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Structure and blood compatibility of highly oriented poly(L-lactic acid) chain extended by ethylene glycol diglycidyl ether

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ABSTRACT

Highly-oriented poly(L-lactic acid) (PLLA) with fibrillar structure and micro-grooves was fabricated through solid hot drawing technology for further improving the mechanical properties and blood biocompatibility of PLLA as blood-contacting medical devices. In order to enhance the melt strength and thus obtain high orientation degree, PLLA was first chain extended with ethylene glycol diglycidyl ether (EGDE). The extending degree as high as 25.79 mol% can be obtained at 0.7 wt% EGDE content. The complex viscosity, storage and viscous modulus for chain extended PLLA were improved resulting from the enhancement of molecular entanglement, and consequently higher draw ratio can be achieved during the subsequent hot stretching. The tensile strength and modulus of PLLA were improved dramatically by stretching. The stress-induced crystallization of PLLA occurred during drawing. The interfacial tension ($\gamma_{s\text{-}blood}$) between PLLA surface and blood decreased by chain extension and molecular orientation, indicating the weakened interaction between bioactive substance in the blood and the surface of PLLA. Modification and orientation could significantly enhance the blood compatibility of PLLA by prolonging clotting time and decreasing hemolysis ratio, protein adsorption and platelet activation. The bionic character of oriented PLLA and its anti-coagulation mechanism were tried to be explored.

1. Introduction

Intense effort has been being made on preparing biomedical materials through centuries because of their extensive and significant importance in biology and medicine science [1]. Poly(L-lactic acid) (PLLA) has been considered to be a good candidate for biomedical materials due to its favorable physical properties, ease of handling and processing, and its biodegradable and biocompatible nature, which have been approved by the Food and Drug Administration (FDA) for numerous clinical applications, such as sutures, bone plates, abdominal mesh, and extended-release pharmaceuticals [2–4].

For biomedical materials, two fundamental requirements are proposed. First, their physical properties such as flexibility or rigidity, mechanical strength, etc., must fulfill the purposes for multiple practices relating with biological preference. In addition, for a biomedical implant material to be in contact with blood, the blood compatibility is another one of the most important properties in order to ensure the security of clinical practice [5]. Although extensive efforts have been devoted to modifying the mechanical properties of PLLA by copolymerization with other monomers or blending PLLA with other materials, the strength and modulus of PLLA are still not sufficient for implant fixation. On the other hand, to improve the blood compatibility of PLLA, surface coating and surface modification, such as chemical modification with drugs and endothelial cell seeding, are the most general approaches. However, these methods still have some problems. Surface chemical modification requires rather complex experimental procedures and involves high costs, and long term stability is additional aspect requiring improvement [6]. Endothelial cell seeding has the potential to provide effective surface modification. However, the adhesion and proliferation of endothelial cells on artificial surfaces are very complex phenomena, so the formation of these cell layers is a very slow process [7].

Solid hot drawing technology presents the advantages of high production rates, high orientation, and significant enhancements in

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the properties without complex processing apparatus [8–11]. Through solid hot drawing technology, first of all, PLLA with sufficient initial strength and sufficient strength retention over a period of time could be prepared to meet the requirement of desirable physical properties for biomedical use. Meanwhile, the surface properties of PLLA were influenced by processing and thus affect the interaction with the biological elements of the organism. And in our previous work, through solid hot drawing technology, highly oriented PLLA/MWNTs composites and PLLA/TPU blends were prepared successfully and the most interesting finding was the fact that the oriented samples showed obviously enhanced in vitro blood compatibility as well as mechanical properties [12].

However, for neat PLLA, it's very difficult to be ultra-drawn due to its low viscosity and poor melt strength. To overcome such shortcomings, chain extension is the main reported way by which the molecular weight and entanglement between PLLA molecules can be enhanced. Chain extenders are usually bifunctional chemicals which can couple the two end groups of polymer, thereby leading to a linear polymer with a relatively higher molecular weight by means of post polymerization reaction carried during compounding, injection molding, or extrusion. Typical chain extenders for polyesters, which contain −OH and −COOH groups, are diisocycanates, bisoxazolines, dianhydrides and bisketeneacetals diepoxides. Ethylene glycol diglycidyl ether (EGDE) is a bifunctional epoxide compounds which has high reactivity with amines, alcohols, phenols, carboxylic acids and thiols [13–14]. Thus, EGDE can be used to chain extend poly(methacrylic acid), polyester, poly(-imidazole) and so on [15–17]. Moreover, EGDE is safe and nontoxic, and due to its biological safety, EGDE is even used to prepare DNA network gels [18–20].

In this work, PLLA was chain extended with EGDE through reactive processing in order to enhance the molecular entanglement and melt strength of PLLA. And then highly oriented PLLA with fibrillar structure as well as submicrometer structures, which were bionic and similar to the intimal layer of blood vessel, can be formed through solid hot drawing. Compared with other most general used approaches such as surface chemical modification with drugs and endothelial cell seeding, formation of highly-oriented fibrillar structure to improve the blood compatibility of PLLA presented the advantages of high efficiency, low costs and significant enhancements in the mechanical properties. The structure and properties of the oriented PLLA were studied, and its bionic character as well as anti-coagulation mechanism were tried to be explored.

2. Experimental section

2.1. Materials

PLLA (3052D) used in this study was supplied by NatureWorks LLC., USA. The molecular weight ($\overline{Mw}$) was about 1×10^5. Ethylene glycol diglycidyl ether (EGDE) (AR) was obtained from Energy Chemical Co. Ltd., China.

2.2. Preparation of the oriented PLLA

2.2.1. Chain extension of PLLA

Prior to chain extending, the PLLA was dried at 70 °C for 5 h in a vacuum oven. Chain extended PLLA were prepared by sequentially mixing with EGDE at varying contents (0.1 wt%, 0.5 wt%, 0.7 wt%, 1 wt%, 3 wt%, 5 wt% by weight based on PLLA, respectively) in a Haake internal melt mixer (Rheocord 90, Germany) at 170 °C. Then, chain extended PLLA were cut into small granules. Dumbbell shaped specimens were molded by micro-injection molding machine at 170 °C. Neat PLLA was treated with the same procedure for comparison.

2.2.2. Orientation of PLLA

The oriented samples of PLLA and chain extended PLLA were prepared by being heated and mechanically drawn. After the desired draw ratio was obtained, the sample was cooled down to room temperature, and then the load was released.

2.3. Measurements

2.3.1. Molecular weight measurement

The molecular weight distribution and relative molecular weight of PLLA and chain extended PLLA were determined by a 110 HPLC permeation chromatography (GPC, Agilent Co, USA). PLLA specimens were dissolved in tetrahydrofuran (THF) at a concentration of 5 mg/mL and 10 mL of the test solution was injected into a GPC apparatus (Shimadzu Co., Kyoto, Japan) equipped with two GPC columns (Super HM-H (6.0 mm*15 cm*2), Tokyo, Japan), a refractive index detector (model RI, Shimadzu Co.) and Class-LC workstation GPC software (Shimadzu Co.). The flow rate of chloroform mobile phase was 0.6 mL/min. Molecular weight values, including molecular weight ($\overline{Mw}$ and $\overline{Mn}$) and molecular weight distribution ($\overline{Mw}/\overline{Mn}$) for PLLA were measured from the comparison with the calibration line which was made with polystyrene standards (Showa Denko, Tokyo, Japan).

2.3.2. ^{13}C NMR spectra

^{13}C NMR measurements of PLLA were performed with Advance Bruker 600 NMR spectrometer (Bruker Co, Germany) at 600 MHz at room temperature, using $CDCl_3$ as solvent.

2.3.3. Dynamic rheological measurement

Dynamic rheological measurement was performed on a dynamic stress AR 1500ex rheometer (TA Instruments, USA). The samples were compression molded into the disk of 25 mm in diameter and around 1 mm in thickness. The measurement was run with a 25 mm-diameter parallel plate geometry and a 1.0-mm sample gap. The dynamic viscoelastic properties were determined with frequencies from 0.01 to 100 Hz at 170 °C, using 1% strain (selected after strain sweep tests) value determined with a stress sweep to keep within the linear viscoelastic region. Specimens were placed between the preheated plates at the experimental temperature and were allowed to equilibrate before each run.

2.3.4. Non-isothermal crystallization analysis

The non-isothermal crystallization was performed with a Netzsch 204 differential scanning calorimetry (DSC) (Phoenix Co, Germany). The temperature scale of DSC was calibrated with indium. Granulated samples of about 10 mg were heated from ambient temperature to 200 °C at a constant rate of 10 K/min under nitrogen atmosphere. X_c can be calculated with the following equation:

$$X_c = (\Delta H_m/\Delta H_0)*100\% \quad (1)$$

where ΔH_m is the melting enthalpy of the samples and ΔH_0 is the balance melting enthalpy, i.e., the melting enthalpy of 100% crystallizing polymer.

2.3.5. Two-dimensional wide-angle X-ray diffraction analysis (2D-WAXD)

Wide-angle X-ray diffraction (WAXD) analysis was conducted at the ambient temperature using a D8 Discover two-dimensional wide angle X-ray diffractometer (2d-WAXD) (Bruker AXS Co,