CHAPTER

Nanoformulations for cardiovascular therapy

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24.1 Introduction

Nanotechnology has also extended into the field of cardiovascular disease. Currently marketed nanoformulations of drugs are used in patients to help overcome challenges with drug solubility and absorption. Several delivery systems are under development to medicinally target pathways of vascular disease (Fig. 24.1).

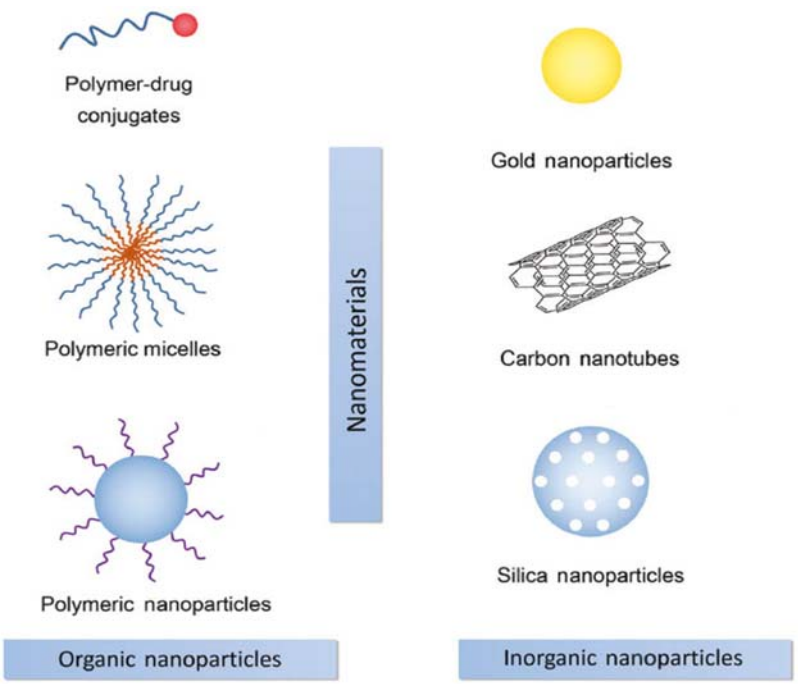

FIGURE 24.1

Nanomaterials representatives (organic/inorganic) applied for diseases therapy.

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Moreover, multifunctional theranostic nanoparticles are very promising for therapeutic delivery. These theranostic nanoparticles can serve to mix treatment with information from one or even multiple imaging modes to assess disease more comprehensively. Former work has highlighted the status of nanomaterials in cardiovascular imaging, including their potential to separately identify vulnerable signs at risk for rupture. This chapter will discuss advances in the nanoformulations application for vascular disease treatment.

24.1.1 Solving inflammation and defective efferocytosis

Atherosclerosis is an inflammatory disease characterized by the accumulation of lipids, diseased cells, and necrotic debris. Proinflammatory cytokines and leukocytes take action at different phases during atherosclerotic plaque formation (Libby, 2012).

Sharp inflammation is driven, in part, by the failure to clear apoptotic tissue from the diseased vessel wall due to a defect in efferocytosis (programmed cell removal), thus apoptotic cells accumulate, become secondarily necrotic, and discharge their proinflammatory intracellular fillings (Kojima et al., 2014; Kojima, Weissman, & Leeper, 2017). Importantly, this nonresolving inflammation leads to dangerous lesions that are at increased risk of rupture and thrombosis. Systemic antiinflammatory treatment is useful in stopping inflammation on cardiovascular disease in high-risk patients due to their ability to attain local delivery, atherosclerosis-targeted nanoparticles may be able to address these risks. Nanoparticles were able to overwhelm rapid elimination and short retention time of the free therapeutic agent in atherosclerotic plaques. Besides, their advantage on plaque progress and stability was importantly noted without side effects, indicated by normal clinical chemistry, hematology, and sustainability of mice following therapy (Wang et al., 2018).

Inflammation-targeting nanoparticles have also been created as theranostic nanoparticles. In a rabbit model of atherosclerosis, magnetic resonance imaging (MRI)−detectable liposomes were synthesized for prednisolone delivery to inflamed vessel wall (Lobatto, Fayad, & Silvera, 2010).

Liposomal encapsulation enhanced the pharmacokinetics of prednisolone and extended its circulating half-life, without general toxicity. After a single dose, rapid and continuous reduction in plaque inflammation was observed by MRI and correlated with 18F-FDG positron emission tomography/computed tomography—a certified method of tracing inflammation in atherosclerosis imaging (Rudd et al., 2008). Multimodal imaging showed that the nanoparticles stored in plaque macrophages without harmful effects, thus acting as a guide for imaging-based efficiency measure and showing the viability of aiming nanoparticles to human atherosclerotic areas.

Sager, Dutta, and Dahlman (2016) combined small interfering RNA (siRNA) targeting multiple cell adhesion molecules into a polymer-based nanoparticle. In apoE$^{-/-}$ mice that underwent coronary ligation, treatment with nanoparticles

encapsulating five siRNAs aiming leukocyte adhesion molecules meaningfully reduced vascular inflammation after myocardial infarction (MI) (Sager et al., 2016). The consequential decrease in leukocyte buildup led to a reduction in tissue damage.

24.1.2 Nanoparticles designed for cardiac regeneration

Nanomedicine can be defined as the application of nanotechnology to medicine for diagnosis and therapy (Pelaz et al., 2017). It aims to minimize the side effects of therapeutic drugs while increasing their selective accumulation, thus enhancing the ability of the treatment in clinics (Davis, Chen, & Shin, 2008). Traditional therapies are—in fact—often related to great side effects due to the natural toxicity of drugs, their broad spectrum of activity and the poor control over delivery (Jabir et al., 2012). Nanoparticles NPs have tunable properties that potentially allow any kind of application. Various types of NPs have been loaded with miRNAs and drugs to be used to transport therapeutic agents by different administration routes, offering several advantages compared to normal therapies (Fig. 24.2). Remarkably, a major drawback in the therapeutic use of miRNAs is their quick clearance and fast degradation in blood circulation and cellular cytoplasm mainly by ribonucleases, resulting in a short half-life (Sioud, 2005).

Furthermore, these molecules cannot enter the cell efficiently (Zhang, Zhao, Jiang, Wang, & Ma, 2007). Extracellular miRNAs are physiologically taken inside the cell by membrane-derived vesicles, lipoprotein and ribonucleoprotein complexes (Boon & Vickers, 2013). Among these systems, exosomes are the main effectors of miRNA carriage and exosome miRNA-loaded release has been

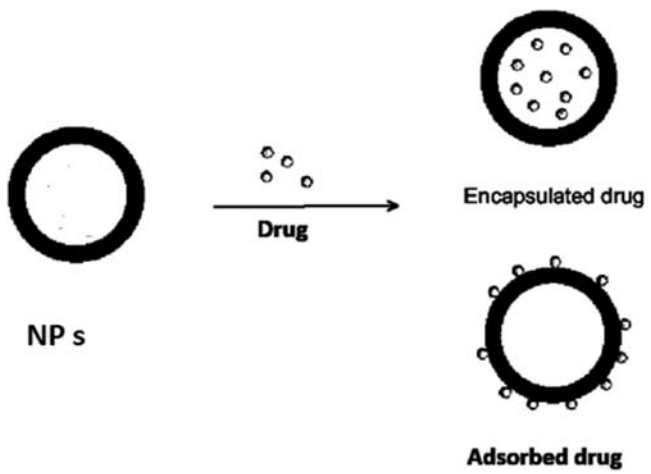

FIGURE 24.2

Schematic diagram of drug-loaded nanoparticles.

found to be participating in intercellular communications (Valadi et al., 2007). Therefore, the use of engineered miRNA nanocarriers represents a nature-inspired approach overcoming many limitations.

Along with miRNA delivery, the use of bioengineered nanocarriers can improve the circulation time, biodistribution and bioavailability of different drugs and proteins, as well as protecting them from degradation and inactivation (Patra, Das, Fraceto, Campos, & Rodriguez-Torres, 2018). Indeed, many currently available drugs are lipophilic and their systemic administration is faced by their limited aqueous solubility, with subsequent poor delivery and therapeutic effectiveness (Kalepu & Nekkanti, 2015). Consequently, the encapsulation of these molecules inside amphiphilic systems may enhance their efficacy and their long-lasting and sustained release at the desired site (Din et al., 2017).

24.1.3 Polymeric nanoparticles

Polymeric NPs have recently attracted interest for their great tunable properties, which make them extremely remarkable tools for controlled drug encapsulation/release (Fig. 24.3). Indeed, their physicochemical properties can be adjusted for accommodating nucleic acids, drugs, and proteins to improve their efficient release inside the cells (Patil & Panyam, 2009). This large group of NP based system include amphiphilic micelles, vesicles, dendrimers and polymersomes having unique structures and properties, which can be adjusted for hosting different kind of carriers (Chandarana, Curtis, & Hoskins, 2018). Most of the designed polymeric NPs offer new synthetic copolymers able to mix different functionalities such as targeting and selective carrier delivery systems (El-Say & El-Sawy, 2017). Moreover, given the developing use of miRNAs for cardiac regeneration many studies had developed polymeric NPs as miRNA carriers, alone or in combination with targeting therapeutic drugs.

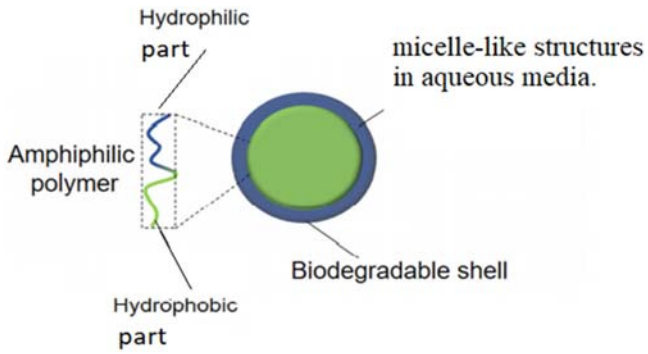

FIGURE 24.3

Schematic diagram of polymeric nanoparticles with overall composition and structure.

24.1.4 Targeting thrombosis

Platelet activation, the coagulation force, and fresh thrombus include unique factors that enable targeted delivery of therapeutic agents. Thrombus-targeted nanoparticles have been established for anticoagulants and thrombolytic agents delivery, which lead to vessel recanalization and reperfusion in most animals.

Nanoparticles were designed for controlled release of tPA (tissue-type plasminogen activator) using transthoracic ultrasound, where the application of ultrasound led to greater tPA offloading and thrombolytic activity at the affected artery. Also, it was found that antithrombin theranostic nanoparticles directly attenuated plaque coagulant activity within the injured arteries (Palekar, Jallouk, Myerson, Pan, & Wickline, 2016).

Investigated by magnetic resonance spectroscopy, nanoparticles were retained within the plaques and exerted rapid inactivation of any locally produced thrombin. These effects were observed without changing activated partial thromboplastin time or other general effects on coagulation.

Moreover, central inhibition of plaque thrombin reduced the expression of plaque inflammatory molecules and enhanced repair of the disrupted vascular endothelium, suggesting the antithrombin nanoparticles supported plaque stability. These studies proved the broad perspective that nanoparticles have for reperfusion therapy and anticoagulation with decreased bleeding consequences.

Biodegradable Polymers have found extensive applications in cardiology as scaffolds and coating matrices for drug-eluting stents (DES). Since polymers degrade once their function is fulfilled as they are required to fulfill special demands with their specific properties and biocompatibility.

In the past, synthetic polymers, like poly(ethylene) (PE), polyurethanes (PUR), poly(glycolide) (PGA), and polylactides (PLA), have been chosen for implants and other medical devices. While PURs are well established as scaffold materials for vascular grafts due to their excellent hemocompatibility (Han, Farah, Domb, & Lelkes, 2013; He, Hu, & Xu, 2013; Hu, Li, & Hu, 2012; Theron, Knoetze, & Sanderson, 2010), PGA is commonly used as a suture material for different surgical applications (Pillai & Sharma, 2010).

Further, PGA-containing scaffolds combined with poly($\in$-caprolactone) (PCL) (Diban, Haimi, & Bolhuis-Versteeg, 2013) are used for PGA-based drug delivery systems (Amjadi, Rabiee, Hosseini, & Mozafari, 2012; Yehia, Elshafeey, & Elsayed, 2012; Yi, Wu, & Jia, 2006). Overall, PLA has been strongly verified as temporary stent material in cardiology due to its long pathway records of in vivo biocompatibility (Bourantas, Papafaklis, & Kotsia, 2014; Onuma, Dudek, & Thuesen, 2013; van Alst, Eenink, Kruft, & Van Tuil, 2009).

Biopolymers coming from natural origin degrade physiologically by hydrolysis and are considered to be very biocompatible (Sisson, Schroeter, Lendlein, Lendlein, & Sisson, 2011). Typical examples of biodegradable polymers are polyhydroxy carboxylic acids, such as PGA, PLA, poly(3-hydroxybutyrate) (P(3HB)), poly(4-hydroxybutyrate) (P(4HB)), and PCL. P(4HB) is applicable for vascular

grafts and heart valves (Williams, Rizk, & Martin, 2013), while P(3HB) has not been approved for vascular applications due to its competency to activate extensive inflammatory responses in porcine models (van der Giessen, Lincoff, & Schwartz, 1996).

DES are specialized vascular stents which allow drugs local delivery in a controlled manner to reduce or prevent in-stent restenosis as a process of increased SMC proliferation (Grube, Gerckens, Muller, & ¨ ullesfeld, 2002; Kukreja, Onuma, Daemen, & Serruys, 2008). Biodegradable polymers, such as PLA and poly(lactide-co-glycolide) (PLGA), were extensively studied to optimize their properties and biocompatibility. Due to the degradation of the polymeric coatings, DES are expected to cause lower stent-thrombosis.

Fully biodegradable scaffold advantage is to provide a temporary mechanical support of narrowed blood vessel. In consequence, the vessel is allowed to heal and recover its physiological function before the implant loses its mechanical integrity (Iqbal, Gunn, & Serruys, 2013). Clinically approved scaffolds are mostly based on PLA (Iqbal et al., 2013). So far, the first clinically available scaffold is provided with a poly(L-lactide) (PLLA) frame and a poly(D,L-lactide) coating carrying Everolimus (BVS, Abbott, United States).

Biodegradable polymers can be produced from natural polymers and synthetic polymers for cardiac tissue engineering (Vroman & Tighzert, 2009). These kinds of polymers offer their advantages and disadvantages in cardiac tissue engineering. Thus, to gather the advantages of both natural and synthetic polymers, natural/synthetic composites have been proposed for some cardiac tissue applications (Hasan, Khattab, & Islam, 2015).

24.2 Natural polymers

Natural polymers are coming from natural sources, such as animals and plants, and since they are natural, they are composed of nanostructured proteins and are considered nanomaterials (Garbayo, Pascual-Gil, Prosper, & Blanco-Prieto, 2017). Due to their biodegradability, renewability, and abundant availability, they have been used in diverse applications in tissue engineering (Puoci, 2015). Some typical natural biodegradable polymers used for cardiac tissue engineering include fibrin gel, collagen, gelatin, chitosan, alginate, and Matrigel (Dhandayuthapani, Yoshida, & Maekawa, 2011).

24.2.1 Collagen

Collagen is one of the most common high-weight molecular natural polymers or proteins used for cardiac tissue engineering (Fig. 24.4). Collagen has advantages including thermal reversibility, biocompatibility, and strong cellular activities for cardiac tissue engineering efforts. Collagen has many different types (28)

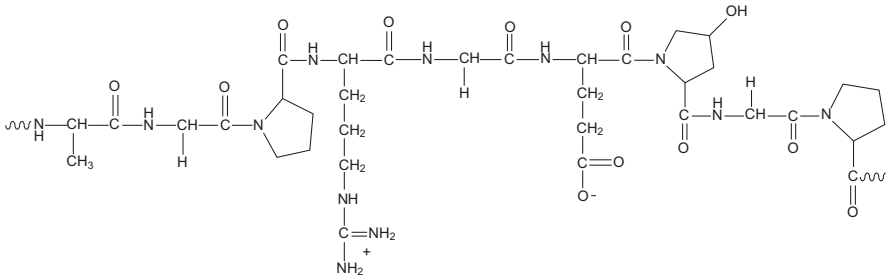

FIGURE 24.4

Structure of collagen.

discovered from various human tissues such as bone, skin, ligaments, tendons, and cartilage (Ricard-Blum, 2011).

However, collagen types I, II, III, and IV are commonly studied in tissue engineering (Nair & Laurencin, 2005), among these types of collagen, type I has been the most commonly used in tissue engineering due to its suitable biocompatibility (Ariganello, Labow, & Lee, 2010; Mirsadraee, Wilcox, & Korossis, 2006; Mirsadraee, Wilcox, & Watterson, 2007; Ravichandran, Islam, & Alarcon, 2015; Xu, Molnar, & Gregory, 2009; Yang, Motte, & Kaufman, 2010).

Collagen is one of most favorite biodegradable polymers in cardiac tissue engineering applications due to its high biodegradability, biocompatibility, low toxicity and hyposensitivity (Punnoose, Elamparithi, & Kuruvilla, 2015). Collagen scaffolds, especially nanofibrous scaffolds, have been examined for cardiac tissue engineering. Joanne et al. examined electrospun collagen scaffolds with biologically compatible solvents and cross-linking agents. This nanofibrous collagen scaffold was planted with human-induced pluripotent stem cell-derived cardiomyocytes and was epicardially delivered in a mouse model of dilated cardiomyopathy. In vivo and in vitro results indicated that a human induced pluripotent stem cell-derived cardiomyocyte seeded electrospun scaffold was a potent biomaterial for the stabilization of dilated cardiomyopathy and thus suitable for future clinical use (Joanne, Kitsara, & Boitard, 2016).

Collagen scaffolds have drawbacks that include low mechanical properties upon hydration. One way to improve the mechanical strength of collagen-based scaffolds is intermolecular cross-linking of collagen scaffolds via chemical and physical methods (Dong & Lv, 2016).

Lin et al. examined stiffness-controlled 3D collagen type I scaffolds for the differentiation and proliferation of mesenchymal stem cells into cardiac progenitor cells. To obtain the stiffness required in 3D collagen type I scaffolds, collagen was cross-linked with different ratios of hydroxyl succinimide (NHS) and 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC) cross-linkers. Results showed that the collagen scaffolds cross-linked with 50/50 EDC mM/NHS mM cross-linkers not only demonstrated a higher Young's modulus but also showed a better

interconnectivity. Another way to improve the mechanical strength of collagen scaffolds is by blending collagen with other materials, such as inorganic materials and natural synthetic polymers (Dong & Lv, 2016).

24.2.2 Chitosan

Chitosan is a linear polysaccharide (Fig. 24.5) derived from chitin by partial deacetylation (Dutta, 2016; Hudson & Smith, 1998). Chitosan is characterized by low toxicity and high biocompatibility due to its structural similarity to natural glycosaminoglycans. Chitosan biodegrades into nontoxic products through enzymatic hydrolysis during in vivo tissue applications. Chitosan, and its derivatives, increase cell recognition and cytocompatibility for tissue-engineering applications, and are often coated or grafted onto scaffold surfaces (Deng, Li, Griffith, Reul, & Suuronen, 2010).

Chitosan hydrogels have also been examined as scaffolds for cardiovascular applications. For example, Aussel et al. investigated chitosan-based hydrogels for developing a small-diameter vascular graft. Results from in vivo studies in different animals and in vitro studies of chitosan-based hydrogels proved the good hemocompatibility properties in vivo and in vitro biocompatibility of hydrogels (Aussel, Thébaud, & Bérard, 2017).

24.2.3 Alginate

Alginate is a natural linear polysaccharide (Fig. 24.6) which is obtained from the cell walls of brown algae (Slaughter, Khurshid, & Fisher, 2009). Alginate is likely a biodegradable polymer for cardiac tissue engineering due to its high biodegradability, nontoxicity, and biocompatibility, as well as its physical gelation process, and nonthrombogenic nature (Rosellini, Cristallini, & Barbani, 2009).

Several methods as crosslinking, immobilization of specific ligands, and the conjugation of other materials have been used for modification of mechanical properties of alginate (Sun & Tan, 2013). Sondermeijer et al. modified an alginate-based scaffold attached covalently with synthetic cyclic RGDfK (Arg-

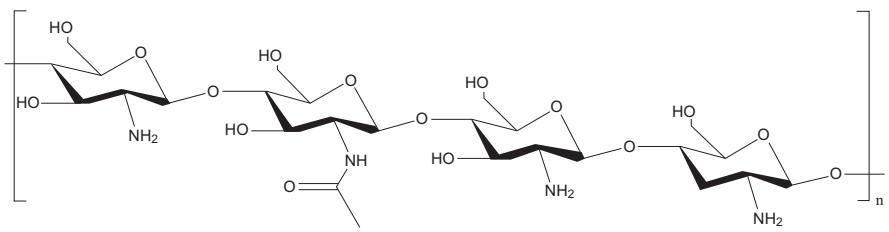

FIGURE 24.5

Structure of chitosan.

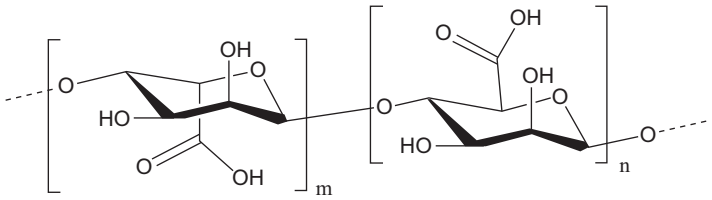

FIGURE 24.6

Structure of alginate.

Gly-Asp-D-Phe-Lys)-peptide to improve the survival of transplanted cells and angiogenesis in damaged myocardium tissue. The modified scaffolds were investigated in rats, it was observed that these scaffolds enhanced cell viability (Sondermeijer et al., 2017).

However, these natural polymers have some drawbacks such as rapid degradation, insufficient electrical conductivity, immunological reaction, and poor mechanical properties for cardiac tissue engineering (Ige, Umoru, & Aribo, 2012).

24.3 Synthetic polymers

Synthetic biodegradable polymers including PLA, PGA, PLGA, polyethylene glycol (PEG), PUR, PCL, and poly(*N*-isopropyl acrylamide) have all been used in cardiac tissue engineering applications. Synthetic biodegradable polymers are considered potential materials for cardiac tissue engineering due to their attractive physical and chemical properties such as strong mechanical properties, controlled structure, great processing flexibility, and no immunological fears (Guo & Ma, 2014).

24.3.1 Poly(ethylene glycol)

PEG, a common synthetic biodegradable polymer, was synthesized by ring-opening polymerization of ethylene oxide and has been used as a tissue engineering biomaterial (Zhu, 2010). PEG properties, like solubility in water and organic solvents, nontoxicity, low cell adhesion, and protein binding, made it a suitable applicant for tissue engineering (Alcantar, Aydil, & Israelachvili, 2000). However, the PEG polymer is bio-inert, thus, it is not an ideal environment for cell growth, adhesion, and survival (Rane, Chuang, & Shah, 2011). PEG-based gels are usually used in cardiac regeneration approaches because they have advantages over natural hydrogels like; easy control of chemical composition and scaffold architecture, and adjustable mechanical properties (Zhu, 2010).

Somekawa et al. examined the effect of thermoresponsive PLA−PEG gel injection in a rat MI Model compared with an alginate gel. Results proved that the PLLA-PEG/ PDLA-PEG and alginate gel well-maintained cardiac function (Somekawa, Mahara, & Masutani, 2017).

24.3.2 Polycaprolactone

PCL is a synthetic biodegradable polymer prepared by the ring opening polymerization of ε-caprolactone (Mclauchlin & Thomas, 2012). This material is one of the most widely used synthetic polymers in tissue engineering due to its excellent elasticity, mechanical properties, toughness, and biocompatibility. PCL is a suitable biodegradable polymer for applications where a long degradable time is needed because it has a long degradation time (about 2−3 years) (Mano, Sousa, & Boesel, 2004).

However, PCL exhibits a long degradation time which it is an obstacle for use in cardiac tissue engineering (Song, Ahmed, & Li, 2017). Two strategies have been used for the modulation and enhancement of mechanical and degradation properties of PCL: the incorporation of nanostructured filler material into the PCL material and the use of PCL as a copolymer or as one of the components of a blended material (Mondal, Griffith, & Venkatraman, 2016).

Ghaziof et al. synthesized PCL/multiwalled carbon nanotube (MWCNT) composite scaffolds, with different amounts of MWCNTs. Results showed that the addition of the MWCNTs in the nanocomposite scaffolds enhanced mechanical properties (Ghaziof & Mehdikhani-Nahrkhalaji, 2017).

24.3.3 Poly (lactic acid)

PLA, a hydrolyzable aliphatic semicrystalline polyester polymerized by lactic acid, is a biodegradable synthetic polymer that has a variety of applications in tissue engineering (Bertuoli, Ordoño, & Armelin, 2019). PLA has a low degradation rate and is more hydrophobic than PGA (Kannan, Salacinski, & Butler, 2005). PLA has been widely studied for cardiac tissue applications because of its biocompatibility, biodegradability, nontoxicity, and good mechanical integrity (Bertuoli et al., 2019). However, the long degradable time of PLA is the main drawback of its use in cardiac tissue applications (Lopes, Jardini, & Maciel Filho, 2012).

The porous nanofibrous PLA scaffolds for the construction of cardiac tissue with CPCs were developed. The CPCs derived from mouse embryonic stem cells were seeded into scaffolds to engineer cardiac constructs in vitro and were implanted subcutaneously in nude mice (Valente et al., 2016).

The combination of PLA/(polyaniline) PANI can be an important candidate for cardiac tissue engineering applications. Electrospun conductive nanofibrous PLA/PANI scaffolds (diameter of the nanofibers were about 500 nm) were

developed by Wang, Wu, and Hu (2017). This nanofibrous sheet acts as a promising potential in cardiomyocyte-based 3D bioactuators and cardiac tissue engineering.

Synthetic polymers, however, have some drawbacks such as a lack of cell attachment and less biocompatibility in cardiac tissue engineering (Do, Khorsand, & Geary, 2015).

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