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Poly (lactic acid)-based biomaterials for orthopaedic regenerative engineering☆

Ganesh Narayanan [a,b,c], Varadraj N. Vernekar [a,b,c], Emmanuel L. Kuyinu [a,b,c], Cato T. Laurencin [a,b,c,d,e,f,g,h,*]

[a] Institute for Regenerative Engineering, University of Connecticut Health Center, Farmington, CT 06030, USA
[b] Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Sciences, University of Connecticut Health Center, Farmington, CT 06030, USA
[c] Department of Orthopaedic Surgery, University of Connecticut Health Center, Farmington, CT 06030, USA
[d] School of Medicine, University of Connecticut Health Center, Farmington, CT 06030, USA
[e] Department of Reconstructive Sciences, University of Connecticut Health Center, Farmington, CT 06030, USA
[f] Department of Chemical and Biomolecular Engineering, University of Connecticut, Storrs, CT 06269, USA
[g] Department of Biomedical Engineering, University of Connecticut, Storrs, CT 06269, USA
[h] Department of Materials Science and Engineering, University of Connecticut, Storrs, CT 06269, USA

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ABSTRACT

Regenerative engineering converges tissue engineering, advanced materials science, stem cell science, and developmental biology to regenerate complex tissues such as whole limbs. Regenerative engineering scaffolds provide mechanical support and nanoscale control over architecture, topography, and biochemical cues to influence cellular outcome. In this regard, poly (lactic acid) (PLA)-based biomaterials may be considered as a gold standard for many orthopaedic regenerative engineering applications because of their versatility in fabrication, biodegradability, and compatibility with biomolecules and cells. Here we discuss recent developments in PLA-based biomaterials with respect to processability and current applications in the clinical and research settings for bone, ligament, meniscus, and cartilage regeneration.

Contents

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* Corresponding author at: Institute for Regenerative Engineering, University of Connecticut Health Center, Farmington, CT 06030, USA.
E-mail address: laurencin@uchc.edu (C.T. Laurencin).

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1. Introduction

Orthopaedics-related medical diagnoses accounted for 225 million visits, costing about 215 billion dollars between the years 2009 and 2011 [1]. These figures include more than a million total hip and knee replacements, and about 100,000 ligament reconstruction procedures performed annually at a cost of about 25 billion dollars [2,3]. Current orthopaedic surgical procedures primarily utilize autografts, allografts, and metal and plastic implants [4]. The metal and plastic implants suffer from a variety of challenges such as low fatigue, creep, poor adhesion, and biocompatibility issues with native tissue [5–7]. Similarly, autografts, currently considered as the gold standard, suffer from donor-site morbidity, pain, and unavailability of large tissue volumes [8]. In the case of allografts, donor-site morbidity is not an issue; however, some of its drawbacks include the risk of communicable diseases, immunogenicity, and inadequate donors [9,10].

In addition, various biodegradable and biocompatible polymers, of both synthetic and natural origin, have been developed for biomedical applications [11]. Some of these polymeric materials have found applications in sutures and are fast emerging as implant-material alternatives. Aliphatic polyesters, also known as poly (α-hydroxy esters), are one such bioresorbable and biocompatible group of polymers that have great potential for use in the regeneration of large tissues. This class of polymers include: poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly (ε-caprolactone) (PCL), poly (dioxanone) (PDO), and poly (trimethylene carbonate) (PTMC) [12,13]. Within this group, PLA possesses chirality enabling the mid-chain residues to exist in three enantiomeric states, L-lactide, D-lactide, and *meso*-lactide [14]. Of these, the most widely used polylactides are the poly (L-lactide) (PLLA) and poly (D-lactide) (PDLA), respectively [13].

PLLA is a slow crystallizing, semi-crystalline polymer with crystallinity, melting, and glass transition temperature values ranging from 40% to 50%, 55–80 °C, and 170–180 °C, respectively [15,16]. Likewise, PDLA, which is also a semi-crystalline polymer has crystallinity, melting, and glass transition temperature values ranging from 30% to 45%, 40–50 °C, and 120–150 °C, respectively [16,17]. Both PLLA and PDLA have comparable tensile strength (4–8 GPa), elongation at break (1–8%), and tensile strength values (40–70 MPa) [17,18]. Their slow crystallizing nature predisposes these materials to be typically hard and brittle. The crystallizability of these materials can be improved by processing *via* isothermal annealing [19], co-polymerizing [20], nucleating by additives [21], and strain induced crystallizing [22]. The random distribution of PLLA and PDLA in PDLLA causes disruption of stereo-regularity, leading to an amorphous poly (D,L-lactic acid) PDLLA [23]. Altering the stereo-regularity of the isomers (PDLLA) is also one way to manipulate the degradation rate of this polymer. *In vivo* studies have shown highly crystalline PLLA to degrade completely in 2–5 years, whereas mostly amorphous PDLLA loses strength in less than 2 months and completely degrade within 12 months [12].

The processability, material properties, degradation rates, and tissue compatibility of PLA have been also modulated by copolymerizing it with other monomers resulting in copolymers such as poly (lactic acid-*co*-glycolic acid) (PLGA), poly (lactic acid-*co*-caprolactone) (PLCL), poly (lactic acid-*co*-ethylene glycol) (PLEG), and poly (lactic acid-*co*-glutamic acid) (PLGM); thus, providing PLA-based biomaterials with tunable-properties for diverse biomedical applications [24–26]. Another advantage with these degradable biomaterials are that unlike non-degradable implant biomaterials, these do not require additional surgery for implant removal [27]. Additionally, the ease of processing PLA-based biomaterials by extrusion, injection molding, stretch blow molding, film casting, thermoforming, foaming, fiber spinning, electrospinning, melt electrospinning, and micro- and nano-fabrication techniques into various shapes and sizes have played a critical role in expanding the applications of these materials [28,29].

In orthopaedic and dental applications, PLA-based materials have been extensively used as fixation-devices such as screws, pins, washers, darts, and arrows in reconstructive surgeries including those of the mandibular joint; facelifts; thoracic, hand, leg, finger, and toe fractures; ligament reconstruction procedures; soft and hard tissue fixations; alignment of osteochondral and bone fragments; meniscus repair; and hyaline cartilage fixation [11]. Some of the PLA-based implants are shown in Fig. 1, and the composition, purpose of those degradable implants are summarized in Table 1. This review summarizes the recent progress in PLA-based biomaterials for bone, ligament, cartilage, and meniscus regeneration.

2. Processing

2.1. Fiber spinning

An advantage of PLA-based biomaterials has been their ability to be fabricated into a variety of structures with the appropriate mechanical properties, topography, geometry, and architecture as required for diverse biomedical applications. One of the oldest methods to fabricate PLA-based products has been fiber-spinning from either polymer solution or melt. As PLA is soluble in a wide array of solvents, solution spinning processes has also been widely utilized to fabricate fibers for biomedical applications [30]. Historically, mono- and multi-filament sutures have been prepared from PLA-based fibers by spinning; but due to their longer degradation times, other aliphatic polyesters such as PGA have now replaced PLA [30]. In addition, woven, knitted, and braided structures produced from spun fibers have found orthopaedic applications in bone, ligament, and cartilage regeneration (discussed later) [31–33].

PLA-based devices currently used for orthopaedic applications (Fig. 1, Table 1) are made by rapid processing techniques resulting in poor mechanical properties and crystallinity. PLA-based fibers are commonly utilized to enhance the crystallinity and mechanical properties of those orthopaedic fixation devices [34]. While evaluating PLA fibers (self-reinforced) reinforced PLA composites (SR-PLLA) for long-term complication and fixation failure rates, Juutilainen et al. noted lower fixation failures (5%), and higher bone mineral density (BMD) in SR-PLLA composites, compared to metal and unreinforced PLA implants [35]. Similarly, another study showed significant improvements in