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Anhydric maleic functionalization and polyethylene glycol grafting of lactide-*co*-trimethylene carbonate copolymers

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ABSTRACT

Lactide and trimethylene carbonate copolymers were successfully grafted with polyethylene glycol via previous functionalization with maleic anhydride and using *N*,*N*′-diisopropylcarbodiimide as condensing agent. Maleinization led to moderate polymer degradation. Specifically, the weight average molecular weight decreased from 36,200 to 30,200 g/mol for the copolymer having 20 mol% of trimethylene carbonate units.
Copolymers were characterized by differential scanning calorimetry, thermogravimetry and X-ray diffraction. Morphology of spherulites and lamellar crystals was evaluated with optical and atomic force microscopies, respectively. The studied copolymers were able to crystallize despite the randomness caused by the trimethylene carbonate units and the lateral groups. Contact angle measurements indicated that PEG grafted copolymers were more hydrophilic than parent copolymers. This feature justified that enzymatic degradation in lipase medium and proliferation of both epithelial-like and fibroblast-like cells were enhanced. Grafted copolymers were appropriate to prepare regular drug loaded microspheres by the oil-in-water emulsion method. Triclosan release from loaded microspheres was evaluated in two media.

1. Introduction

Polylactide (PLA) is currently the main biobased thermoplastic polymer that can be manufactured at a more competitive price than petroleum based polymers. Furthermore, polylactide has suitable properties for both commodity and specialty applications [1]. For example, low toxicity and environmentally benign characteristics have made PLA an ideal material for food packaging and film wrap, as well as for other consumer products [2,3]. PLA has also been widely used for biomedical applications such as medical implants in the form of screws, pins, rods, and meshes [4,5], bioabsorbable sutures [6–8], tissue engineering scaffolds [9] and drug-delivery systems [10] because of its ability to biodegrade into innocuous lactic acid under physiological conditions and its exceptional qualities, like biocompatibility, FDA approval for clinical use, low immunogenicity and good mechanical properties. Despite these advantages, its hydrophobicity may hinder certain biological and biomedical applications. In this sense, different PLA-based amphiphilic block copolymers (e.g. those constituted by poly(ethylene glycol) (PEG)) have been designed and synthesized [11] from maleic anhydride grafted PLA, a method first reported by Carlson et al. [12]. Moreover, modification with polar groups to increase hydrophilicity has been proved to improve cell adhesion without any harmful effect.

Polyethylene glycol grafted polylactides (PEG-*g*-PLA) have also been considered to improve the ductility of PLA. In fact, PEG has excellent plasticizing abilities, although the amount introduced in PLA must be lower or equal to 20 wt.% to avoid phase separation [11,13–15]. Reactive blending of a maleic anhydride grafted PLA with hydroxyl functionalized PEG has been proposed as an easy way to prepare PEG-*g*-PLA copolymers, which should create more interactions between the so-functionalized polyester matrix and non-grafted PEG [16]. In situ reactive grafting of hydroxy terminated poly(ethylene glycol) (PEG) plasticizer onto maleic anhydride modified PLA in PLA/PEG blends had a positive impact on mechanical properties and lowered the glass transition temperature significantly compared to the blends where no grafting could occur (neat PLA + PEG).

Polytrimethylene carbonate (PTMC) is a well-known biodegradable polymer with rubbery characteristics and suitable properties as a biomaterial for biomedical applications [17]. In fact, segmented copolymers constituted by glycolide-*co*-trimethylene carbonate, and even glycolide-*co*-caprolactone-*co*-trimethylene carbonate soft segments, have been widely employed for preparation of monofilament surgical sutures since stiffness of polyglycolide hard blocks can be reduced [18,19]. In the same way, efforts to improve the mechanical properties (e.g. ductility) of PLA for use in a wide range of applications have been conducted; specifically, random and sequential copolymerizations of lactide and trimethylene carbonate have been considered [20–22].

The aim of the present work is to prepare PEG grafted poly(lactide-*r*-trimethylene carbonate) (PLA-*r*-PTMC) copolymers via maleic acid

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functionalization and evaluate the effect of PEG chains on properties, degradability and cytotoxicity. Potential applications of the new biodegradable systems as drug delivery nanospheres are also considered.

2. Experimental section

2.1. Materials

Grafted copolymers were synthesized following the scheme in Fig. 1. All solvents, triclosan, *N*,*N*′-diisopropylcarbodiimide, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) and cell culture labware were purchased from Sigma-Aldrich (Spain). L-Lactide, polyvinyl alcohol (PVA) and polyethylene glycol (550 g/mol) were purchased from Sigma-Aldrich, whereas trimethylene carbonate (1,3-dioxane-2-one) and maleic anhydride were purchased from Boehringer and Fluka, respectively. All solvents, polymers and reagents were used as received.

The enzyme used in the degradation studies (i.e. lipase from *Rhizopus oryzae*) and Dulbecco's phosphate buffered saline medium were also purchased from Sigma-Aldrich.

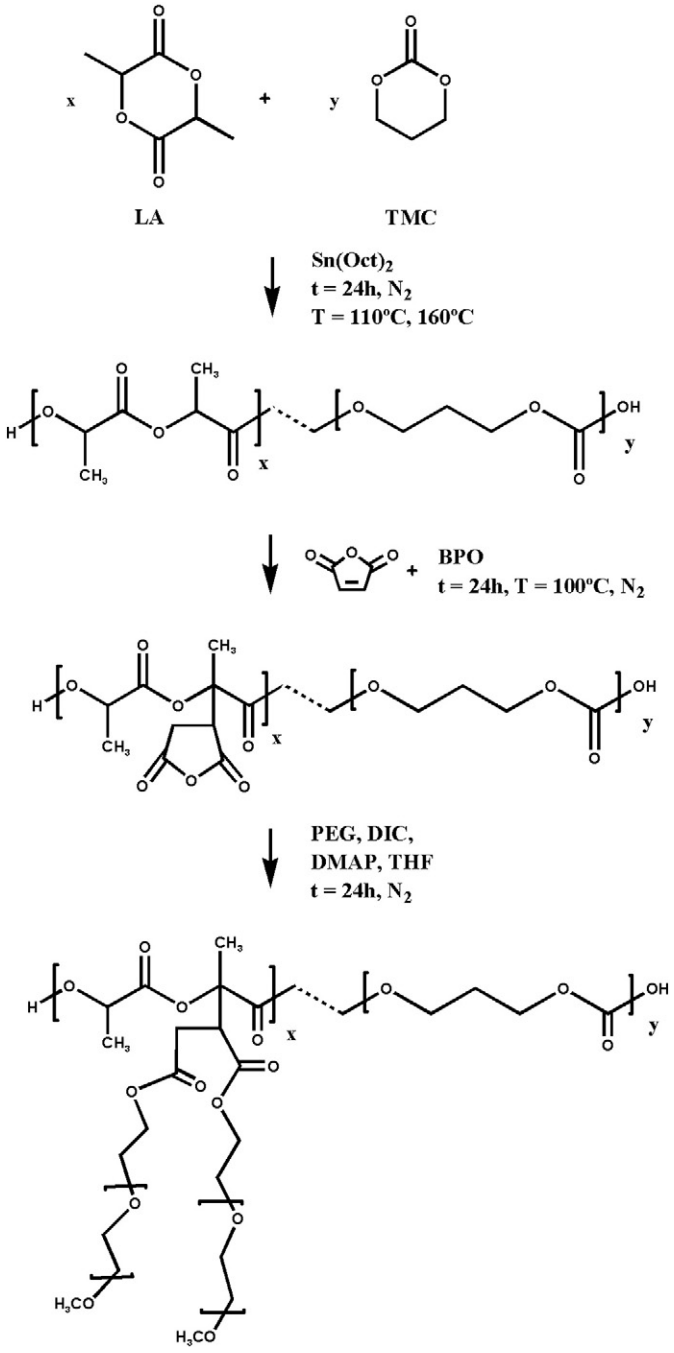

Fig. 1. Synthesis scheme for PEG grafted polymers derived from lactide and trimethylene carbonate.

2.2. Synthesis of PLA and PLA-r-PTMC samples

PLA and PLA-*r*-PTMC were synthesized by bulk ring-opening polymerization of L-lactide (LA) and its mixture with appropriate amounts of trimethylene carbonate (TMC). $Sn(Oct)_2$ (0.05 M solution in dry chloroform) was used as a catalyst, with the monomer/catalyst ratio always close to 5000. The monomers and initiator were mixed in a silanized glass flask equipped with a magnetic stirrer and gas inlet and outlet tubes. Chloroform was subsequently removed under vacuum. Polymerizations were performed under a nitrogen atmosphere at temperatures of 140 °C and 160 °C for the homopolymer and the trimethylene carbonate copolymers, respectively, for 24 h. Temperature was increased for the preparation of the copolymer due to the lower reactivity of TMC. Reported synthesis data of the PTMC homopolymer indicated that temperatures around 160 °C were appropriate for reaction times close to 24 h [23,24]. Samples were purified by precipitation from dichloromethane solutions with methanol and stored under vacuum.

2.3. Maleic anhydride functionalization

One gram of the appropriate polymer or copolymer sample in powder form was mixed evenly with benzoyl peroxide (BPO), which was used as an effective radical initiator as reported in the literature for the functionalization of polymers based on lactide and ε-caprolactone [25–27]. The mixture was introduced in a round bottom flask and vacuum dried at room temperature for at least 4 h. Toluene (5 mL) was added to dissolve the sample, purged with pure nitrogen and then heated to 100 °C. Maleic anhydride (MA) was dissolved in toluene (2 mL) in a second flask, purged with nitrogen, heated to 100 °C and finally added to the first polymer or copolymer solution. Reaction was performed at 100 °C for 24 h, the ratios (*w*/*w*) of polymer/copolymer to MA and BPO being 1:1 and 18:100, respectively. The solution was then dialyzed against chloroform using a membrane (Zellu Trans, Roth) with a nominal M*w* cut-off of 1000 g/mol for 48 h. The final product was recovered from the dialysis bag solution by rotavaporation and then stored under vacuum.

2.4. Grafting with polyethylene glycol

One gram of the maleinized sample and 1 mmol of 4-dimethylaminopyridine (DMAP) were completely dissolved in 4 mL of anhydrous tetrahydrofurane (THF) and kept at room temperature for 30 min. PEG (1 mmol) and diisopropylcarbodiimide (DIC) (1.3 mmol) were mixed in 2 mL of THF and slowly transferred into the polymer solution using a syringe. The solution was stirred at room temperature for 24 h. At the end of the reaction time, the solution was concentrated by removing most of the solvent. The new polymer was dissolved in dichloromethane and precipitated in cold methanol.

2.5. Measurements

Molecular weight was estimated by size exclusion chromatography (GPC) using a liquid chromatograph (Shimadzu, model LC-8A) equipped with an Empower computer program (Waters). A PL HFIP gel column (Polymer Lab) and a refractive index detector (Shimadzu RID-10A) were employed. The polymer was dissolved and eluted in 1,1,1,3,3,3-hexafluoroisopropanol containing CF_3COONa (0.05 M) at a flow rate of 0.5 mL/min (injected volume 100 μL, sample concentration