®. Apligraf® consists of bilayer collagen gels loaded with human fibroblast in the lower layer and keratinocytes in the upper layer; it acts as a dermal matrix of artificial skin products.[74]

Gelatin is obtained by acid or alkaline hydrolysis of collagen. It has the advantage to enhance cell adhesion, low antigenicity and easy chemical modification. Gelatin microspheres seeded with mesenchymal stem cells can increase re-epithelization to promote the healing of wounds.[75] Silk fibroin is a natural biofiber obtained from insects, spiders and silkworm.[76] It has in vivo microenvironments and provides adjustable tissue reconstruction.[77] silk fibroin scaffolds have an advantage for the release of growth factors such as stromal-derived factor, transforming growth factor to facilitate injury repair.[78] In vivo studies of Silk fibroin – polyethyleneimine loaded with fibroblasts showed that they can enhance wound healing for pressure sores.[79]

Fibrin is a biological-based polymer obtained from the pooled plasma. It accelerates tissue regeneration and wound healing as they have innate property as fibrin, a precursor of fibrinogen.[80,81] Fibrin 3D porous matrix loaded with vascular endothelial growth factor (VEGF) useful in treating ulcer wounds.[82] Fibronectin is a glycoprotein derived from bovine or human plasma that can easily solubilize in human blood and potentiates wound healing.[83]

Synthetic polymers

The synthetic polymers are manufactured by the polymerization technique. These polymers have good physical and mechanical properties and so provides the required strength to act as a wound dresser. They are preferred to fabricate polymer based scaffold.[84] They are classified as Poly esters (e.g.: poly caprolactone, polylactic acid, polyglycolic acid), Polyalcohol (e.g.: polyvinyl alcohol), Copolymer (e.g.: poly [lactic-glycolic acid]).

Polyesters

Polyesters are widely preferred for nanofiber fabrication as they have the advantage of good biodegradability, innate biocompatibility. Poly caprolactone(PCL) is an inexpensive polymer with good mechanical properties.[85] Li et al. have used PCL as a scaffolding material loaded with human mesenchymal stem cells for multiphasic tissue engineering.[86] A herbal drug such as *Memecylon edule*, *Azadirachta indica* loaded on PCL nanofibers exhibits cell proliferation and accelerates the production of growth factors.[87] Polylactic acid(PLA) is a hydrophobic aliphatic polyester used as suture material, cell carriers, and scaffolds.[88] Polyglycolic acid (PGA) is more hydrophilic than PLA and PCL. PGA fibrous scaffolds play a key role in the loading of monocyte chemoattractant protein -I (MCP-1) for drug delivery in treating diabetic wounds.[89]

Polyalcohols

Poly vinyl alcohol (PVA) is a hydrophilic polymer that belongs to class of polyalcohol. They show good mechanical strength, biocompatibility and have potential application as wound dresser, surgical repairs and artificial skin. 3D hybrid PVA scaffolds used for the release of antimicrobial agents such as rifampin, vancomycin shows good result against bacterial biofilms.[90]

Copolymers

They are the polymers which have different monomers linked together by covalent bonds. For example, an addition of one or more poly(oxyethylene) (PEO) monomers into preformed hydrophobic polymers can enhance hydrophilicity and mechanical properties to serve their purpose in biological application.[91] The various copolymers includes poly (dimethylsiloxane), poly(epichlorohydrin), poly(l-lactide), poly (N-isopropyl acrylamide), poly(tetrahydrofuran), n- butyl acrylate/methyl methacrylate.one such polymer is PLGA comprises PLA and PGA moieties, PLGA microspheres loaded with gentamycin, serratiopeptidase accelerates re-epithelialization with minimum disturbance of wound bed.[92]

Combination of polymers

Natural polymers have the property of biodegradability and biocompatibility but fail to have appropriate mechanical properties. Synthetic polymers have better mechanical properties than natural polymers but they may contain impurities and can become toxic and limits the growth of cells. Since both natural and synthetic polymers have strength of their own so blending of these components provides optimal properties to enhance the activity of scaffolds. Polyvinyl alcohol combined with gelatin loaded with Cefradine shows hemostatic and nonadherent properties.[93] A Polycaprolactone – collagen nanofibers seeded with epidermal growth factors potentiate wound healing than the separate ones.[94]

SURFACE MODIFICATION OF SCAFFOLD

Surface modification of polymers provides biomimetic surfaces as skin with improved cell response compared to nonmodified polymers. It does not change the native material tends to provide alteration in structural, mechanical properties and added functionality. Topographical modification is the simplest approach that undergoes alteration of the physical state of scaffold structure and there by alters the cell response.[95] The modification process includes alkali acid etching, an increase of surface roughness, and hydrophilicity. Acid etching of PLGA polymer leads to 500% increase in surface roughness and enhanced vascular cell attachment.[96] The bioactive molecules and ECM proteins loaded on to scaffold show weak adsorption due to electrostatic interaction and weak van der Waals forces. Protein adsorption facilitates the adsorption of desired molecules or protein on the polymers such as poly ethylene glycol.[97,98] The process is initiated by various factors such as solution Ph, temperature, ion concentration, and buffer composition.[99] Fibronectin and laminin adsorbed scaffolds show greater cell adhesion and proliferation than unmodified scaffolds.[100] The PLA, PLGA and PCL scaffolds are functionally inactive due to the presence of noncarbon or hydrogen element, oxygen which is responsible for polyester bonds. The addition of functional groups such as amines, carboxylic acid, thiols provide direct cell adsorption or other targeted molecules. These surfaces directly alter cell response and biomolecule immobilization. The common methods for functionalization modification are plasma deposition, physical entrapment of functional molecules, aminolysis and hydrolysis. Plasma deposition and titanium oxide sputter coating on PLGA films increases hydrophilicity and improves human dermal fibroblast adhesion and proliferation.[101] The ECM proteins, enzymes, antibodies can be semi permanently incorporated in scaffolds. The molecules such as collagen and glycosaminoglycans can be entrapped by crosslinking to the surface using

mild chemical reaction without changing its intrinsic properties.[102,103] The widely used cross linking agents are acetone, glutaraldehyde, 1-ethyl-3-(-3- dimethylaminopropyl) carbodiimide (EDC), *n*- hydroxyslufosuccinimide (NHS), SPDP. 70% acetone can be used to entrap bioactive gelatin and chitosan molecules were immobilized using hydrolysis.[104]

COMMERCIAL SCAFOLDS FOR WOUND HEALING

These commercialized scaffolds were approved by FDA and produced in larger scale. The problems associated with large scale fabrication are safety assessment, differences in bioavailability and scale up issues can be addressed.

The commercial scaffold details are given in the table I

Trade name	Polymer	Properties / Mechanism of Action	Commercial Application
HYAFF®	Hyaluronic acid	Induces angiogenesis.	Wound dressing application.
Biobrane ® & Alloderm ®	PCA	Acts as component of skin	Wound dressing.
CYTOPLAST™ Resorb	PLGA - Collagen	Provides matrix structure of injured tissue.	Tissue regeneration membrane.
Apligraf ®	Collagen loaded with human neonatal fibroblast and keratinocytes	Stimulates differentiation and proliferation of active cells.	Living skin substitutes
Dextran	Dextran – PEG diacrylate	Provides cellular infiltration	Wound dresser
Derma graft ®	Polyglactin seeded with fibroblast	Facilitate secretion of growth factors and cytokines	Ulcer wound treatment
Promogran Prisma ® Matrix	Collage - cellulose	Forms as biodegradable gel by absorbing wound exudate.	Diabetic foot ulcer and pressure ulcer treatment.
Talymed ®	n- acetyl glucosamine	Stimulates cell migration by interacting with fibroblast and endothelial cells.	Venous leg ulcer treatment
3M Tegagen, Algisite, Algifiber	Collagen – calcium alginate	Converts as gelatinous mass on contact with wound exudate and controls mild hemorrhage.	Fibrous scaffold
Integra™	Collagen – chondroitin 6-sulfate	Accelerates capillary growth	Surgically debrided / excised wound treatment
Tegaderm ™, Bioclusive ™, Opsite	Polyurethane	Maintain moist environment for wound healing.	Treatment of superficial wounds with low wound exudate

CONCLUSION & FUTURE PERSPECTIVES

This review shows that scaffold is emerging as potential wound dresser by accelerating regeneration of injured tissue and healing process. The choice of polymer plays a critical role in fabrication of scaffold. The natural polymers mimic the innate properties of skin, a widely preferred one is collagen. Many successful scaffolds are developed with biopolymers yet they need advancement to have appropriate natural and biochemical stimuli to increase vascularization. Synthetic polymers are also preferred for wound healing to act as carrier for keratinocytes, fibroblast and stem cells. The challenge remains to maintain balance between cellular viability and mechanical integrity under load. There are several fabrication methods are available in which 3D printing and CAD technologies are preferred as they show precised size control and reproducibility of results. New fabrication methods that are cost effective and less time consuming can be developed. Nanofibers is an ideal wound dresser as they can mimic ECM, allows oxygen and nutrient interchange. Many commercial scaffolds have been reported yet many scaffolds have been stagnant at *in vivo* research, so a complete standard characterization of materials is needed. If they can be clinically proved, this will reduce wound debriments, surgical operation and can reduce the incidence of infection.

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