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Poly(lactic acid) as Biomaterial for Cardiovascular Devices and Tissue Engineering Applications

Waled Hadasha and Deon Bezuidenhout

Abstract Synthetic bioabsorbable polymers, such as poly-lactic acid (PLA) and its copolymers (PLA-based polymers), have attracted a lot of attention in the medical field. With their excellent biocompatibility, mechanical properties, and tunable biodegradability, PLA-based polymers have found uses in various clinical applications, including sutures and orthopedic fixation devices (e.g. pins, plates, and screws). PLA-based polymers have also been the materials of choice for various cardiovascular applications. For example, they are extensively used as coatings for metallic drug-eluting coronary stents and in the development of the new generation of fully bioresorbable vascular scaffolds. In addition, the emergence of tissue engineering and regenerative medicine (TERM) has further extended the applications of PLA. In this chapter, we discuss the importance of PLA-based polymers as biomaterials and review the applications of this family of materials in cardiovascular applications, specifically in coronary stenting and TERM approaches to vascular grafts, heart valves, and cardiac patches. A brief insight is also given into the current market value and growth potential of PLA-based biomaterials.

Keywords Biomaterial • Cardiac patches • Heart valves • PLA • Stents • Tissue engineering • Vascular grafts

Dedication This paper is dedicated to the late Prof. Ronald D. Sanderson, founder of the Institute for Polymer Science (now incorporated into the Department of Chemistry and Polymer Science) at the University of Stellenbosch.

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1 Introduction

In the latter half of the twentieth century, the focus on inertness and stability of biomaterials led to the development of many medical devices that were intended to have minimal interaction with the host tissue. Although these devices have saved, and improved, the quality of many lives, no material is completely inert in the body and long-term negative host responses eventually lead to device failure [1].

This is illustrated by the following examples in the field of cardiovascular implants: (1) mechanical heart valves (introduced in 1952) are extremely durable but require lifelong anticoagulation because of inherent thrombogenicity of the metals and polymers/pyrolytic carbon from which they are made [1]; (2) crosslinked bioprosthetic (BP) heart valves (1972) do not require anticoagulation but have a limited lifespan as a result of calcific degeneration, especially in younger patients [2]; (3) polyethylene terephthalate (PET; 1954) and expanded polytetrafluoroethylene (ePTFE; 1975) small-diameter vascular grafts have high failure rates due to mid-graft stenosis and anastomotic intimal hyperplasia associated with thrombogenicity and mechanical mismatch (respectively) [3]; and (4) a high percentage of bare metal coronary stents fail because of restenosis after implantation [4].

Although there have been improvements in these outcomes by more controlled anticoagulation for mechanical heart valve recipients, improved crosslinking and anticalcification treatment of BP tissues [2], heparinization of ePTFE grafts [5], and the development of drug-eluting stents [4], these implants persist in the body and eventually may lead, respectively, to thromboembolic or bleeding events, degeneration to a point of failure, depletion of eluted drugs, or occlusion due to thrombosis [6].

The generation of living structures and organs through recent advances in tissue engineering (TE) and regenerative medicine (RM) promises not only long-term function, but also the potential for growth when used in young individuals [7, 8]. Because these technologies often rely on the use of temporary scaffolds to guide and optimize tissue growth, there is a great need for suitable biocompatible and resorbable materials. In addition to natural materials employed in some applications, a range of synthetic degradable polymers has been developed for this purpose

[9, 10]. Of these, poly(lactic acid) (PLA) and its copolymers, including poly(glycolic acid) (PGA), polycaprolactone (PCL), poly(lactide-*co*-caprolactone) (PLA–PCL) and poly(lactic-*co*-glycolic acid) (PLGA) have probably been the most extensively investigated. They are therefore included in discussion in this chapter [8].

2 Poly(lactic acid) as Biomaterial

PLA is biocompatible, considered safe for direct contact with biological tissue, and is one of the few degradable materials approved by the US Food and Drug Administration (FDA) and many other regulatory agencies [11]. PLA is usually produced by two methods: direct polycondensation reaction of 2-hydroxy propionic acid (lactic acid) and ring-opening polymerization of lactide (a cyclic dimer of lactic acid). Lactic acid exists in two isomeric forms, L-lactic acid and D-lactic acid, which can produce four distinct materials: poly(D-lactic acid) (PDLA), a crystalline material with a regular chain structure; poly(L-lactic acid) (PLLA), which is semicrystalline, and likewise with a regular chain structure; poly(D,L-lactic acid) (PDLLA) which is amorphous; and meso-PLA, obtained by polymerization of meso-lactide. The meso-isomer is rarely used in biomedical applications and amorphous PDLLA is generally selected for drug-eluting applications. The semi-crystalline PLLA is preferred for uses where mechanical strength is required and is also preferred over PDLA, as the former degrades to the naturally occurring L(+) lactic acid [12–14].

PLA production is a multistep process that includes the production of lactic acid through either fermentation of carbohydrates by a bacterial or a synthetic approach. Approximately 90% of all lactic acid produced is made by bacterial fermentation because it has the lowest energy consumption and provides high product specificity (i.e., L-lactic acid or D-lactic acid) [1, 2]. PLLA of variable molecular weight is produced by polycondensation or ring-opening polymerization. Whereas polycondensation usually produces relatively low molecular weight PLLA, high molecular weight PLLA can be obtained through ring-opening polymerization. Production of medical grade PLLA-based polymers requires the use of reagents of high purity and nontoxic catalyst systems, such as stannous octoate. The latter has been approved by the FDA as biologically safe for use in medical and food applications, including the production of PLLA. PLLA usually passes through extensive purification processes, which may significantly increase its production costs and market price [15, 16].

These polymers, however, do have disadvantages that may limit their applications as homopolymers, including slow degradation, poor mechanical ductility, and lack of biological interaction [17]. To overcome these limitations and tailor PLA properties to suit applications, PLA has been modified using the following approaches [17–20]:

- *Copolymerization* with glycolic acid or polyethylene glycol (PEG) to impart hydrophilicity and modulate the degradation rate
- *Crosslinking* with gamma irradiation in the presence of crosslinking agents to improve thermal and mechanical properties
- *Blending* with other degradable or nondegradable polymers to tailor mechanical and degradation properties, or to alter processability without sacrificing degradability and biocompatibility
- *Plasticization* with oligomeric lactic acid, PEG, etc. to improve elongation at break
- *Reinforcement* with fillers or fibers
- *Chemical or physical surface modification* to improve biocompatibily and cellular interaction
- *Chemical modification* of the backbone by cleavage of some ester groups and appending biomolecules, such as adhesive peptides.

In vivo degradation times for PLA depend on the application and circumstances. It typically varies from 50% in 1–2 years to 100% in 12–16 months, whereas PLGA (75:25) is typically fully degraded in 50–100 days [21]. The hydrolytic degradation of PLA and PLGA is characterized by hydration, loss of mechanical strength caused by breakdown of the backbone and formation of acidic oligomers, mass loss, further water absorption as a result of diffusion of oligomers and water, and finally polymer dissolution/phagocytosis [22]. The hydrolysis may involve enzymatic action [21, 22]. The lactic and glycolic acids formed are further metabolized to carbon dioxide and water in the Krebs cycle [23, 24]. The acidic breakdown products of PLA can lead to a local decrease in pH of the tissue surrounding the implant, which may result in cell necrosis and inflammation [25].

The general characteristics of biocompatibility, biodegradability, thermoplastic processability, and tunable chemical and physical properties of PLA and its copolymers lend themselves to a variety of biomedical applications. The polymers' high mechanical strength makes them especially suitable for applications such as orthopedic screws, rods/pins, and plates (many of which are now in clinical use), and PLGA (Vicryl®) resorbable sutures (introduced in the 1970s) [26, 27]. The use of PLA in drug delivery systems and TE is, however, with a few noted exceptions, still in the experimental and preclinical phases. In addition to the clinical application of drug-eluting stents (discussed in detail in the Sect. 3.1), PLA has been extensively used to develop carriers (nanoparticles, microparticles, and microcapsules) for the controlled release of drugs, peptides/proteins, polysaccharides, and genetic material (DNA, RNA) [12, 21, 22].

PLA-based materials have also been widely used to fabricate 3D TE scaffolds for orthopedic [28], nerve [29] and cardiovascular [30–32] applications, in which not only the actual material but also the scaffold design, architecture, microstructure, and physical strength play important roles.

This chapter focuses on the use of PLA and its copolymers in cardiovascular applications, specifically in drug-eluting and degradable stents, and in TE approaches to heart valves, vascular grafts, and cardiac patches for treatment of myocardial infarction.

3 Cardiovascular Applications

3.1 Coronary Stents

Coronary artery disease (CAD), the narrowing of coronary arteries by fatty deposits that leads to inadequate blood flow and eventually stenosis (blockage), is a major cause of morbidity and mortality worldwide. Left untreated, CAD leads to angina (chest pain) and myocardial infarction (heart attack). In advanced pathologies, coronary artery bypass grafting, in which the obstruction is bypassed with healthy autologous vessels (from the patient's own body) during open-heart surgery, is the best recourse. For less severe cases, percutaneous transluminal coronary angioplasty, which involves widening the vessel with a balloon through minimally invasive percutaneous catheterization techniques, is used. This technique was introduced in the late 1970s by Andreas Gruentzig [33]. Acute occlusive dissection (4–8%) and a high incidence of restenosis (30–50%) of the vessel after angioplasty led to the development of the vascular stent (an artificial tubular mesh), by Palmaz in 1985, as an alternative treatment procedure to reopen narrowed vessels and provide continued mechanical support to the healing vessels. Stainless steel was initially the preferred metal for balloon expandable stents, with cobalt alloys (Co-Cr and Co-Pt) gaining increasing favor because of their superior mechanical properties. In many cases, however, (16–44% [33]), these bare metals stents led to persistent local inflammation [34] of the vessel wall, which led to excessive neointimal proliferation and (in 16–44% of cases) to in-stent restenosis (ISR) (narrowing of more than 50% in the stented area of the vessel) [35].

To overcome these complications, drug-eluting stents (DESs) were introduced in 2002/2003 [36]. DESs consist of a metallic structure coated with a thin polymer layer that elutes a drug to reduce the proliferation and thus prevent ISR. First generation DESs used durable polymers (e.g., poly(styrene-*b*-isobutylene-*b*-styrene) or poly-*n*-butyl methacrylate) to elute drugs with anti-inflammatory and antiproliferative action, such as dexamethasone, rapamycin, and paclitaxel. Lincoff et al. was one of the first to use a PLLA/dexamethasone-coated titanium stent as a sustainable site-specific drug delivery system [37]. Short-term in vivo results showed that the DES was an effective drug delivery approach that caused minimal thrombosis and inflammatory response.

Although ISR was reduced to approximately 10% with drug elution, the presence of a foreign body long after the drug was completely released could potentially lead to delayed healing and local chronic inflammation, and potentially to late and very late stent thrombosis (ST; 3% at 4 years) [33].

Second generation DESs saw the use of more biocompatible durable coatings (fluorinated polymers and phosphoryl choline-containing polymers) as well as the introduction of absorbable materials (e.g., PLA), resulting in improvements in outcomes to ISR of 6–8% and ST of 1% at 3 years [33, 38]. Several companies have since developed various DESs using PLA-based polymers as coatings with various drugs, as summarized in Table 1.

Table 1 Various PLA-based drug-eluting stents, adapted from [38, 39]

Stent	Mesh material	Drug	Polymer coating	Manufacturer
BioMime	Co-Cr	Sirolimus	PLLA/PLGA	Meril Life Sciences (India)
DESyne BD	Co-Cr	Novolimus	PLLA	Elixir Medical (USA)
Synergy	Pt-Cr	Everolimus	PLGA	Boston Scientific (USA)
BioMatrix	SS	Biolimus A9	PDLLA	Biosensors (Switzerland)
Nobori	SS	Biolimus A9	PDLLA	Terumo (Japan)
Yukon Choice PC	SS	Sirolimus	PDLLA	Translumina (Germany)
Orsiro	Co-Cr	Sirolimus	PLLA	Biotronik (Germany)
Ultimaster	Co-Cr	Sirolimus	PDLLA/PCL	Terumo (Japan)

SS stainless steel, *Co-Cr* cobalt chromium, *Pt-Cr* platinum chromium

In addition to these delayed complications, persistent metallic stents have drawbacks related to the need for removal/replacement if repeat procedures are required, due to restenosis of previously stented vessels. Furthermore, the lack of a permanent foreign object would reduce the risk of late ISR and thrombosis, and thus the development of bioresorbable vascular scaffolds (BVSs) is inevitable.

Third generation vascular stents are made from biodegradable/bioresorbable materials (metals such as magnesium or iron, or various synthetic polymers) as their structural elements. Because of their strong mechanical properties and tunable degradation rate, semicrystalline PLA-based polymers have been widely employed in either drug-free or drug-eluting BVSs [39–42]. The degradation rate of BVSs is an important parameter that can affect vessel remodeling and healing, as premature degradation can lead to acute vessel recoil and prolonged degradation can result in chronic inflammation and, hence, delayed healing [43, 44].

The concept of a BVS was introduced in 1988 by Stack et al., who created a knitted PLA stent design that could withstand a crush pressure up to 1,000 mmHg and maintain its radial strength for 1 month [45]. The stent was successfully implanted in an animal model and showed significant improvement in reducing inflammatory response; however, neointimal growth was observed because of vessel wall injury. These results inspired others to investigate BVSs as an alternative to permanent metal-based stents. To reduce vessel wall injury, the original knitted design of BVSs was changed to a coil design, which significantly reduced the risk of blood vessel wall injury and, hence, reduced neointimal hyperplasia.

The first human trial of a BVS was conducted using the Igaki-Tamai stent (Igaki Medical Planning Company, Kyoto, Japan), fabricated from drug-free high molecular weight (HMW) PLLA in a zig-zag helical configuration (see Fig. 1c and Table 2) [46]. The stent design significantly reduced vascular injury at the implantation site, leading to a reduction in initial thrombus deposition and blood clots, and presented no major cardiac complications, with only 10.5% restenosis at 6-month follow-up. The 4- and 10-year follow-up results demonstrated the feasibility and safety of PLLA-based bioresorbable stents.

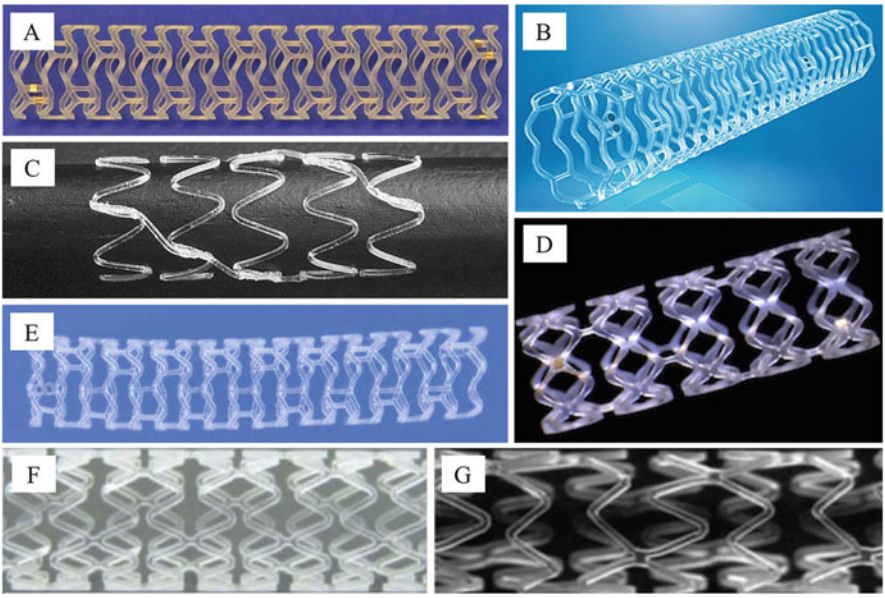

Fig. 1 Various BVSs in clinical or preclinical use. (**a**) Fortitude (Amaranth Medical, USA), (**b**) DESolve 100 (Elixir Medical, USA), (**c**) Igaki-Tamai (Kyoto Medical, Japan), (**d**) ART18Z BRS (Arterial Remodeling Technologies, France), (**e**) Absorb BVS 1.1 (Abbott Vascular, USA), (**f**) Xinsorb (Huaan Biotech, China), and (**g**) Acute BRS (OrbusNeich Medical, USA). Images adapted from [46, 47]

Table 2 Summary of various bioresorbable vascular scaffolds. Adapted from [39, 41]

Stent	Mesh material	Drug	Polymer coating	Manufacture	Current status
Igaki-Tamai	PLLA	–	–	Kyoto Medical	CE mark
Fortitude	PLLA	–	–	Amaranth	Clinical trails
Mirage BRMS	PLLA	Sirolimus	–	Mirage BRMS	Clinical trails
Absorb BVS	PLLA	Everolimus	PDLLA	Abbott Vascular	CE mark
Xinsorb	PLLA	Sirolimus	PLA	Huaan Biotech	Clinical trails
Acute	PLLA–PCL	Sirolimus	PLA	OrbusNeich Medical	–
DESolve	PLLA	Myolimus	–	Elixir Medical	EC mark
DESolve 100	PLLA	Novolimus	PLLA	Elixir Medical	EC mark
MeRes	PLLA	Paclitaxel	PLGA	Meril Life Sciences	Clinical trails
ART18Z BRS	PDLLA	Sirolimus	PLLA	Arterial Remodeling Remodeling Tech	Clinical trails
FADES	PLGA/Mg	–	–	Zorion Medical	–

BVSs may of course also serve as a drug delivery system, as demonstrated by Yamakawi et al., who incorporated an antiproliferative agent (tyrosine kinase inhibitor) in PLLA-based stents. The results obtained suggested that the stent was able to suppress neointima hyperplasia caused by balloon injury [48]. Analogous to regular DESs, drug-eluting BVSs generally consist of a platform made of biodegradable materials, such as PLA or Mg with a thin layer of drug-loaded biodegradable polymer such as amorphous PDLLA or other PLA-based polymers [42, 49, 50]. The stent platform usually has a slow degradation rate to provide mechanical support of suitable duration, whereas the degradation of the outer thin layer is usually tuned to allow uniform dispersion and controlled drug release.

Various PLA-based drug-eluting BVSs either have received the CE mark or are currently undergoing clinical trails. Abbott Vascular produced the first drug-eluting BVSs, Absorb BVS (Fig. 1e and Table 2) (PLLA with everolimus/PDLLA coating). It is now widely available, including in the USA and Europe, with more than 150,000 having been implanted [51]. In a preclinic in vivo study, the stent showed similar drug release profiles to those obtained from previously approved DESs, and the stent exhibited positive vessel remodeling and full absorption of platform in a 2-year clinical trail. Table 2 summarizes a number of BVSs currently under development and/or in clinical use.

3.2 Tissue Engineering

The term "tissue engineering" was introduced by Dr Fung of California University in 1987. Since then, TE has been widely used and has emerged as a potential alternative to organ transplantation or as a treatment method for repair of damaged tissues and organs. Ultimately, the purpose of TE is to generate compatible, healthy, and functional tissue and organs that are readily available for implant. Accordingly, this should contribute to overcoming the shortage of tissue donors, as well as minimizing the use of artificial implants and the need for prolonged medication and/or additional procedures to remove the implants.

TE is a multidisciplinary field that combines various aspects of materials science, biology, engineering, and medicine, with the aim of fabricating biological substitutes that are able to repair, maintain, or replace damaged tissues and organs. The generation of new tissue can either be in vitro, usually known as "tissue engineering", or in vivo, usually referred to as "regenerative medicine" [52–54]. In the TE approach, the new tissue is generated in vitro by seeding isolated cells (same cell types as the native tissue cells) onto a 3D scaffold and culturing in a dish or bioreactor prior to implantation. However, in the RM approach, the tissue is fabricated in vivo by implanting an acellular 3D scaffold that guides and directs the migration of native cells to regenerate new tissue, using the host as bioreactor. As the new tissue is formed, the 3D scaffold degrades into metabolically removable materials, leaving behind fully functional and compatible new tissue or a new organ [52, 54]. For the

sake of simplicity, the "TE" will be used throughout this chapter to describe both approaches.

In natural tissue, cells are surrounded by a connective network of extracellular matrix (ECM) that provides an essential physical framework, and crucial biochemical and biomechanical cues required for cellular constituents during tissue development and maturation. TE scaffolds mimic the development of growth and generation of tissue to produce a functional organ. Therefore, developing a successful and effective TE approach relies on the appropriate combination of three important components that exist in natural tissue: (1) a 3D scaffold, (i.e., organ-specific composition and shape), (2) isolated cells (i.e., cell population, culture) and (3) cell signaling cues (i.e., chemical and physical cues).

One of the key elements in TE strategies that determines the function and shape of the engineered tissue is the 3D scaffold. Mimicking ECMs, the scaffold serves as a temporary artificial template that supports and regulates cells' activities, from attachment to differentiation. To fulfill the ECM function, the scaffold should exhibit organ-specific composition, and mechanical and architectural characteristic features. Therefore, the scaffold should (1) comprise a biocompatible, bioactive, and degradable material; (2) exhibit suitable mechanical and physical properties, compatible with the mechanical function of engineered tissue; and (3) have an appropriate macro- and microstructure design.

The scaffold material should be compatible with the tissue and be able to degrade biologically at a suitable rate, specifically, a rate that matches the formation rate of new ECM, and with predictable degradation kinetics, byproducts, and rates.

The resorption of scaffold materials is a critical parameter in tissue regeneration. In order to generate healthy new tissue, the scaffold should maintain sufficient physical and mechanical features until the formation of adequate new ECM. Therefore, as mentioned, the scaffold degradation rate should match the rate of new ECM formation. Whereas fast degradation can result in mechanical instability and poor tissue formation, slow degradation leads to excessive chronic inflammation and the formation of unhealthy tissue.

Ideally, the scaffold should display physical and mechanical properties similar to those of the targeted tissue in its native state. For example, scaffolds intended for blood vessel engineering should have resistance, elasticity, or resilience compatible with the dynamic nature of the cardiovascular system. This is particularly important in TE of cardiovascular and cardiac tissue, where tissue undergoes continuous and variable mechanical stresses that can influence the behavior of seeded cells. For example, mesenchymal stem cells (MSCs) have been found to differentiate into neural, myogenic, or osteogenic tissue according to scaffold stiffness. Scaffolds intended for heart valve (HV) replacement should have a stiffness of approximately 0.5 MPa.

Other important characteristic features of a scaffold in TE that significantly influence cell behavior and function are the scaffold morphology and the macro- and microstructure. During tissue formation, the various activities that cells perform require highly porous structures to ensure a constant supply of nutrients and oxygen. Without a scaffold, most cells tend to aggregate to a certain thickness

(ca. 1–2 mm) before apoptosis arises because of the lack of an adequate supply and exchange of nutrients, oxygen, and waste metabolites [55–57]. Thus, growing large organized cell aggregates capable of tissue regeneration demands scaffolds of appropriate design that are able to provide the necessary environments for cellular activities. These activities typically require scaffolds with microstructures of interconnected pores to permit sufficient flow of gases, nutrients, and other signaling molecules that regulate cell behavior. Such microstructure features are also important for angiogenesis (i.e., formation of new blood vessels) as well as cell proliferation, differentiation, and motility. The average pore size, volume, and shape, as well as the overall morphology, are all important parameters that depend on the type of cell and tissue. The scaffold design, therefore, must be tailored and optimized to resemble the in vivo cellular macro- and microenvironments in native tissues.

The design of an effective scaffold with optimum structural features typically depends on the material used and the scaffold fabrication method. The selected method should be efficient and capable of producing scaffolds with complex architectures that mimic the macro-, micro-, and nanostructure of natural ECMs. Several fabrication techniques have been developed and optimized for fabricating highly porous scaffolds, for example, electrospinning, 3D printing, emulsion freeze-drying, and salt leaching [56, 58–61]. These methods have enabled the fabrication of scaffolds of various shapes and morphologies. For example, electrospinning has been widely used to fabricate fibrous scaffolds with tunable microstructure, thickness, and composition from a wide range of polymeric materials. The high surface area-to-volume ratio and interconnected porous microstructure of nanofiber-based scaffolds offers highly attractive features for many TE applications. Detailed descriptions of various scaffold fabrication techniques are reported in many excellent reviews [10, 60–63].

As a conceptual creation in TE, the scaffold that is used should be temporary and biologically degradable. Therefore, consideration of the biodegradability of the material is of great importance when designing implantable scaffolds. Various biodegradable polymeric scaffolds have been used in many TE applications, including polymers of natural [64, 65] or synthetic [28, 66–68] origin, as well as decellularized tissue [69–72].

Natural polymers (e.g., chitosan, collagen, and cellulose) generally have better interactions with cells and better bioactivity compared with synthetic polymers; however, poor mechanical performance, and high risk of immunogenic response and infection have limited their application [53]. In recent years, various biodegradable synthetic polymers such as PLA, PGA, and PCL have been used to overcome the limitations associated with natural polymers [73]. PLA-based polymers have received significant attention in many TE applications. Their use in cardiovascular applications is described in the following sections.

3.2.1 Tissue-Engineered Heart Valves

The human heart consists of four heart valves that synchronically open and close to maintain unidirectional, unhindered blood flow during a person's lifetime. If one of the valves malfunctions (a condition commonly known as valvular heart dysfunction) and is left untreated, it could lead to heart failure and even death. The best available treatment for such a condition is surgical valve replacement with artificial valves. Artificial heart valves, such as mechanical and biological valves, are clinically used. However, the success of this approach requires the use of postoperative medication for a prolonged period as well as routine follow-ups, or even the need for reoperation (especially in young patients). TE represents a potential alternative treatment that can provide suitable valve replacements that are capable of growth and self-remodeling in vivo. Hence, the complications associated with traditional approaches can be avoided.

The generation of fully functional valve substitutes through TE strongly depends on the design and materials of the scaffold, as well as the selection of suitable cell types [74]. In addition to the general scaffold requirements of biocompatibility and biodegradability, the materials should mimic the mechanical and physical properties of native valvular ECMs [75]. The scaffold design should be nonobstructive, with the ability to adapt to change in physiological conditions and to withstand the mechanical loading during opening/closing of cyclic beating.

The concept of the tissue-engineered heart valve (TEHV) was introduced by Shinoka et al. in 1995 [76]. It involves the use of artificial scaffolds to direct the proliferation and growth of cells into a fully functioning valve, as schematically shown in Fig. 2. Thereafter, many other research groups investigated the concept further, using different types of cells and scaffolds, including decellularized [78, 79], biologically based [80, 81], and synthetic-based polymers, including PLA-based polymers [82–85].

PLA-based polymers have been used as synthetic materials to fabricate scaffolds for TEHVs [86]. For example, Mayer et al. [87, 88] investigated an in vitro TEHV using PGA and PGLA scaffolds. In this study, HV-shaped scaffolds consisted of a woven PLA mesh sandwiched between two nonwoven PGA fibrous scaffolds and seeded with endothelial cells (ECs) and myofibroblast cells. Histological examinations revealed the formation of cellular architecture and ECMs similar to those of native valves [89].

In a similar study, Sutherland et al. utilized PGA/PLLA (50:50 blend) scaffolds seeded with bone-marrow-derived MSCs to fabricate autologous semilunar TEHVs in vitro. The obtained valves were implanted into the pulmonary position of sheep on cardiopulmonary bypass. Histology analysis showed the deposition of ECM and distribution of cell phenotypes in the engineered valves similar to that displayed in native pulmonary valves. The obtained TEHVs functioned well in vitro for 4 months and underwent extensive remodeling in vivo [74].

Hinderer et al. [90] used different scaffolds consisting of electrospun PEG dimethacrylate–PLA, which showed biomechanical properties similar to those of

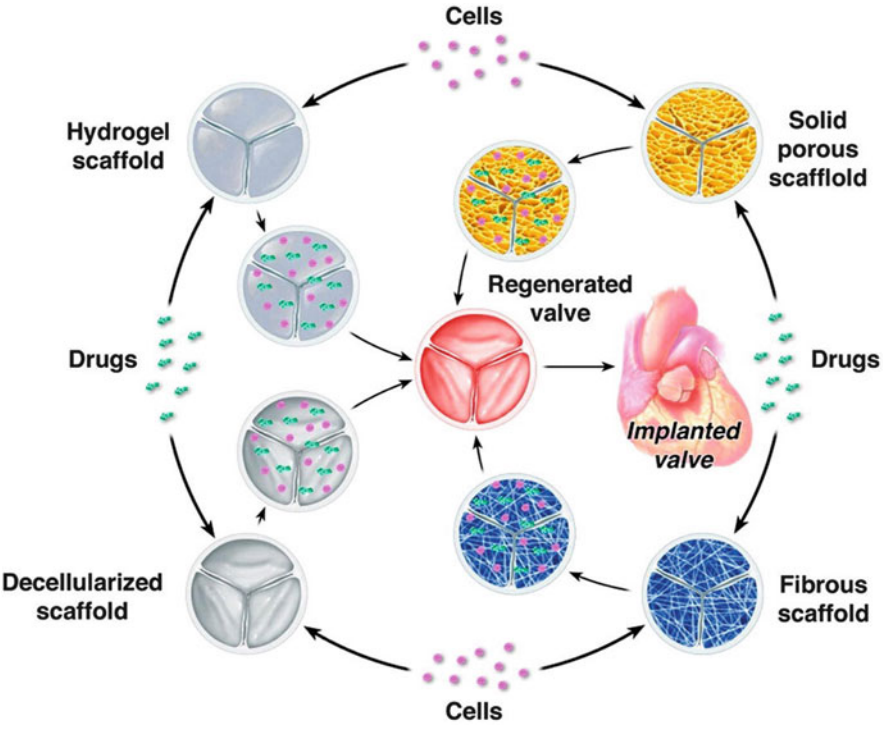

Fig. 2 Diagrams of aortic heart valve tissue engineering. Living cells are grown onto a supporting three-dimensional biocompatible structure to proliferate, differentiate, and ultimately grow into a functional tissue construct [77]

natural valve leaflets. The scaffolds were UV crosslinked before being seeded with valvular ECs and valvular interstitial cells and cultured in a bioreactor under physiological conditions [90, 91]. Three-dimensional (3D) printing is a versatile technique for producing many types of medical implants. It was used by Lueders et al. [92] to fabricate scaffolds suitable for TEHV from PGA/PLA copolymers.

TEHVs have also been fabricated using a combination of PLA-based polymers and natural materials. For example, Novakovic et al. [93] fabricated highly porous scaffolds using a composite of PDLLA–PCL or PLGA and type I collagen. The scaffolds were then seeded with neonatal heart cells and cultured for 8 days. Compared with controls made of individual materials, the composite scaffolds showed higher cell densities with higher cardiac marker expression and contractile properties. The results were attributed to the suitable porosity, mechanical properties, and degradability of the scaffolds.

PLA-based hydrogels have also been developed and used as scaffolds for TEHVs. Anseth et al. investigated the attachment of valvular interstitial cells on biodegradable hydrogel scaffolds prepared from a photo-crosslinkable PLA–poly

(vinyl alcohol) multifunctional macromere and found improved cell attachment by increasing the PLA segments [94].

The limited use of PLA-based polymers to produce scaffolds for TEHVs can be attributed to its low flexibility and long degradation times. As a result, other degradable polymers (poly-4-hydroxybutyrate, PCL and copolymers with PGA) are now preferred.

3.2.2 Tissue-Engineered Vascular Grafts

Cardiovascular disease, including stenosis/occlusion and damage of blood vessels, is one of the leading causes of death worldwide. One of the available treatments for vascular pathologies is surgery utilizing either natural autologous (from the patient's own body) or synthetic vascular grafts [e.g., ePTFE (Teflon), polyurethane, and PET (Dacron®)] for replacement or bypass grafting. However, this approach is usually limited either by the availability of healthy and suitable autologous vessel replacements or by hyperplastic stenosis and/or thrombus formation [31, 95, 96]. To overcome such limitations, TE techniques were proposed by Weinberg and Bell for fabrication of native-like vascular prostheses [97]. TE of vascular grafts is currently a very active research area in which PLA-based polymers have been widely used to fabricate scaffolds for tissue-engineered vascular grafts (TEVG).

The scaffold material plays a key role in TE applications because it should have appropriate mechanical properties to match the native vessels, especially as they are under cyclic stress. Various PLA-based polymers, such as PLLA, PLA–PCL, PLGA copolymers/blends, and PLA combined with other natural polymers, have been used to fabricate scaffolds for TEVG applications, with the advantage that mechanical properties of these polymers can be tuned by varying the concentrations of the constituents [98–103].

Several research groups have used these polymers to fabricate highly porous scaffolds suitable for VGTE though different fabrication methods, such as freeze-drying (Fig. 3) and electrospinning (Fig. 4).

Many studies have employed electrospinning techniques to fabricate tubular fibrous scaffolds of PLA-based materials, as it provides an efficient and effective

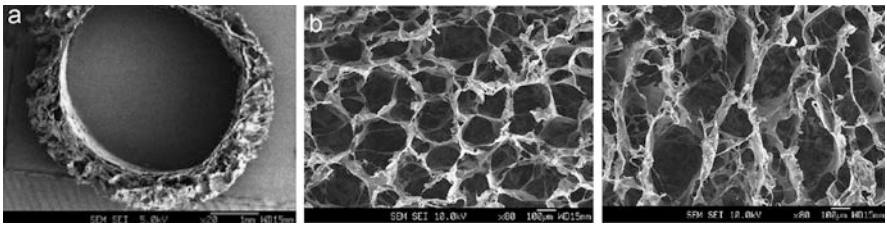

Fig. 3 SEM images of freeze-dry fabricated PLGA/collagen scaffolds: (**a**) cross-section of tubular collagen scaffolds, (**b**) inner surface of collagen scaffolds, and (**c**) outer surface of collagen scaffolds [98]. Scale bars 1 mm for (**a**) and 100 μm for (**b**) and (**c**)

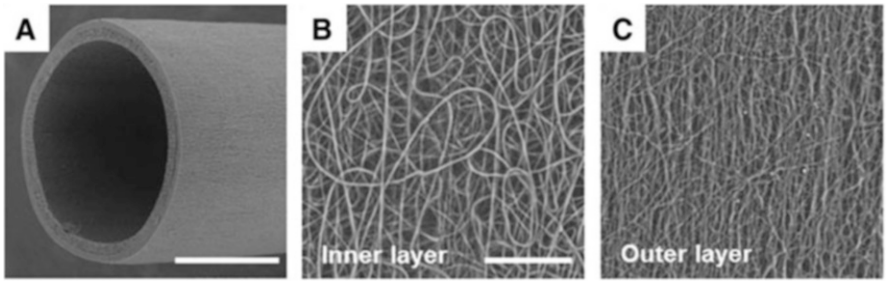

Fig. 4 (**a**) SEM image of bilayered electrospun vascular graft; *scale bar* = 500 μm. (**b**) PLLA microfibers on the inner surface and (**c**) PLCG + PCL nanofibers on the outer surface of the graft; *scale bar* = 50 μm. Picture obtained from [104]

approach to the fabrication of tubular scaffolds of any diameter required for vascular conduit specification [105]. The fibrous scaffolds obtained generally have highly porous structures and good mechanical properties, suitable for vascular applications. In efforts to produce blood vessels by means of TE, PLGA has been electrospun into tubular scaffolds. A blend of PLGA, PCL, and elastin, in addition to heparin and vascular endothelial growth factor, was used to fabricate a scaffold by electrospinning. In vivo results showed that the scaffolds promoted the recovery of damaged vessels and enhanced cell attachment and proliferation [106].

Li et al. [104, 107, 108] seeded bone marrow MSCs onto modified nanofibrous PLLA scaffolds (see Fig. 4). The scaffolds showed reduced in vivo thrombotic response as compared to unseeded scaffolds. Kurobe et al. [109] fabricated small diameter TEVGs (<6 mm) using electrospun PLA scaffolds for implantation in mice. Significant increase in expressions of smooth muscle cell (SMC) markers, collagen I, and collagen III with excellent overall patency rate and tissue remodeling with autologous cells were seen after 12 months. Mooney et al. [110] fabricated TEVGs by seeding SMCs onto PLLA- and PGLA-coated PGA tubular scaffolds. The PLLA-coated tubular scaffolds were implanted in rats the scaffolds maintained their tubular structures during fibrovascular tissue ingrowth.

PLA–PCL copolymers have also been extensively used by several research groups [30, 111, 112]. Patterson et al. [112] fabricated TEVG utilizing bone-marrow mononuclear cells (BM-MNCs) seeded onto PLA–PCL copolymers [102, 113]. Initially, they seeded mixed cells obtained from femoral veins onto tube-shaped biodegradable scaffolds composed of 50:50 copolymer of PLA–PCL, reinforced with nonwoven PGA (PLA–PCL/PGA) to fabricate inferior vena cava (IVC) [114]. They subsequently investigated the use of scaffolds consisting of poly (chitosan-*g*-PLA)/PGA and BM-MNCs as a cell source for TEVGs [115]. The BM-MNCs were seeded onto the scaffold and cultured before implantation as interposition grafts replacing the intrathoracic IVC in an adult beagle model, with harvesting over a 2-year period. The TEVGs showed no evidence of thrombosis, stenosis, or aneurysm formation.

Following these results, the investigators adapted this approach to fabricate TEVGs for clinical use, employing slower degrading scaffolds than the original PGA scaffolds. In these studies, PLA–PCL/PLA scaffolds were seeded with BM-MNCs and cultured in vitro before being implanted in young patients aged between 1 and 24 years [115–117]. Late-term follow-up analysis showed that the implanted TEVGs remained patent with no evidence of rupture, aneurysm dilatation, or calcification. These studies illustrate the importance and advantage of PLA-based polymers in the field of TEVG.

Niklason et al. [32, 118] prepared tissue-engineered small-diameter vascular grafts using a bioreactor system that applies mechanical stimulation. PLGA/PGA scaffolds were seeded with bovine SMCs and ECs in the bioreactor system under physiologically relevant strain and pulsatile flow. Grafts showed the formation of an ECM with architecture and compliance comparable to the natural vasculature. Mechanical analysis of these grafts showed that the vessel strength increased when mechanical stimulation was applied compared with vessels produced under static culture. In vivo investigations revealed that one of these engineered vessels remained patent, without detectable stenosis or dilation, for up to a month when implanted in Yucatan minipig as saphenous vein grafts [119].

Traditional TE approaches involve long production times and a risk of infection or mismatch, which are disadvantages compared with the production of off-the-shelf vascular grafts. The utilization of acellular scaffolds that are patient-specific offers an alternative and faster approach to the production of vascular grafts in which cell-free scaffolds are implanted into the affected area, allowing in vivo tissue regeneration. This approach is particularly important in tissue replacement or repair of defective tissue in children, as these treatments require multiple interventions to replace the implanted device/tissue as the child matures. In regenerative tissue, the newly formed tissue matures spontaneously, similar to natural tissue.

The use of PLA-based scaffolds in a regenerative medicine approach to TEVGs, where TEVGs were produced by implanting acellular scaffolds, has also been followed [120]. In an in vivo study [103], scaffolds consisting of either PGA, PLA–PCL, or PGA–PCL implanted in dogs as a pulmonary artery replacement exhibited patency for up to 12 months. Examination of the explants revealed the formation of SMC and EC layers with ECM content similar to that found in natural tissues.

The use of PLA-based polymers to fabricate scaffolds suitable for TEVG has been explored with some positive results, including encouraging clinical application. The lack of cell recognition sites as well as scaffold hydrophobicity, limit the success of the approach. However, these initial positive results indicate promising findings that could lead to more success in this field.

3.2.3 Tissue-Engineered Cardiac Patches

Myocardial infarction (heart attack) is caused by ischemia (lack of blood flow) that results in irreversible damage to the heart muscle and fibrous scar formation that can eventually lead to heart failure. Ideally, a heart transplant is the treatment of choice to replace the damaged heart; however, due to low organ-donor availability,

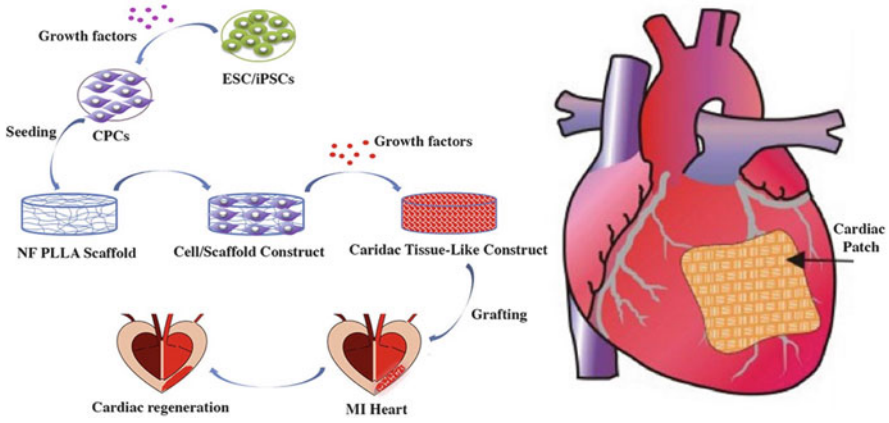

Fig. 5 Illustration of tissue engineered heart patch. Adapted from [121, 122]

high costs of surgery, and the risk of rejection complications, alternative treatments are required. Two approaches have been used in the treatment of heart failure, cell therapy and tissue-engineered heart constructs. In the cell therapy approach, isolated cell types are implanted at the affected area to regenerate the damaged tissue. In the TE approach, a cell-seeded scaffold (prepared in vitro) is implanted at the affected area to replace the damaged tissue, as illustrated in Fig. 5 [121–123].

One of the major challenges in tissue-engineered heart patches, and TE in general, is the design and fabrication of tissue-like scaffolds capable of supporting cell activities. The scaffolds should display mechanical and functional properties similar to native cardiac tissues, such as coherent contractility and low diastolic tension. Fabricating such scaffolds requires biocompatible materials with suitable and tunable mechanical properties. PLA-based scaffolds have been used in several studies to fabricate a construct with mechanical properties suitable for cardiac TE [124, 125].

PLGA scaffolds with different PLLA contents have been used to investigate rat cardiomyocyte (CM) cell attachment and proliferation behavior. In vitro studies revealed that CM cells had higher activity on scaffolds with high PLLA content than on the other scaffolds considered. This was attributed to the hydrophobicity of PLLA [126]. These studies also demonstrated that CM cells seeded on electrospun PLLA scaffolds developed mature contractile machinery (sarcomeres, as indicated by optical imaging using voltage-sensitive dye) [126]. Furthermore, Simon-Yarza et al. [127] implanted PLGA-based scaffolds containing a cardiovascular growth factor, neuregulin-1, into a rat model of myocardial ischemia. Histological analysis revealed the presence of an inflammatory response and an increase in the M2:M1 macrophage ratio, indicating the induction of constructive tissue remolding.

Several other studies have explored the use of PLGA scaffolds to fabricate TE cardiac tissue [128–132]. Yu et al. utilized the electrospinning technique to fabricate peptide-loaded PLGA scaffolds to investigate the in vitro behavior of rat CM cells [130]. Two adhesive peptides, *N*-acetyl-GRGDSPGYG (RGD) and *N*-acetyl-GYIGSRGYG (YIGSR), covalently conjugated to poly-L-lysine, were incorporated

into fibrous PLGA scaffolds through solution mixing before electrospinning. The results suggested that YIGSR-incorporated PLGA scaffolds were better candidates for the formation of cardiac patches because cells cultured on these scaffolds showed physiological-like morphology.

PLA-based scaffolds have also been used in TE of cardiac patches to stimulate revascularization and preserve the left ventricular (LV) function [133]. In a study carried out by Kellar et al., knitted vicrylic meshes (PGA-to-PLA ratio of 90:10) were used to fabricate heart patches via seeding with human dermal fibroblast cells. Following cell culture, the patches were implanted in mice with induced heart infarction. Results showed that the use of engineered patches improved the LV function and attenuated further loss [134]. Ramakrishna and coworkers [135] investigated the differentiation behavior of pluripotent embryonic stem cells (ESCs) seeded on electrospun PLGA and PLGA/collagen scaffolds. Results showed that ESCs and PLGA/collagen were comparable with the PLGA scaffolds.

In another study, Prabhakaran et al. [136] used electrospun scaffolds consisting of poly(1,8-octanediol-*co*-citrate) (POC) and PLLA–PCL to fabricate scaffolds suitable for cardiac TE. They found that scaffolds of POC and PLLA–PCL (40:60) have mechanical properties similar to native cardiac tissue. The proliferation in vitro experiments also showed, with increasing POC content in the scaffolds, an increase in the proliferation of cardiac rat myoblast cells from days 2 to 8. Bhaarathy et al. [137] fabricated PLA–PCL-based scaffolds through electrospinning with silk fibroin and aloe vera to improve cell functionality. These scaffolds exhibited elasticity and mechanical properties comparable to myocardium, which enhanced cell activities (e.g., adhesion, proliferation, and morphology).

Ozawa et al. [138] carried out a study in which PLA-reinforced PCL–PLA sponges were seeded with SMCs and cultured to generate patches. These patches were then implanted in rats to replace a surgically induced defect in the right ventricular outflow tract. Histological examination showed that the PCL–PLA scaffolds were replaced by more SMCs and more elastin-rich ECMs compared with patches made of gelatin gel or PGA. Results of the study indicated that the use of these PLA-based scaffolds permits the construction of autologous patches to repair congenital heart defects.

The beating action of the heart is a result of synchronous contractile activity of the cardiomyocytes through continuous electrical signals. One of the major challenges in cardiac TE using biological or synthetic scaffolds is achieving synchronous contractility of the engineered patches. In an attempt to overcome these challenges, researchers have used various techniques, including the addition of inorganic materials such as carbon nanotubes (CNTs) [139], gold, and electroactive polymers (e.g., polypyrrole; PPy) [140, 141], among other techniques [139, 142–146]. In this regard, Webster et al. [147, 148] investigated the viability of cardiac tissue cell functions, including cardiomyocytes and neurons, seeded on conductive scaffolds made of PLGA with embedded CNTs. Results showed that the conductivity of these scaffolds increased with increasing CNT content. Scaffolds of PLGA and CNTs (50:50) exhibited significantly higher adsorption of specific proteins (fibronectin and vibronectin), which promotes the adhesion and proliferation of CM

cells, compared to pure PLGA scaffolds. Mooney et al. [149] also used PLA/CNT scaffolds to investigate MSC differentiation. It was found that these scaffolds provide a cardiomimetic cue that directs MSC differentiation into cardiomyocyte cells. In addition, the cells also adopted elongated morphology and reoriented perpendicularly to the direction of the current after stimulation using an electrophysiological bioreactor.

Another commonly used method to enhance conductivity is the incorporation of conductive polymers such as PPy or polyaniline (PANi) [150–152]. Hsiao et al. [153] used PLGA/PANi fibrous scaffolds to enhance the attachment of CM cells. Hydrochloric acid was used to dope PANi to induce positive charges on the scaffolds, which attract the negatively charged adhesive proteins fibronectin and laminin, and hence improve CM cell attachment on the scaffolds. Jin et al. [154] used PPy to enhance CM cell proliferation through surface modification of PLLA fibrous scaffolds. In this study, pyrrole was polymerized on the surface of electrospun PPLA fibers, resulting in scaffolds with a 3D interconnected pore structure. In vitro investigations using CM cells showed that these scaffolds provided suitable 3D micro-environments for the proliferation of CM cells, as indicated by the increase in cell proliferation rate. Results were better than with PPy mesh scaffolds.

Although further investigations into the use of such scaffolds is required, there are already indications that PLA-based polymers provide promising scaffolds that can stimulate the growth and activity of cardiomyocytes and potentially imitate the contraction of normal heart tissue [147, 148, 155].

4 Market Status

Economic and technological developments and growing environmental concerns have driven considerable scientific and engineering efforts into the utilization of biosourced polymers to replace petroleum-based polymers [156–158]. With increasing worldwide consciousness of environmental protection, the use of biobased and ecofriendly polymers, such as PLA and starch, has become more desirable over the last two decades. The growing interest in biobased polymers can be seen by the steadily growing production capacity of these polymers; global production is expected to increase from ~0.7 million tons in 2014 to 1.2 million tons in 2019 [159]. Of the biobased polymers, PLA represents an ideal biosourced polymer, with its low energy consumption production and excellent properties that have attracted great attention in applications such as packaging, textiles, construction, and low volume/high value medical applications [158].

In 2014, the global PLA market, by application, was valued at ~$300 million, which is projected to reach $850 million at a compound annual growth rate of 22.8%

over the period 2014–2019. Although the packaging application is still the largest market segment of PLA, ongoing extensive research in the biomedical field is expected to increase the demand for PLA-based polymers [158]. Biomedical application of PLA-based polymers is still a relatively new targeted industry; it requires high value and low volume medical grade PLA. Although the application of PLA-based polymers represents a small fraction of the overall PLA raw materials market, the real contribution of PLA is seen in its high value products. Generally, medical grade PLA polymers command prices that are orders of magnitude higher than polymers used in other consumer devices because of the extensive synthetic and purification processes involved. In other words, the small amounts of PLA used as biomaterials do not accurately reflect the impact that PLA has in medical and, specifically, cardiovascular applications. An example of a high value/low volume PLA application are BVS contrary stents; DES/BVS stents, which contain a very small amount of PLA-based polymer, can sell for thousands of US dollars [160]. The current value of the BVS market, with only a few approved products, was valued at $18 million in 2015. However, due to the efficiency and advantages of BVSs, with the addition of almost-approved products, the market is expected to grow and reach $1.7 billion by 2024 as the market progresses at a CAGR of 30.1% [161].

5 Conclusions

Poly(lactic acid) is an ideal example of a biocompatible and biodegradable polymer with excellent properties, indicating a promising future for applications. The use of PLA in the medical field is rapidly expanding because of its biocompatibility, availability, processability and, most importantly, regulatory approval by the FDA. The ability to modify PLA through copolymerizing or blending represents another advantage that extends PLA application. PLA has already made a significant contribution to the development of therapeutic procedures to overcome various diseases. In the cardiovascular field, for example, PLA-based polymers have made the most clinical impact in the treatment of coronary diseases through drug-eluting and bioresorbable vascular stents, for which it is well suited. Other exciting cardiovascular applications of PLA-based polymers include vascular grafts and heart patches. Furthermore, there is large growth potential for the use of this family of polymers in the myriad of tissue engineering applications currently under development.

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Potential Conflict of Interest None.

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