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Surface Modification with Gelatin for Polyurethane Vascular Grafts: A Review

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Article Info

Abstract

The means for developing synthetic vascular grafts to replace blood vessels is increasing extensively because of the limited supply of autologous vessels. Synthetic polymers as the alternatives still suffer from restenosis and thrombus formation. Natural polymers, on the other hand, are commonly biocompatible and biodegradable, compliment the synthetic ones. Blending, grafting and coating of natural polymers have been proposed to improve surface properties of synthetic polymers. Gelatin is a promising candidate to help improving synthetic vascular grafts surface owing to its ability to promote cell adhesion without promoting platelet aggregation at its surface. In this review, several techniques to incorporate gelatin onto synthetic polymers, mainly polyurethane, for vascular grafts application are summarized, together with the recent updates and potential development in the future.

INTRODUCTION

Because the availability and quality of the autologous vessels are often limited, the means for developing synthetic vascular grafts to replace blood vessels are increasing extensively. Almost 800,000 coronary bypass graft surgeries are performed worldwide each year (Patel et al., 2015). Materials such as polyethylene terephthalate (PET) and expanded polytetrafluoroethylene (ePTFE) are used as alternatives. Although these materials are available commercially and have been used in clinical applications, they are only successful to replace large diameter arteries (>6 mm). These materials are not viable for small diameter grafts (< 6 mm) because of high rate of vessel blockage after implantation. The thrombogenicity makes them ineffective (Han et al., 2011; Wong et al., 2013; He et al., 2013).

Vessel blockage is mostly caused by atherosclerosis, a build-up of fatty plaques in the arteries. It is a chronic inflammatory disease, producing arterial plaques characterized by inflammatory infiltrates, lipid accumulation, cell deaths and fibrosis (Andersson et al., 2013).

To treat this disease, a procedure called percutaneous coronary intervention (PCI) is commonly used to mechanically improve myocardial perfusion without resorting to surgery (Zhang et al., 2014). A stent, usually made of metal, is used to perform PCI since 1980s. The gold standard for vascular replacement aforementioned is autologous native vessel, but is limited by its availability.

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An ideal vascular substitute is essential in blood vessel-related surgery. Blood vessels have a complex structure and functionally dynamic tissue, with minimal regeneration potential (Thottappillil & Nair, 2015). The diverse functions performed by blood vessels are maintained by the complex extracellular matrix (ECM) of blood vessels. ECM varies in its composition, thickness, and overall architecture, differing between arteries, capillaries and veins (Rhodes & Simons, 2007).

Polymers remain the most-used biomaterials for scaffold fabrication. Because of their mechanical properties and degradation rates that closely match those of proteins in soft and hard tissues, they are good candidates for the development of vascular grafts (Goonoo et al., 2013).

An ideal vascular grafts is supposed to replicate the properties of the blood vessels in terms geometry, mechanical properties and interaction with cells, and degrade into non-toxic degradation products as the need for mechanical support decreases (Boffito et al., 2014; Adipurnama et al., 2017). The scaffold should have an interconnected porous structure, a high surface-to-volume ratio and appropriate porosity and pore dimensions to favor cell homing and migration, vascularization and nutrient and oxygen diffusion (Chan & Leong, 2008; Soichet 2010; Boffito et al., 2014; Adipurnama et al., 2017).

Several synthetic vascular grafts have been approved by the U.S. Food and Drug Administration (FDA) and millions of patients have benefitted from these polymers. Among them are polyethylene (PE), poly(methyl methacrylate) (PMMA), polyurethane (PU), polyglycolide (PGA), and polylactide (PLA). They have been selected for implants and other medical devices due to the ease of their synthesis, controlled adjustment of their properties, high reproducibility and rapid availability (Burke & Hasirci, 2004).

Polyurethanes are synthetic polymers that are recently intensively investigated for biomedical applications (Kucińska-Lipka et al., 2014). They contain urethane (or carbamate) bonds (-NH-COO-) in their main chains. PU generally consists of three molecular domains: a diisocyanate hard domain, a chain extender, and a diol soft domain. Soft domains provide flexibility while hard domains impart strength and toughness. The most common medical grade polyurethanes are based on soft domains made from polyester, polyether or polycarbonate. Various components have been added to the graft design to improve its function and yield biohybrid conduits (Rafi & Chaikof, 2010). Thus a great variety of building blocks can be incorporated into the PU chain, tailoring their material properties to a wide range of purposes (Burke & Hasirci, 2004).

Vascular tissue engineering with the use of polymeric scaffolds represents a promising approach in meeting the growing demand for blood vessel replacement. However, the risk because of thrombosis and occlusion in small-diameter vascular grafts are still the main challenge to be solved. Thus, new strategy to improve compliance and hemocompatibility of synthetic vascular grafts has become important (Qi et al., 2013; Li et al., 2014; Adipurnama et al., 2017).

Blending, grafting and coating of natural polymers have been proposed to improve the synthetic vascular grafts. Blends of synthetic and natural polymers can form a new class of materials with improved mechanical properties and biocompatibility compared to those single components (Goonoo et al., 2013; Kucińska-Lipka et al., 2014).

Various natural polysaccharide- and protein-based hydrogels have been studied for use in vascular grafts, including chitosan, fibrinogen, tropoelastin, elastin, collagen and gelatin (Lin et al., 2005; Xu et al., 2008; Sell et al., 2009; Caves et al., 2010; Wong et al., 2013; Kucińska-Lipka et al., 2014; Catto et al., 2015; Stoppel et al., 2015; Elomaa & Yang, 2017). The disadvantage of these natural polymers is that even though these scaffolds are biocompatible, they lack mechanical strength (Kucińska-Lipka et al., 2014). Combining these natural polymers individually or together with synthetic polymers produced scaffolds with improved stability and mechanical strength (Wong et al., 2013).

Gelatin is a promising candidate to improve synthetic vascular grafts surface owing to its ability to promote cell adhesion. Gelatin is biodegradable, biocompatible, non-immunogenic, low cost, and the most important, it can promote endothelial cells adhesion and proliferation while reduce platelet activation (Pezzoli et al., 2017).

In this review, we elaborate the main properties of both synthetic and biopolymers specifically for polyurethane and gelatin, namely

	Tensile Strength (MPa)	Young's Modulus (MPa)
Native Vessels	2.5^{10}	1^{10}
Bio, synthetic polymers and their blends	$0.2 - 4$	$0.44 - 20$

	Approximate degradation time
Biopolymers	12 hours – 5 months
Synthetic polymers	1 – 24 months

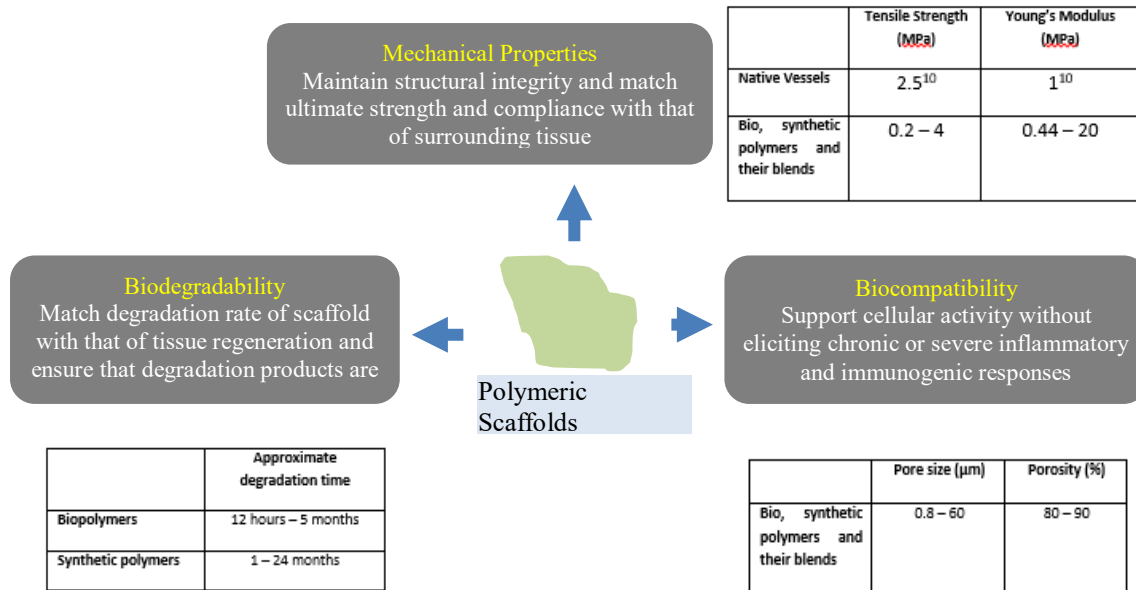|	Pore size (µm)	Porosity (%)
Bio, synthetic polymers and their blends	$0.8 - 60$	$80 - 90$

Figure 1. Major requirements for vascular tissue engineering in each property: Mechanical properties, Biodegradability, and Biocompatibility.

their biocompatibility, biodegradability and mechanical properties, to their applications as scaffolds for vascular grafts application.

Vascular Tissue Engineering

As mentioned before, the development of tissue-engineering vascular grafts has been triggered by the need for small-diameter vascular bypass conduits (Singha & Singha, 2012; Rocco et al., 2014). A vascular scaffold should be capable of withstanding physiological hemodynamic forces in addition to supporting the attachment, spreading and proliferation of smooth muscle cells and endothelial cells (Goonoo et al., 2013). Elasticity is a critical factor in vascular tissue engineering, allowing the vascular graft to stretch under stress and recover to its original dimensions when the load is released. The major requirements for vascular tissue engineering were illustrated in Figure 1.

Baguneid et al. (2006) summarized all ideal properties of the ideal arterial substitute as follows: 1) Strong, 2) Compliant, 3) Kink resistant, 4) Good suture retention, 5) non-toxic, 6) non-immunogenic, 7) low thrombogenic, 8) biocompatible, 9) readily available in a variety of lengths and 10) low manufacturing process. Up to now, there is no such vascular graft with those ideal properties mentioned. However, acceptable patency rates are achievable using commercial prosthetic material such as ePTFE or Dacron to bypass to large diameter vessels (Seal, 2001; Ravi

& Chaikof, 2010). Meanwhile, the small diameter prosthetic conduits have an unacceptably poor patency rate. This is because of low-flow conditions within a narrow vessels and compliance mismatch between prosthesis and native artery. The major contributing factors for those problems are intimal hyperplasia and inherent thrombogenicity of prosthetic materials.

Because of those ideal parameters, the design of vascular grafts with improved biocompatibility and mechanical stability is critical. The development of small diameter vascular grafts relies on our understanding of the anatomical structure and biological function of blood vessels. Blood vessels have three distinct tissue layers composing of different cells that exhibit discrete functions: the intima that contacts blood circulation and maintains the anti-thrombogenic lining of endothelial cells (ECs), the media that provides optimal mechanical properties with smooth muscle cells (SMCs) and elastin fibers, and the adventitia that is composed of fibroblasts and connective tissues. Ideally, the design of vascular grafts should mimic the distinct properties of each tissue layer (Shin et al., 2003).

Currently, the most important trend in tissue engineering is focused on the design of biomimetic materials, capable of eliciting specific cellular responses and directing new tissue formation mediated by biomolecular recognition (Sartori et al., 2008). An approach used to realize these objectives is the usage of biomolecules that

take part in specific interaction with cell receptors, such as component of extracellular matrix (ECM; e.g, fibronectin, collagen, laminin, and osteopontin) or cell-binding peptides, via chemical or physical modification to impart the desired biological characteristics (Meyers & Grinstaff, 2012). The success of this approach, however, is dependent on appropriate cell migration, adhesion and proliferation, as well as ECM production, on the biomimetic surfaces (Ravi & Chaikof, 2010). More on this approach will be elaborated in the next section.

An ideal coronary artery bypass graft has layered structure. Synthetic polymer can serve as its elastic basement layer while its surface was modified by grafting with biomolecules to enhance cell attachment, migration and proliferation on the surface. Qi et al. (2013) summarized strategies developed in the past 30 years. Bioinert and bioactive coatings are based on the regulation of physical, chemical or biological properties. It is yet still difficult to prepare ideal surface grafts with anticoagulant properties, endothelialization promotion and smooth muscle cells (SMC) inhibition. Thus, the "Biomimic" approach has been established to develop self-healing system to accelerate endothelialization with the usage of bio-inspired materials. These bio-inspired materials may have taken the form of natural polymers in which their purpose is to improve properties of synthetic polymers. In this review, we are focusing more on polyurethane as synthetic polymers, and its modification using natural polymers, specifically, gelatin.

Polyurethanes

Polyurethanes were first produced and investigated by Dr. Otto Bayer in 1937. Polyurethane is a polymer in which the repeating unit contains a urethane moiety. Urethanes are derivatives of carbamic acids which exist only in the form of their esters (Howard, 2002). They exhibit high tensile strength and melting points making them more durable. In addition, PUs also exhibit high resistance to degradation by water, oil and solvents.

After years of production, PUs were found susceptible to degradation. Howard et al. summarized the biodegradation of PU using microorganisms and esterase. Microbial degradation has been hypothesized to be mainly due to the hydrolysis of ester bonds by esterase (Howard, 2002).

The first biomedical grade polyether polyurethane was synthesized by Boretos and Pierce (Pierce et al., 1968). They introduced the biomedical application of segmented polyether polyurethanes containing hard segments of urea and soft segments of polyether linked by the urethane group. These material exhibit high elastic modulus, biocompatibility, resistance to flex-fatigue and good stability over long implantation.

Sagarito et al. (2015) reported the mechanical properties and hydrolytic degradation behaviour of a series of biodegradable PUs prepared by varying the hard segment weight percentage from 60-100. The results showed that PU with 80% hard segment and below completely disintegrated leaving no visual polymer residue in 18 weeks and the degradation medium turned acidic due to the accumulation of by-products from the soft segment degradation.

Generally, polyether-based PUs are more stable than polyester-based PU (PEU) and poly(carbonate urethanes) (PCU) in hydrolytic degradation *in vitro*. However, they seem to degrade significantly faster under enzymatic attack and in oxidative environment *in vivo* (Ren et al., 2015; Adipurnama et al., 2017). There are several factors that can be summarized regarding to the failure mechanisms affecting polyether PUs under strain with the term environmental stress cracking (ESC) (Zhang et al., 39).

Thrombogenicity remains the main cause of the implant failure, especially for small diameter conduits. Thrombogenicity is caused by platelet adhesion and the failure of rapid endothelialization, which is a big challenge (Ferreira et al., 2015; Adipurnama et al., 2017). To overcome this limitation, Punnakitikashem et al. (2014) fabricated biodegradable elastic nanofibrous scaffold with drug release from a mixture of PU and drug dipyridamole (DPA). Other works reported that porosity of PU should be sufficient to allow tissue infiltration (Hashizume et al., 2013) and chemistries that reduce platelet and white blood cell activation are essential (Sharifpoor, 2011; Ye et al., 2014).

In the other works, Zhou et al. modified the surface of PU with poly(ethylene oxide) (PEO) to improve its hemocompatibility (Zhou et al., 2014). Here PU was treated by ozone oxidation to formed peroxides group and then immersed in

toluene solution containing 6 wt% of PEO. This modification was successfully performed to improve the surface properties, notably hemocompatibility.

Tan et al. reported their works to incorporate phospholipids grafted carbon nanotubes (CNT) to improve surface properties of polyurethane (Tan et al., 2015). The multiwalled CNTs were functionalised with phospholipids through zwitterion-mediated cycloaddition reaction and amide condensation with high efficiency.

Aside aforementioned works, there are several usage of natural polymers to improve PUs limitation, including blending, surface modification through cross-link or electrospinning process.

Natural Polymers

An alternative strategy to improve synthetic polymer-based vascular grafts is the manipulation of ECM proteins as mentioned in previous section. Several proteins that mimic native structural proteins and adopt the unique characteristics of the inner surface offer a unique approach to improve vascular grafts. Such proteins that readily available are mostly natural polymers.

The use of natural polymers such as collagen, gelatin, fibrin, silk fibroin, alginate, cellulose, chitosan and hyaluronic acid has been described in a number of research works (Chatelet et al., 2001; Ma et al., 2007; Mano et al., 2007; Saucedo-Rivalcoba eet al., 2011; Han et al., 2011; McKenna et al., 2012; Wang et al., 2013; Li et al., 2014; Thakur & Thakur, 2014; Catto et al., 2015; Chen et al., 2015; Ren et al., 2015; Zia et al., 2015; Zuber et al., 2015; Junter et al., 2016; Yamamoto et al., 2016; Adipurnama et al., 2017; Salehi et al., 2017). They have been extensively investigated for clinical application due to their high biocompatibility (Boffito et al., 2014; Soichet, 2010). Moreover, they have the advantage of inducing a weak inflammatory response *in vivo*, thus enhancing cell adhesion and proliferation. On the other hand, they usually exhibit poor mechanical properties, fast degradation kinetics and high composition variability (Boffito et al., 2014). Synthetic polymers play an important role in vascular grafts as their mechanical properties make it possible to compensate the drawbacks of natural polymers.

Type I collagen is a major ECM component in the blood vessel. This fibrous structural protein can be found abundantly in the bodies of living organisms (Zuber et al., 2015). Collagen fibers function to limit high strain deformation, thereby preventing the critical rupture of the vascular wall. Collagen gels and fibers reconstituted from purified collagen are ideal in artificial blood vessel development due to their low inflammatory and antigenic responses. Moreover, integrin binding sequences in collagen allow for cell adhesion during fibrillogenesis (Ravi & Chaikof, 2010).

In the early 2000s, Park et al. (2011) successfully immobilized type I atelocollagen molecules on PU's surface through inducing covalent binding between the materials. This immobilization greatly enhanced fibroblast attachment and proliferation on PU surfaces because collagen provides a favorable biological environment as a supporting matrix for enhancing the cellular activity in the hybrid biomaterials (collagen-PU).

According to Zuber et al. (2015), there are several techniques for the synthesis of natural polymers, specifically collagen-PUs that consist of: 1) covalent or chemical immobilization, 2) oxygen plasma treatment, 3) electrospinning technique, 4) double-nozzle-low-temperature-deposition manufacturing system.

In the same paper, Zuber et al. (2015) also mentioned a variety of collagen blend with PU, such as collagen and chondroitin sulfate, collagen blends with k-elastin, hyaluronic acid and chondroitin sulfate, collagen/chitosan-PU blends scaffolds, and heparin-conjugated polycaprolactone (hPCL) and PU-collagen type I.

Another review regarding natural polymers is about the usage of starch, a natural, renewable, abundant and biodegradable polymer, which can be found from many granules of plants. Zia et al. (2015) in their review elaborated the use of starch and divide them as follows: 1) Starch based PU grafts and interpenetrating network (IPN), 2) Starch based PU/WPU films and composites, 3) Starch mixed waterborne PU ionomer dispersions, and 4) Starch modified PU as biomedical material.

Zia et al. (2015) in their review article also summarized alginate-based PUs. Recently the increasing utilization of polysaccharide in various

Table 1. Amino acid composition of gelatin (Farris et al., 2010)

Amino Acid	Gelatin (mol %)	Amino Acid	Gelatin (mol %)
Alanine	11.05	Leucine	2.35
Arginine	4.96	Lysine	2.65
Asparagine	0.6	Methionine	0.32
Aspartic acid	4.42	Phenylalanine	1.38
Cysteine	n/a	Proline	13.10
Glutamic Acid	7.10	Serine	3.40
Glycine	32.20	Threonine	1.80
Histidine	0.45	Tryptophan	n/a
Hydroxyproline	9.80	Tyrosine	0.35
Hydroxylysine	0.75	Valine	1.90
Isoleucine	1.02		

industrial fields is due to its structural diversity, biodegradability, biocompatibility, abundance, non-toxicity, and specific bioactive properties. In their review, they elaborated alginate based PU into: 1) PU-alg hydrogel, 2) PU-alg blend, 3) PU-alg elastomer and 4) PU-alg nanocomposite.

While collagen has been utilized to couple with several synthetic polymers through several techniques and reactions, it has some drawbacks because of its complex structure. Strong organic solvent sometimes causing the denaturation of collagen into gelatin (Nagiah et al., 2015). Instead of using collagen, several researches suggest using collagen-derivatives, i.e. gelatin.

Gelatin

Gelatin, derived from collagen, is inherently biocompatible with cells because it contain amino acid sequence Arg-Gly-Asp (arginine, glycine, aspartic acid, RGD), which modulates cells adhesion (Mahmoudi, 2019). Gelatin is considered "generally regarded as safe" (GRAS) material by FDA and has been commonly used in pharmaceuticals, cosmetics and food products manufacturing (Huang et al., 2011).

Gelatin is a natural hydrogel-forming biopolymer consisting of a mixture of high molecular weight polypeptides obtained by the partial hydrolysis of collagen. Gelatin is also biodegradable and commercially available at a relative low cost. There are two types of gelatin extracted from collagenous tissue: type A, processed by an acidic pretreatment, and type B, processed by an alkaline pretreatment. The main difference between these two is that type B has higher carboxylic acid content than type A (Sell et al., 2009; Duconseille et al., 2015).

Gelatin has been found to improve the spreading and proliferation of endothelial cells. Furthermore, gelatin does not promote platelet aggregation, making gelatin a promising nonthrombogenic candidate for vascular grafts applications (Kucińska-Lipka et al., 2014; Pezzoli et al., 2017; Wei et al., 2008; Wang et al., 2011; Xiong et al., 2014; Singh et al., 2002). There are several early works to incorporate gelatin onto synthetic polymers surface or blends with other polymers. All of these works indicated the ease of using gelatin in experimental process.

Gelatin composition and structure

Table 1 summarized the composition of gelatin in amino acid reported in the literature (Farris et al., 2010). However, the amino acid composition of gelatin is not clearly defined. Indeed, in mammalian gelatins, proline and hydroxyproline represent about 23-30% of total amino acids.

The structure of gelatin changes during gelation. According to the state of the gel, the chains have different space arrangements and different interactions. These characteristics depend on the gelatin concentration, temperature and the energy necessary for the formation of the secondary structure (Duconseille et al., 2015).

Nature of gelatin interactions

Duconseille et al. (2015) categorized the nature of gelatin interactions into: 1) Hydrogen bonds, 2) Hydrophobic interactions, 3) Electrostatic interactions, and 4) Covalent bonds. Among those four interactions, covalent bonds (cross-link) is considered the best in terms of surface modification. Covalent bonds found in

collagen could also be found in gelatin. Collagen has various cross-links. In skin, type III, VI, VII and XVI collagens can form disulfide bonds and type I, III, V and VII collagens can form N(γ-glutamyl)lysine isopeptide.

Cross-linking reactions imply the presence of the aldehyde groups, imines or ketones. These groups exist not only naturally in raw material but also in drugs contained in pharmaceutical capsules. Chemical compound which have been identified as favoring cross-link formation are aldehydes, imines, ketones, saccharides (glucose and aldose sugars), dyes, calcium carbonate, hydrogen peroxide, sulfonic acids and p-toluene sulfonic acid, (1-ethylene 3-(3-dimethylamino propyl) carbodiimide (EDC), guanidine hydrochloride, benzene and terephthaloyl chloride (Singh et al., 2002; Farris et al., 2010).

The level of crosslinking increases with temperature. Heating dried gelatin to 105 °C should lead to the formation of cross-links between free amino groups of amino acids and thus to its insolubilization. Although the temperature can increase the crosslinking level, the mechanism involving in this phenomenon is still unknown. On the other hand, light and UV-light also increase cross-link formation in gelatin (Rabotyagova et al., 2008).

Gelatin molecule is 13% positively charged amino acids (arginine and lysine), 12% negatively charged amino acids (aspartic acid and glutamic acid), and 11% of the polymer chain is comprised of hydrophobic amino acids (alanine, methionine, valine, leucine and isoleucine), and amino acids glycine, proline and hydroxyproline form the rest of chain (Mahmoudi, 2019). From its composition it is widely accepted that the crosslinking of gelatin is mediated through unprotonated ε-amino groups of lysine and hydroxylysine and the amino groups of the N-terminal amino acid (Farris et al., 2010). Therefore, the pH becomes important to control the crosslink reaction. At high pH, few amino groups are protonated; thus more free amino groups are available for the crosslink reaction. Meanwhile lowering the pH will increase the amount of protonated amino groups; thus, the possibility of crosslink reaction may be significantly decreased.

METHODS TO INCORPORATE GELATIN AS HYBRID CONSTRUCT ELEMENTS

Some researchers summarized their study about biomimetic approach for tissue engineering including engineered nano-fibrous materials, composite and nano-composite materials, surface modification, and bioactive molecule/gene delivery system (Mahmoudi, 2019; Huang et al., 2011; Ma, 2008). In this section, we only focus on nano-fibrous materials, surface modification and some other methods.

Nano-fibrous materials/Electrospinning

Electrospinning's core concept is based on the stretching of a viscoelastic solution into nano/microfibers using a high electrostatic force. In brief, the material to be electrospun is loaded into a syringe and pumped at a specific flow rate with a syringe pump, while a high DC voltage is applied (Hasan et al., 2014). This method offers ability to fine-tune mechanical properties during the fabrication process while controlling the necessary biocompatibility and structure of the tissue engineering grafts. Thus, it is particularly attractive for tissue engineering vascular graft, where mechanical durability is required and in addition, the incorporation of natural polymers can promote the formation of a continuous monolayer of endothelial cells and proliferation of other cell types (Hasan et al., 2014). In this section, several highlighted methods to incorporate gelatin by electospinning will be discussed and elaborated.

Nagiah et al. (2015) have successfully developed three types of coaxially electrospun 3D nanofibrous vascular scaffolds, using a mixture of polymer solutions with a fixed ratio 1:5 between hydrophobic-biodegradable synthetic polymers (PCL, PLA and PU) and a hydrophilic gelatin, as shown in Figure 2. The hybrid nanofibers demonstrate multi-layered structure showing hydrophobic core, a gelatin sheath and an interactive layer.

With a similar technique, Han et al. (2011) developed co-electrospun blends of PLGA, gelatin and elastin as potential nonthrombogenic scaffolds for vascular tissue engineering. Torricelli et al. (2014) successfully co-electrospun poly(L-lactic acid) (PLLA) and gelatin fibers.
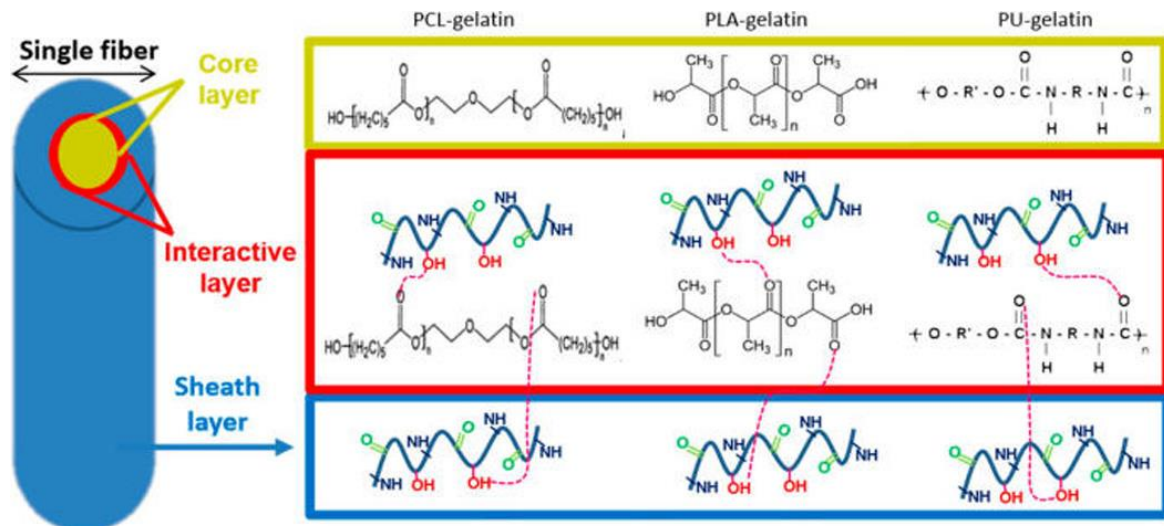
Figure 2. Schematic representation of the interactions between sheath and core layers in the coaxially electrospun nanofibrous system by Nagiah et al. (2015).

Some works showed that gelatin itself can be electrospun into a scaffold. Jalaja et al. (2015) prepared gelatin nanofibrous mats by electrospinning process and using acetic acid as a solvent and later was crosslinked with oxidized sucrose by periodate oxidation. Zhan et al. (2016) prepared electrospun gelatin nanofiber by adjusting the gelatin concentration with glutaraldehyde (GA) as the crosslinking agent.

Wang et al. (2011) developed tubular scaffolds composed of a PU fibrous outer-layer and a gelatin-heparin fibrous inner-layer fabricated by bi-layer electrospinning technology. The adhesion and activation of the platelets were remarkably decreased by the hydrophilic surfaces on the scaffolds. Moreover, the addition of heparin improved hemocompatibility of the scaffolds. Similar works reported for PU/gelatin-heparin nanofibrous layer as potential artificial blood vessels (Wang et al., 2012).

Li et al. (2006) successfully generated a biocompatible fibrous scaffold by blending an inherently conductive form of polyaniline (C-PANi) with gelatin. Their results confirmed that the blend fibers are biocompatible, and able to support attachment, migration and proliferation of cardiac myoblasts.

Detta et al. (2010) concluded that gelatin fibers contributed to the overall mechanical properties of the composite mesh as compared to plain PU (Tecoflex). Furthermore, endothelial cells cultured on the composite electrospun substrate attached, survived, and proliferated significantly higher compared to cells on meshes made of PU alone.

Surface modification

The principle of surface modification is to radically change the surface properties of the substrate and for covalently binding to other biomolecules. Thus, the surface of the substrate is improved without detrimentally affecting the bulk properties (Alves et al., 2009). In this section, several methods using the principle of surface modification to immobilize gelatin will be discussed and elaborated.

Early works by Zhu et al. (2004) introduced free amino groups onto PU membrane and the vascular scaffold surface through an aminolysing reaction with 1,6-hexanediamine. These amino groups provided the opportunity to immobilize biomacromolecules such as gelatin, chitosan or collagen onto PU surface. These biomacromolecules had a positive effect on accelerating the endothelium regeneration *in vitro*.

Sartori et al. (2008) modified the surface of PU by plasma glow discharge to immobilize bioactive monolayers (gelatin and poly-L-lysine). The PU surface was grafted with acrylic acid after treating with argon plasma, and then the carboxyl groups formed on the surface were used to covalently bind bioactive macromolecules (gelatin and poly-L-lysine), leading to enhanced cell adhesion and proliferation. Figure 3 describes the immobilization process.

Chen et al. (2011) modified poly(lactic acid) (PLLA) nanofibers (NF) with cationized gelatin (CG) to improve their biocompatibility. PLLA NF were treated with oxygen plasma, followed by covalent grafting of CG molecules on
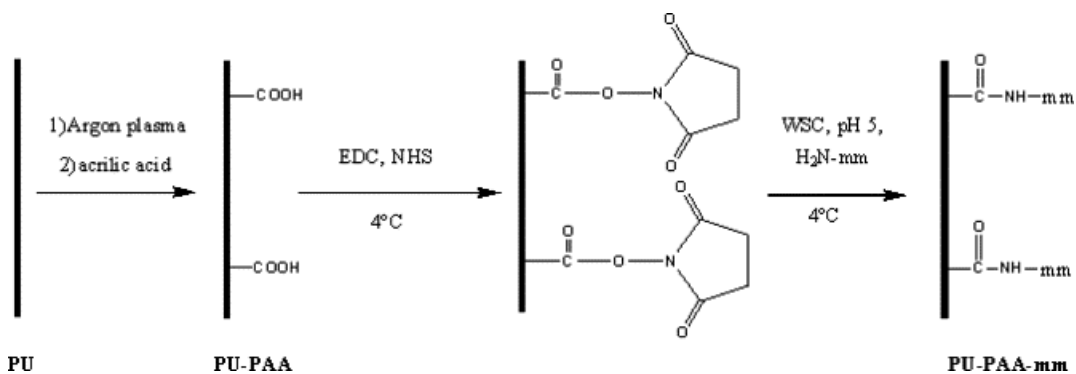
Figure 3. Schematic diagram shows PAA grafting and biomolecules immobilization. NH_2-mm indicate macromolecules (gelatin and polylysine) carrying amino groups (Sartori et al., 2008).

the surface using carbodiimide as crosslinking agent.

In the work done by Butruk-Raszeja et al. (2016), the surface of PU was successfully modified using Ce(IV)-initiated graft polymerization to bind acrylic acid onto the surface. The carboxyl groups formed on the surface has the possibility to graft other biomolecules as well.

Zhu et al. (2002) also developed surface modification of polycaprolactone (PCL) with poly(methacrylic acid) (PMA) followed by covalent immobilization of gelatin. They combined photo-oxidation and grafting copolymerization under UV irradiation. Gelatin was further immobilized on the PMA-grafted PCL through condensing agent which then increased its surface hydrophilicity.

With similar materials, Yuan et al. (2012) has successfully modified PCL via the conventional chemical immobilization and surface initiated atom transfer radical polymerization (ATRP) of glycidyl methacrylate (GMA). The amount of immobilized gelatin increase with an increasing concentration of epoxide groups on the grafted P(GMA) brushes.

Hou et al. (2014) reported a promising way ensuring a higher efficiency for endothelialization. Their study described the synthesis of honeycomb microstructured gelatin-grafted polyurethane/ polyhedral oligomeric silsesquioxane (PU/POSS) as shown in Figure 4. In their work, surface modifications of PU were achieved by incorporating POSS, followed by alteration of the surface topography via the breath figures (BF) method and then the surface chemistry was also modified by the immobilization of gelatin molecules using EDC as the crosslinking agent. They concluded the

incorporation of POSS nanostructured molecules and surface modifications through simple BF method and subsequent biomacromolecule immobilization were shown to have positive effect on improving endothelium regeneration *in vitro*.
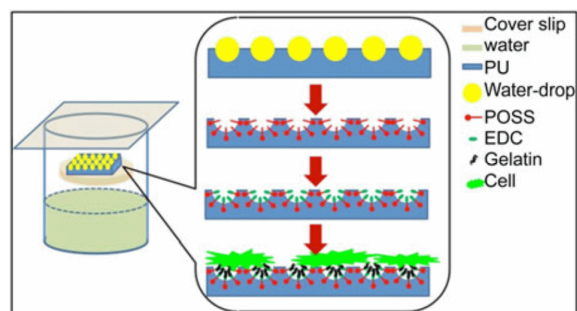

Figure 4. Schematic diagram showing the preparation of a honeycomb-structured gelatin-grafted PU/POSS film via the breath figures method (Hou et al., 2014).

Through Atom Transfer Radical Polymerization (ATRP) system, Xiong et al. (2014) successfully incorporated gelatin into the surface functionalized polycaprolactone (PCL) via poly(glycidyl methacrylate) [P(GMA)] brushes. The immobilization of gelatin on the P(GMA) brushes successfully decreased the risk of thrombogenicity as their evident showed in the expression of thrombogenic markers and production of nitric oxide from endothelial cells. Similar works done by Wang et al. (2012), was achieved through combining electrospinning and ATRP.

Based on Michael-type addition reaction, Pezzoli et al. incorporated gelatin onto electrospun poly(ethylene terephthalate) (ePET) by using crosslinking agent. Their study showed that it was possible to obtain thin gelatin coatings that maintained the nanofibrous structure typical of
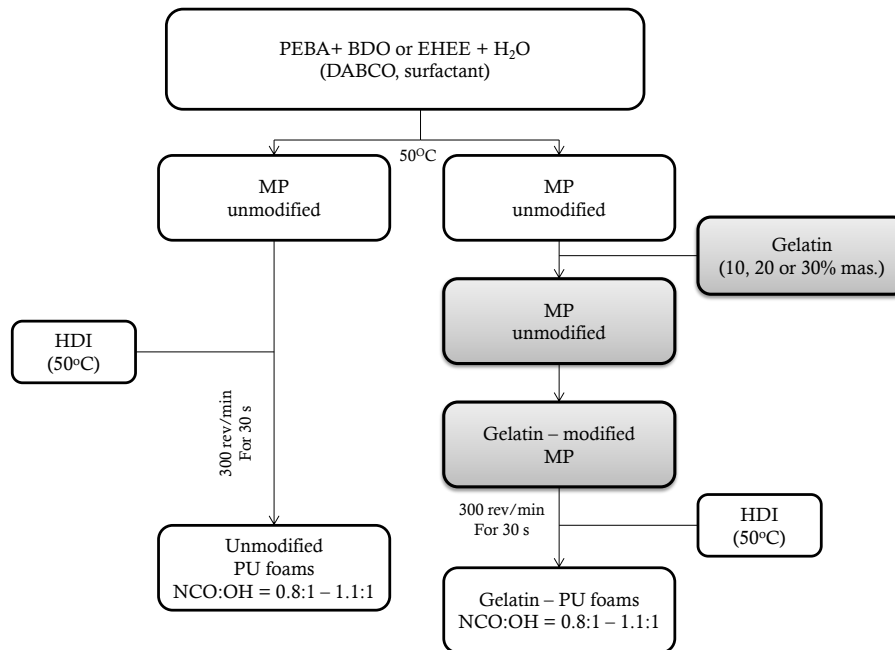
Figure 5. Schematic diagram showing the synthesis of unmodified and gelatin-modified polyurethane foams. (Kucińska-Lipka et al., 2013).

ePET. Cell adhesion and proliferation were enhanced on the optimized coated surface, demonstrating that the technique can combine the advantages of the nanofibrous structure of ePET with those of a biomimetic gelatin coating (Pezzoli et al., 2017).

Other Methods

This section elaborates several methods other than electrospinning and surface modification.

He & Wang (2011) used a double-nozzle, low-temperature (-20°C) deposition technique and successfully deposited onto a PU tube with adipose-derived stem cells encapsulated in a hydrogel composing of gelatin/alginate/fibrin, resulting a tubular PU with bilayered cell/hydrogel construct.

Liu & Chan-Park (2009) developed gelatin-bonded-dextran based hydrogel with relatively high modulus. They fabricated the hydrogel using bifunctional dextran modified with methacrylate and aldehyde groups mixed with gelatin, to encapsulate vascular SMCs. The incorporation of gelatin provided cell adhesive and increasing the compressive modulus and strength.

Mironov et al. (2005) fabricated tubular tissue constructs by centrifugal casting of cells suspended in an *in situ* crosslinkable hyaluronan-gelatin hydrogel. Living cells were suspended in a solution and hydrogel was formed during the rotation of the rotating device (operating at 2000 rpm for 10 min). This process would enable rapid fabrication of tissue engineered vascular grafts.

Unlike other methods which incorporate several techniques, Kucinska-Lipka et al. (2013) blended gelatin when processing PU. They then obtained a series of novel unmodified and modified PU foams in two-step polymerization process from 1,6-hexamethylene diisocyanate (HDI), poly(ethylene-butylene adipate) (PEBA) and 1,4-butanediol (BDO) or 1-ethoxy-2(2-hydroxethoxy)ethanol (EHEE) used as chain extenders. The gelatin was added *in situ* (in the first step of synthesis) into PU solution to increase their biocompatibility and biodegradability. Figure 5 describes the modification process of gelatin onto PU.

Losi et al. (2015) successfully prepared a gelatin-based PU vascular graft through spray and phase-inversion. This technique allows the production of a microporous tubular structure for vascular applications by using thermodynamically unstable polymer solutions. This unstable-solution was prepared by adding a non-solvent to a dilute polymer solution and membranes were obtained by simultaneously spraying unstable polymer solution and non-solvent from separate spray-guns onto a sliding and rotating mandrel.

In the works of Salehi et al. (2017), conduit for transplantation of Schwann cells was prepared from PU and gelatin nanofibrils (GNF)

Table 2. Modification for polyurethane vascular grafts with gelatin. These methods were classified into 3 categories: nanofibrous (electrospinning), surface modification and others.

| Methods	Polymers & Process	References
Nano Fibrous (Electrospinning)	(PCL, PLA, PU – as hydrophobic layer) coaxial-3D electrospinning with gelatin as hydrophilic layer	Nagiah et al., 2015
	(PANi, PLGA, PLLA, PU) – co-electrospun with gelatin	Li et al., 2006; Detta et al., 2010; Han et al., 2011
	Gelatin electrospun	Torricelli et al., 2014; Jalaja & James, 2015; Zhan et al., 2016
	PU (outer layer) – gelatin & heparin (inner layer) via bi-layer electrospinning	Wang et al., 2012
Surface Modification	PU – aminolyzing reaction – immobilization of gelatin	Zhu et al., 2014
	PU, PLLA NF– plasma treatment – gelatin, cationized gelatin and poly (L-lysine)	Sartori et al., 2008 Chen & Su, 2011
	PU – surface modified by Ce (IV) – acrylic acid grafting	Butruk-Raszeja et al., 2016
	PCL – surface modified with PMA via photo oxidation – grafting copolymerization and covalent immobilization of gelatin using condensing agent	Zhu et al., 2002
	PCL – chemical immobilization and surface initiated atom transfer radical polymerization (ATRP) of GMA	Yuan et al., 2013
	PU-POSS – altering topography via breath figures	Hou et al., 2014
Others	PU bilayered cell-hydrogel (gelatin, alginate, fibrin) via double nozzle low temperature deposition system	He & Wang, 2011
	Gelatin-MA bonded dextran based hydrogen	Liu & Chan-Park, 2009
	Centrifugal casting of cells in suspended in an in situ hyaluronan-gelatin hydrogel	Mironov et al., 2005
	Blending gelatin with HDI, PEBA and BDO	Kucińska-Lipka et al., 2013
	PU-gelatin graft via spray, phase inversion technique	Losi et al., 2015
	PU – gelatin nanofibrils via thermally induced phase separation technique (TIPS)	Salehi et al., 2017
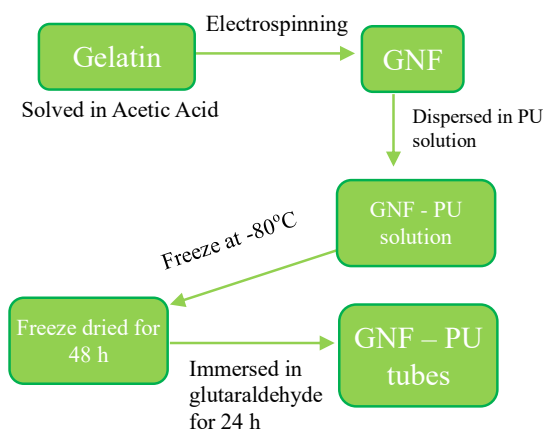
Figure 6. Schematic diagram showing the preparation of GNF-PU tubes via thermally induced phase separation (TIPS) (Salehi et al., 2017).

using thermally induced phase separation (TIPS) technique and filled with melatonin (MLT) and platelet-rich plasma. They combined electrospinning and TIPS technique to incorporate GNF with the PU solution. The results showed that the prepared conduit enhanced the regeneration of the created defect, although it was still unsuccessful to restore the animal's function. Figure 6 schematizes the preparation process of GNF-PU.

Table 2 summarizes all the methods described above, including nano-fibrous technique, surface modification and other methods.

CONCLUSION

There is an increasing need for new materials for small-diameter vascular grafts. However, thrombosis, restenosis, and low long-term patency always hinder and limit the commercially available synthetic polymers vascular grafts. One of the advantages of using synthetic polymers is good mechanical

performance but lacking in biocompatibility and cytocompatibility. Natural polymers on the other hand generally having better properties in which the synthetic polymers are lacking. Combining these two is one of the solution to solve these challenges.

With current trends in biomimetic approach for tissue engineering, more strategies need to be studied on how to incorporate such biomimetic materials to improve overall performance needed for vascular grafts application.

This review mainly focused on polyurethane as synthetic polymers, gelatin as natural polymers, and techniques to incorporate these two polymers to improve performance on vascular grafts application. Although many reports claimed that PU possessed adjustable biological, biochemical and biomechanical properties, it still has a problem of thrombogenicity. On the other hand, gelatin is a promising candidate for vascular grafts applications because of lower thrombogenicity.

Techniques to incorporate gelatin onto surface of polymers have been studied including blending, electrospinning, coaxial 3D electrospinning, photo-grafting, aminolyzing reaction, surface initiated atom transfer radical polymerization, surface topography via breath figures, hydrogel-construct, thermally induced phase separation, spray-phase inversion and more.

However, more basic experiments, animal tests, and clinical data are needed to be carried out to provide theoretical and practical outcomes. Immobilization of gelatin onto PU using either traditional method or advanced biomimetic strategy will become more interesting in developing small diameter vascular grafts devices in the future.

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