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Investigating composite systems based on poly L-lactide and poly L-lactide/triclosan nanoparticles for tissue engineering and medical applications

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ABSTRACT

In this study, the encapsulated triclosan with a low molecular weight PLLA (LATC30) is dispersed into a PLLA having higher molecular weight via melt blending to increase the overall properties and particularly antibacterial activity of the system. The proposed method results in a completely homogenous composite as 5% LATC30 improved mechanical properties. For instance, the elongation at break was increased ca. 3%. The mechanical properties of the fabricated composites were also affected by the plasticizing role of LATC30. The kinetics of hydrolytic degradation in an accelerated condition was obtained using a novel method by the Beer–Lambert equation. It was found that the incorporation of LATC30 into the composite increases the rate of hydrolytic degradation. The calorimetry showed a reduction in crystallinity upon addition of LATC30. Moreover, the degradation of the composites was studied and fully described the kinetic analysis by the Flynn–Wall–Ozawa (FWO) method. From which, it was found that the activation energy of the system was decreased. As the LATC30 content of the composite was increased, the hydrophilicity of the composite was increased. The fabricated scaffolds with 5% LATC30 demonstrated a good osteoblast cell attachment and mineralization on the composite scaffolds. This composite is a suitable antibacterial candidate for the bone tissue engineering and medical applications since the real dosage of triclosan stays at ca. 1.5%.

1. Introduction

The biocompatible and biodegradable polymers have attracted many attentions from both the biomedical and ecological outlooks for the past few years. The degradable polymeric biomaterials are the preferred candidates for developing therapeutic devices such as temporary prostheses, three-dimensional porous structures (as scaffolds for tissue engineering), and as the controlled/sustained release drug delivery vehicles [1,2]. The biodegradable synthetic polymers offer a number of advantages over other materials for developing scaffolds for tissue engineering (as biomaterials). The key advantage is the ability to tailor mechanical properties and degradation kinetics for various applications [3]. Poly(α-esters) such as poly(lactide), poly(glycolide), poly(trimethylene carbonate), poly(ε-caprolactone), and their copolymers are the most common synthetic biodegradable polymers widely used for medical applications. Poly(α-esters) can be developed from a variety of monomers via the ring opening and condensation polymerization routes depending on the monomeric units. The bacterial bioprocess routes can also be used to develop some poly(α-esters) [2–4]. Poly-(L-lactide) (PLLA) is a crystalline polymer (37–42% crystallinity) as the degree of crystallinity depends on the molecular weight and the processing parameters. This polymer has a glass transition temperature from 60 to 65 °C and a melting temperature of ca. 175 °C. Moreover, it has a large tensile strength, elongation, modulus, good bioresorbability and biocompatibility, making it more suitable for load bearing applications such as sutures, tissue culture, wound closure, the controlled release systems and orthopedic fixation [4–6]. In biomedicine, scientists have employed some design rules found in nature to fabricate the PLA-based bionanocomposites. The incorporation of functional nanoparticles in the PLA matrix has improved the physical properties and changed the surface characteristics of the matrix. They are important for tissue engineering and artificial bone reconstruction [7]. Furthermore, the tissue engineering scaffolds need to have antibacterial properties because of the infection risk [8]. In fact, ideally, the implant should have the ability to regenerate bone tissue and treat the infection by delivering an antibacterial agent in a controlled manner. The localized release of an antibacterial agent at the surgical site, after removing the necrotic tissue, could provide a targeted treatment for the infection [9,10]. A large variety of nanomaterials for efficient antibiotic drug delivery have been developed and their efficacy has been demonstrated [11]. In the last decade, several compounds have been used as antibacterial agents. For example, titanium dioxide (TiO_2), chlorinated

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compounds, selenium, various polycations such as the quaternized poly(2-dimethylamino ethyl methacrylate) as well as silver ion and nanoparticles of silver and triclosan have been considered as the dispersed antibacterial and antimicrobial agents for polymeric matrix [12,13]. Triclosan is a well-known commercial and a Food and Drug Administration (FDA) approved-synthetic-non-ionic-broad-spectrum antimicrobial agent that was chosen as the antibacterial agent in this research [13]. It is chemically stable and may be heated up to 200 °C for up to 2 h. Therefore, such a good level of thermal stability making it suitable for incorporation into various reinforced plastic materials [14]. In our previous work, the PLLA/triclosan nanoparticles were prepared by the emulsification–diffusion process and LATC30 with 30% of triclosan was selected among the other samples due to its larger encapsulation efficiency, better molecular dispersion and the best release profiles according to the fitted data over several models. It was also found that triclosan could be molecularly dispersed and attached to PLLA with high stability. Moreover, it was suggested that the use of synthesized PLLA/triclosan nanoparticle is safer and more efficient suggesting the great potentials for application as antibacterial agent for the personal care and wound-dressing, drug delivery systems, and new antibacterial nanoparticle for application in implantable surgical products such as sutures and screws [15].

In the current study, at first, L-lactide monomer was synthesized according to our previous study, and then, PLLA was synthesized via the ring opening polymerization using stannous octoate and triphenyl phosphine as catalyst mixture in a glass ampule [16]. The gel permeation chromatography (GPC) technique was used to obtain the molecular weight of PLLA. Afterwards, the prepared PLLA/triclosan nanoparticles (LATC30) with various quantities were added to the newly synthesized PLLA with higher molecular weight via an internal mixer. The structure and chemical composition as well as the hydrolytic degradation kinetics were investigated using the Fourier transform infra-red (FTIR-ATR). To examine the mechanical properties of composites, tensile, hardness, impact and dynamic mechanical thermal analysis (DMTA) tests were conducted. The thermal properties of composites were studied using the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The hydrophobicity and surface properties of composites were studied using the water contact angle measurements. To study the processability of the composites, the rheological properties were investigated as well. The in vitro tests, specifying the biological properties and hydrolytic degradation were also carried out. In addition, the release of drug from the composites was measured using the UV–Visible spectroscopy. The corresponding kinetics was validated using five different models. The antibacterial studies as well as the MTT assay were performed as proofs for cell viability. A scaffold has also been prepared from the optimum sample using leaching method, and the morphology of composites and scaffolds was observed using the scanning electron microscopy (SEM) technique.

2. Experimental

2.1. Materials

The L-lactide monomers were synthesized from 90% L-lactic acid solution (Merck, Darmstadt, Germany) according to our previous work [16]. The L-lactide monomers were purified by several recrystallizations from dry ethyl acetate, and finally, were eluted by the dried diethyl ether to remove some trace impurities. Then, L-lactide monomers were dried under vacuum at room temperature for 24 h. Stannous octoate, ($C_{16}H_{30}O_4Sn$ or $Sn(Oct)_2$), as catalyst was purified by the vacuum distillation and the co-catalyst, triphenyl phosphine ($P(C_6H_5)_3$ or PPh_3 ($P\phi_3$)), were purchased from Sigma Aldrich. The PLLA/triclosan nanoparticles (LATC30) were prepared according to a procedure from our previous work [15]. Triclosan was supplied by (KAF Co., a branch of DAROUGAR group, Iran) originally bought from Dekaben TC Premium, Jan Dekker. All the other chemical and solvents were the reagent grade from Merck and used without further purification.

Table 1
Composition of PLLA/LATC30 composites.

Samples	LATC30 content (%)
PLA 0	0
PLA 1	1
PLA 2	3
PLA 3	5
PLA 4	7
PLA 5	10
PLA 6	20

Table 2
Average molecular weight, polydispersity index and intrinsic viscosity of PLA0.

Sample	GPC				Ubbelohde	
	M_w	M_n	PDI	[η]	[η]	M_w
Synthesized PLLA	210,400	107,300	1.96	4.191	4.1546	207,900

2.2. Polymerization

Some amounts of L-lactide were placed in a glass tube and a mixture of Stannous octoate and triphenyl phosphine was added (a monomers/catalyst mixture mole ratio was kept constant at 5000). The glass tubes were sealed using oxygen flame and kept in an oil bath at 130 °C for one hour, so that PLLA was polymerized and as was reported the polymerization had a duration of 45 min [17]. It should be mentioned that the polymerization occurs according to the coordination insertion mechanism. At the end of reaction, the tubes were broken and the contents were dissolved in chloroform, filtered and finally precipitated in cold methanol. The purified products were dried under vacuum for 24 h and then placed in an oven at 100 °C under reduced pressure for 2 days in order to eliminate residual solvent and moisture.

2.3. Polymer processing

Prior to blending, PLLA and nanoparticles were dried in an oven at 80 °C for 4 h. PLA was premixed in an internal mixer, Brabender mixer 50 EHT (Germany), for 5 min and then nanoparticles were added at varying weight ratios (1–20%) within 15 min. The melt mixing was performed at 170 °C at a rotor speed of 60 rpm. The obtained blends were molded in specific shapes according to the test procedure by a

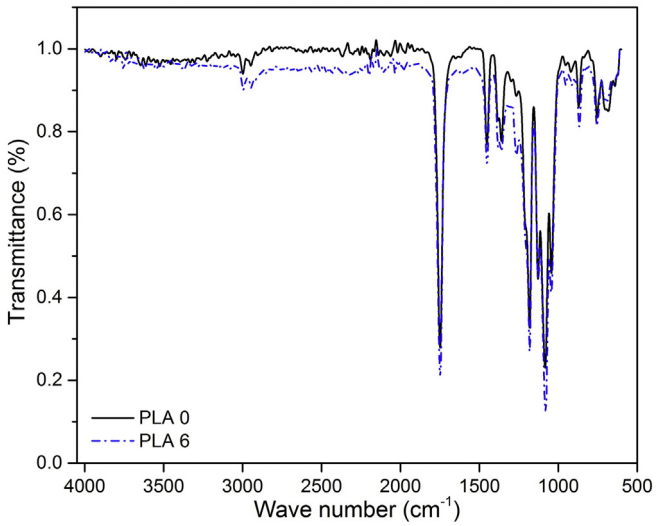

Fig. 1. FTIR spectra of PLA0 and PLA6.