

Fabrication and characterization of six electrospun poly(α -hydroxy ester)-based fibrous scaffolds for tissue engineering applications

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Abstract

The most common synthetic biodegradable polymers being investigated for tissue engineering applications are FDA approved, clinically used poly(α -hydroxy esters). To better assess the applicability of the electrospinning technology for scaffold fabrication, six commonly used poly(α -hydroxy esters) were used to prepare electrospun fibrous scaffolds, and their physical and biological properties were also characterized. Our results suggest that specific, optimized fabrication parameters are required for each polymer to produce scaffolds that consist of uniform structures morphologically similar to native extracellular matrix. Scanning electron microscopy (SEM) revealed a highly porous, three-dimensional structure for all scaffolds, with average fiber diameter ranging from 300 nm to 1.5 μ m, depending on the polymer type used. The poly(glycolic acid) (PGA) and poly(D,L-lactic-co-glycolic acid 50:50) (PLGA5050) fibrous structures were mechanically stiffest, whereas the poly(L-lactic acid) (PLLA) and poly(ϵ -caprolactone) (PCL) scaffolds were most compliant. Upon incubation in physiological solution, severe structural destruction due to polymer degradation was found in the PGA, poly(D,L-lactic acid) (PDLLA), PLGA5050, and poly(D,L-lactic-co-glycolic acid 85:15) (PLGA8515) fibrous scaffolds, whereas PLLA and PCL fibrous scaffolds maintained a robust scaffold structure during the same time period, based on macroscopic and SEM observations. In addition, PLLA scaffolds supported the highest rate of proliferation of seeded cells (chondrocytes and mesenchymal stem cells) than other polymeric scaffolds. Our findings showed that PLLA and PCL based fibrous scaffolds exhibited the most optimal structural integrity and supported desirable cellular response in culture, suggesting that such scaffolds may be promising candidate biomaterials for tissue engineering applications.

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1. Introduction

A tissue engineered scaffold is a three-dimensional, bio-material matrix that may be used as a vehicle to deliver therapeutic cells or bioactive factors to the defect region or as a space filler to recruit surrounding cells into the scaffold for the tissue repair process. The goal of scaffold design for tissue engineering is to produce a biomaterial

matrix that can replace the natural extracellular matrix (ECM), until the seeded cells can produce a new natural matrix and regenerate the desired tissue structure. Critical parameters for tissue engineering scaffold thus include biocompatibility, biodegradability, optimal mechanical strength, and ability to regulate appropriate cellular activities [1].

A large number of polymeric biomaterials, including non-biodegradable and biodegradable polymers, have been tested and analyzed for tissue engineering applications [2]. Since non-biodegradable polymers would interfere with tissue turnover and remodeling, the current trend is to use biodegradable polymers in tissue engineering,

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although the non-biodegradable polymers have the advantage that their properties, both chemical and mechanical, are less affected by the cellular and tissue milieu. On the other hand, polymer biodegradation via the combined effect of enzymatic and hydrolytic activities generates space within the scaffold to allow for cell proliferation and the deposition of newly synthesized ECM [3]. Ideally, optimal tissue regeneration occurs upon complete biodegradation of the polymeric matrix followed by restoration of biological functions.

Poly(α -hydroxy esters), including poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and their copolymer poly(lactic-co-glycolic acid) (PLGA), are the most commonly used synthetic polymers in tissue engineering, because of their well characterized biodegradable property and the fact that they are approved by the United States Food and Drug Administration for clinical use. PGA is soluble in highly fluorinated organic solvents, due to its high crystallinity [4]. With the addition of a methyl group, PLA is more hydrophobic than PGA but soluble in common organic solvents [4]. The three isomers of PLA [D(-), L(+), and D, L], that differ based on the position of a methyl group in the lactic acid monomer, exhibit distinct properties. To expand the spectrum of applications, PGA and PLA have been copolymerized in different ratios to form new polymers, PLGA. The PLGA copolymer is amorphous because the PGA and PLA polymer chains are not packed tightly [4]. Another family member in the poly(α -hydroxy ester) group is poly(ϵ -caprolactone) (PCL), a semicrystalline, hydrophobic, biodegradable polymer. Compared to other polyester family members such as PLA, PGA, and PLGA, PCL has been used less frequently as a material for fabricating biomaterial scaffolds, mainly because of concern over its slower degradation kinetics. However, PCL may be suitable for applications such as long-term drug delivery [5], and in addition, its mechanical properties and degradation profile can be modified by blending or copolymerizing PCL with other polyesters [4].

Electrospinning has been used to fabricate tissue engineered scaffolds comprising non-woven, three-dimensional, porous, and nanoscale fiber-based matrix. The characteristics of fibrous scaffolds, such as high surface area to volume ratio and similar structural morphology to the fibrillar ECM, suggest they may serve as effective tissue engineering scaffolds [6–8]. In this study, in order to better evaluate their applicability for tissue engineering, six commonly used poly(α -hydroxy esters) were electrospun into fibrous scaffolds, including PGA, poly(L-lactic acid) (PLLA), poly(D,L-lactic acid) (PDLLA), poly(D,L-lactic-co-glycolic acid 50:50) (PLGA5050), poly(D,L-lactic-co-glycolic acid 85:15) (PLGA8515), and PCL, and their physical properties were characterized. In addition, two candidate cell types applicable for skeletal tissue engineering, chondrocytes and multipotential mesenchymal stem cells, were used to evaluate their biological responses upon seeding into the fibrous scaffolds.

Table 1

Optimized fabrication parameters used in electrospinning process polymeric fibers^a

Polymer	Solvent	Voltage (in kV)
PGA	40 mL Hexafluoro-2-propanol	15
PDLLA	5.7 mL THF + 5.7 mL DMF	10
PLLA	25 mL chloroform + 2.5 mL DMF	16
PLGA5050	5.7 mL THF + 5.7 mL DMF	12
PLGA8515	6.7 mL THF + 6.7 mL DMF	15
PCL	14 mL THF + 14 mL DMF	12

^a Poly(glycolic acid) (PGA); poly(L-lactic acid) (PLLA); poly(D,L-lactic acid) (PDLLA); poly(D,L-lactic-co-glycolic acid 50:50) (PLGA5050); poly(D,L-lactic-co-glycolic acid 85:15) (PLGA8515); poly(ϵ -caprolactone) (PCL); tetrahydrofuran (THF); *N,N*-dimethylformamide (DMF).

2. Materials and methods

2.1. Polymers and reagents¹

The poly(α -hydroxy ester) polymers and reagents in this study were obtained from the following sources: PGA (MW = 150,000), PLLA (MW = 50,000), poly(2-hydroxyethyl methacrylate) (poly-HEMA), Polysciences (Warrington, PA); PDLLA (MW = 109,000), PLGA5050 (MW = 79,000), PLGA8515 (MW = 123,000), Alkermes (Cincinnati, OH); PCL (MW = 80,000), Aldrich (Milwaukee, WI); 1,-1,-1,-3,-3,-3-hexafluoro-2-propanol, Sigma (St. Louis, Mo); tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF), chloroform, Fisher Scientific (Pittsburgh, PA); Dulbecco's modified Eagle's medium (DMEM, high glucose), Eagle's minimum essential medium (MEM) vitamin solution, penicillin-streptomycin, phosphate-buffered saline (PBS), 0.25% trypsin, Gibco BRL Life Technologies (Grand Island, NY); fetal bovine serum (FBS), L-ascorbic acid 2-phosphate, glutaraldehyde, Sigma (St. Louis, MO); Hanks' Balanced Salt Solution (HBSS), BioSource International (Camarillo, CA); CellTiter 96™ Aqueous One Solution Cell Proliferation Assay, Promega (Madison, WI); RPMI 1640, Invitrogen (Carlsbad, CA).

2.2. Electrospun fibrous matrices

Each polymer solution was prepared by dissolving 4 g of polymer in an optimal amount of organic solvent mixture and mixed well by vortexing overnight. The solvent type used and the concentration of each polymer solution prepared for electrospinning are listed in Table 1. For the electrospinning process, used in our previous studies [6], the polymer solution was placed in a 10 mL glass syringe fitted with a 10 cm, 18-G blunt tipped needle. The syringe was fixed vertically at the support in a custom-designed

¹ Certain commercial materials and equipment are identified in this paper in order to specify adequately the experimental procedure. In no case does such identification imply recommendation by the National Institute of Standards and Technology nor does it imply that the material or equipment identified is necessarily the best available for this purpose.

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