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Poly (lactic acid) applications in biomedical engineering

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Abstract. Medical devices like implants are playing a pivotal role in medicine. As a polyester, Polylactic acid (PLA) and its copolymers are widely used in the medical area. They are used in several sections including cardiovascular and orthopedic devices, as well as advanced technologies of tissue engineering and drug delivery. In this paper, cardiovascular devices including applications of PLLA coating as drug delivery system and BVS material are introduced. Specifically, PLA can be used to foster scaffolds for bone tissue and cardiovascular tissue engineering. Then this paper introduces PLA applied in the form of nanoparticles and micelles in drug delivery. The special degrading process makes PLA an active drug delivery carrier. And it could also be used to produce biodegradable orthopaedic operation devices and offer the advantage of being free from taking out of the human body. Processing techniques are pivotal prerequisites of applications of medical usage, like electrospun fibers are used in cardiovascular and drug delivery applications. The paper summarizes the use of PLA material in those areas, and foresees the future for a prediction of the attractive prospect. Although the applications are faced with limitations like mechanical properties now, they still have a promising future in biomedicine.

Keywords: polylactic acid, nanofiber, electrospun fiber, tissue engineering.

1. Introduction

PLA is a hydrolysable polyester, it has ester bond linkages in its carbon backbone. PLA was first synthesized more than 150 years ago, but high-weight polymer product was not compounded until 1950s [1, 2]. Because of the lactic acid's chirality, there are mainly three kinds of PLA material: PLLA, PDLA, and PDLLA. The PLLA is thought to have the lowest toxicity.

As a kind of biomaterial, PLA has good properties of biodegradability, biocompatibility, and nontoxicity. Different from some plastics like Polyethylene terephthalate (PET) and Polyethylene (PE), PLA could be fully degraded in the environment into carbon dioxide and water and does not cause white pollution. In human bodies, it can also be metabolized into urine and sweat without metabolic product residue.

The PLA is commonly synthesized from the starch of corn or cassava. The raw material is renewable and it has broad applications in industry and medicine, its application in medicine has been approved by the US government. For better capabilities, lactic acid is usually compounded with other monomers like glycolic acid. The copolymer is poly (lactic-co-glycolic acid) (PLGA), which has better solubility and higher biodegradation rate. PLA can also be composited with carbon-based nanomaterials (CBNs) to

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improve mechanical properties [3]. PLA has flexible processing methods; e.g., the electrospinning method could spread out liquid thread to form thin fibers [4]. This shows the strong plasticity of PLA.

Based on the advantages of PLA and its co-polymers, they can be widely used in biomedicine. The following sections will introduce the applications of PLA in cardiovascular devices, tissue engineering, drug delivery, and orthopedic devices.

2. Cardiovascular devices

The implant devices play a more and more important role in medical equipment and show significant growth, particularly in the past five years. Cardiovascular stents are the most used medical implant devices to cure cardiovascular diseases. In clinics, the traditional nitinol (NiTi) cardiovascular stents still occupy a large part. But not all the operations are successful. Because of different reasons, the implant devices may fail before their expected period of validity of about 10-15 years. With normal drug-eluting stents (DES), the in-stent restenosis (ISR) rate could be reduced to nearly 10%. So, surgeons want a kind of new implant which has minimal long-term negative effect. Nanotechnology already has wide applications in medicine because of its unique properties. But because the implant surface needs careful design, the nanotechnology field of implants has not been widely explored [5]. In endovascular stents, the main limitation is restenosis [5, 6].

PLA could be used as a fabricated platform to reinforce traditional stents' ability to resist post-operational thrombosis and restenosis, it is used to build a nanofiber platform for drug loading and delivery on the surface of ordinary cardiovascular stents [7, 8]. One common drug is dipyridamole (DPM), with the function of anti-platelet. The PLA nanofiber is used to encapsulate the loaded drug. The scaffold made up of nanofibers could be used to maintain and control drug release. Bakola et al. used electrospun nanoplatforms of PLA to load DPM for a cardiovascular stent [8]. Then, they measured the contact angle to evaluate the hydrophobic behavior. It showed that PLA nanoplatform drug coating stents were valuable for atherosclerosis treatment. According to the research of Karagkiozaki et al., the nanocoating designs improved reendothelialization on the struts and possibly reduced late thrombosis – the Achilles' heel of modern vascular stents. One possible mechanism is the topology of the stent's nano-surface influences platelets behavior. The rougher the surface of carbon nanocoatings is, the weaker the platelets adhesion will be, and result in less thrombogenic (Figure 1). So, controlling deposition conditions of the nanocoatings of stents can get desired surface properties [6, 7].

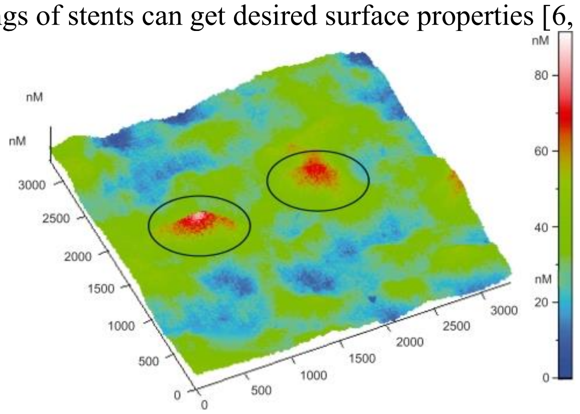

Figure 1. The AFM topography image showing the effect of nanocoating of stents on the activation of platelets (in circles) [6].

Another possible improvement is developing biodegradable vascular scaffolds (BVSs). They are temporary stents in blood vessels. They are either entirely made of bioabsorbable metals or entirely made of polymers. A BVS could also be a DES. The Absorb BVS from Abbott Vascular has a coating of PDLLA which contains everolimus with base material of PLLA. As a BVS material, there are some concerns about its mechanical properties. One solution is developing composite material using PLA (e.g., PLA-cellulose material) [4]. Jia et al. reported cellulose nanofiber/ PLA composite material could be used to manufacture vascular stents [9]. Compared with PLA stents, the composite stents' transverse supporting ability increases by 47.6%, and the longitudinal flexibility increases by 20.2%. The composite material has sufficient strength and could maintain its shape for a longer time.

3. Tissue engineering

The concept of tissue engineering was first raised in 1987. In this area, PLA materials could be used in cardiovascular and orthopedic applications.

3.1. Cardiovascular tissue engineering

Mechanical heart valves were introduced in the 1950s, but it has serious problems of coagulation; Other materials like crosslinked bioprosthetic (BP) also have problems like calcific degeneration. In the cardiovascular area, tissue engineering is used in heart valves, vascular patches, and vascular grants [10]. Building a cardiac valve needs a 3-D scaffold. The material acts as a scaffold for different cells to climb on and grow, proliferate, and differentiate on it in a specific order and becomes a functional structure. Hinderer et al. built an electrospun PLA scaffold successfully, suitable to the topography and mechanical properties of human valve leaflets [10].

In the cardiac area, the living surroundings of cells have another feature of electrical rhythm. Yan et al. filled a silk fibroin (SF)/PLA nanofiber scaffold with electroactive carbon quantum dots (CQDs). The structure was used for the conveyance of cardiomyocytes [11].

3.2. Orthopedic tissue engineering

In the orthopedic area, PLA composite materials could be used to produce the scaffold needed for bone tissue engineering for regeneration. In a research, Zhou et al. found that chitosan used in PLA/ chitosan composite material as a bone tissue scaffold obviously neutralizes the acidity caused by the degradation of PLA [12].

Grémare used the fused deposition modeling (FDM) method to build PLA bone tissue engineering scaffolds and evaluated its biological properties [13]. It was found that no cytotoxicity showed to human bone marrow stromal cells (HBMSCs) and FDM is a suitable technology to build 3-D scaffolds for tissue engineering. The PLA nanofibers are favorable for tissue engineering scaffold fabrication because of their high surface-to-volume ratio. The high porosity of nanofibers benefits for transportation of nutrients, metabolic wastes, and degradation products.

In another research, Zhu et al. used single or double syringes to spin the electrospun PLLA scaffold. The Fourier transform infrared (FTIR) spectroscopy showed the PLLA could be well contained in the SF fibers. The test on the adhesion ratios of cells showed SF/PLLA nanofibers were much higher than that of the sole kind of fiber [14].

4. Drug delivery

The therapeutic use of small molecule drugs comes up with many serious problems, such as insolubility and instability. Drug delivery systems (DDSs) are developed to solve these problems. It is necessary for controlled drug delivery to reduce side effects and enlarge the therapeutic window. Many polymers are used in controlled drug delivery, among which PLA possesses many advantages to be developed into a DDS. For PLA, the carriers can be made in many forms, for example, nanoparticles, microspheres, and scaffolds. PLGA is attractive in drug release for its flexibility of varying the composition, molecular weight (Mw) and chemical structure [15]. The usual preparation methods for PLGA nanoparticles include precipitation and emulsification.

As a DDS, the electrospun fibers have a high surface-to-area ratio [16]. To fulfill the clinic needs, sometimes modifications are needed (Figure 2). For example, Poly (ethylene glycol)-poly (lactide) can be modified by galactosamine to be a targeted delivery to the liver with the property of sustained release [17]. Microspheres and nanoparticles have the advantages to pass through cells to deliver drugs.

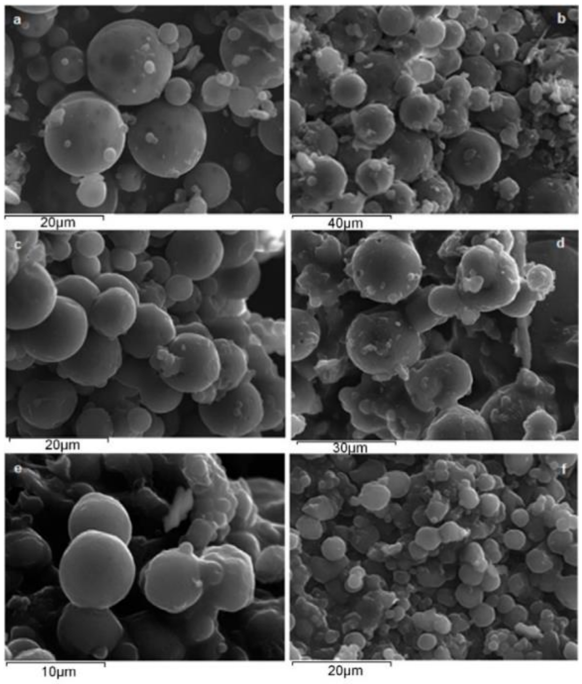

Figure 2. Different SEM graphs of risperidone microspheres produced by PLA materials [17].

With the development of DDS, PLA may have the properties of actively controlling drug release. Pure PLA degrades not fast so polymers with higher degradation rate, such as PLGA, have attracted wide attention. Kohno et al. synthesized different PLGA microspheres with different molecular weights, and found that the drug release rate from PLGA microspheres was decided by the manufacturing process and the properties of the polymer, as well as by any polymer-drug interactions and other critical formula parameters. They found that the in-vitro release curve is related to the polymer molecular weight, as well as the glass transition temperature Tg, the size and the porosity of the particles, and the interactions between the polymer and the drug [15].

5. Orthopedics

In orthopedic and dental areas, a lot of fixation medical equipment is needed like plates, pins, and screws [2, 18]. About 7.7 million patients go to the hospital to take orthopedic replacement operations each year in the USA [5]. Inertial metallic materials like Titanium alloy used to be the main material for many implants. But these metallic parts will lead to a permanent presence in patients' bodies. That is why biodegradable materials like PLA becomes popular, it could get rid of the bother of a second operation to take the device out. The PLA orthopedic devices are used in various conditions including ankles, elbows, jaws, and hips. Haers et al. found that the PLA plates dissolve 6 weeks after the operation, and the device has good biocompatibility.

As a plastic polymer, PLA has some advantages other polymers have, like high lubricity. PLA has the advantage of processing flexibility of 3D printing material. But the PLA has an intrinsic setback of low mechanical abilities. Fouly et al. argued that adding date-pit particles into PLA could raise the compressive strength and stiffness but will deteriorate the elongation and toughness [19]. Both the finite elemental model result and the experiment result show the enhancement of composite load-bearing capacity.

6. Conclusion

As a kind of biodegradable polyester, PLA has many distinct advantages like abundant raw material, adequate biodegradability, and biocompatibility. These abilities enable broad applications of PLA, and make it a focus in medical research. New research areas of controlled drug delivery, BVS and regeneration scaffold will attract the most attention in future researches. And the new simulation methods of FEM and machine learning will benefit the researchers with a lighter work burden. However, to develop a new implant equipment or drug for clinical use, it needs a long test of toxicity, effectiveness, and safety. It is foreseeable that with the accumulation of technological advancement and financial support, more kinds of PLA-based biomaterials will be developed.

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