Reactive and Functional Polymers 119 (2017) 37–46

Contents lists available at ScienceDirect

Reactive and Functional Polymers

journal homepage: www.elsevier.com/locate/react

# Tuning properties of poly(ethylene glycol)-*block*-poly(simvastatin) copolymers synthesized via triazabicyclodecene

Theodora A. Asafo-Adjei[a], Thomas D. Dziubla[b], David A. Puleo[a,*]

[a] F. Joseph Halcomb III, M.D. Department of Biomedical Engineering, University of Kentucky, Lexington, KY, USA
[b] Department of Chemical and Materials Engineering, University of Kentucky, Lexington, KY, USA

ARTICLE INFO

*Keywords:*
Poly(simvastatin)
Simvastatin
Diblock copolymer
Triazabicyclodecene
Drug delivery

ABSTRACT

Simvastatin was polymerized into copolymers to better control drug loading and release for therapeutic delivery. When using the conventional stannous octoate catalyst in ring-opening polymerization (ROP), reaction temperatures ≥ 200 °C were required, which promoted uncontrollable and undesirable side reactions. Triazabicyclodecene (TBD), a highly reactive guanidine base organocatalyst, was used as an alternative to polymerize simvastatin. Polymerization was achieved at 150 °C using 5 kDa methyl-terminated poly(ethylene glycol) (mPEG) as the initiator. ROP reactions with 2 kDa or 550 Da mPEG initiators were also successful using TBD at 150 °C instead of stannous octoate, which required a higher reaction temperature. Biodegradability of the poly(simvastatin) copolymer in phosphate-buffered saline was also improved, losing twice as much mass than the copolymer synthesized via stannous octoate. The three copolymers exhibited modified rates of simvastatin release, demonstrating tunability for drug delivery applications.

## 1. Introduction

A wide range of catalysts with different mechanisms of action have been used to synthesize degradable polyesters for biomedical applications. Common catalysts that mediate ring-opening polymerization (ROP) of lactone-incorporated monomers include tin (II) ethyl-hexanoate (stannous octoate) and other organotin compounds [1]. Aluminum-, lanthanum-, and zinc-based alkoxides have also been used in the synthesis of high molecular weight (MW) poly(lactic acid) (PLA), poly(lactic-*co*-glycolic acid), and poly(ε-caprolactone) [1–3].

Stannous octoate and other metal and alkaline earth catalysts are known to be efficient [4], while enzymatic, acidic, and organic catalysts have reportedly shown lower reactivity, producing low MW polymers [1,5]. Catalyst reactivity, however, can be altered by modifying reaction conditions, the type or size of lactone monomer incorporated into the feed, or functional groups of these catalysts. For example, changing the diamine bridge of aluminum salen complexes from ethylene to dimethylpropylene led to significantly increased polymerization rates of small L-lactide, ε-caprolactone, ε-decalactone, and β-butyrolactone monomers, while low reactivities with ω-pentadecalactone and other macrolactones were not significantly affected [6]. Also, ROP reactions with diazabicycloundecene and *N*-methylated triazabicyclodecene (TBD) organocatalysts generated polylactide MWs of 18 and 21 kDa, respectively, in the presence of pyrenebutanol in chloroform under optimized conditions [7]. The type of catalyst used under specific reaction conditions can affect the degree of polymerization and the resulting quality of the polymer synthesized.

In our previous studies, stannous octoate-mediated coordination-insertion ROP was used to synthesize a newly developed poly(simvastatin)-poly(ethylene glycol) diblock copolymer with potential anti-inflammatory, angiogenic, and osteogenic properties following degradation. While the catalyst was successful in mediating poly(simvastatin) propagation with a methyl-terminated poly(ethylene glycol) (mPEG) initiator, a narrow and high reaction temperature window served as a limitation that also promoted undesirable transesterification reactions. After preliminary attempts with other metal and organocatalysts, TBD was ultimately selected because of its efficient performance at ambient temperatures [7], ability to work without a co-catalyst, metal-free process, and accessibility. TBD was also reported to rapidly catalyze synthesis of 26 kDa PLA, of which the MW could be modified by changing the molar ratio of initiator to monomer in the feed [8].

In the present study, the TBD-mediated poly(simvastatin) reaction was compared with the stannous octoate-mediated reaction under similar conditions. Polymerization via TBD was also evaluated with different MW mPEGs, catalyst percentages, and molar ratios of simvastatin to mPEG. Hydrolytic degradation of the resulting poly(ethylene glycol)-

* Corresponding author at: F. Joseph Halcomb III, M.D. Department of Biomedical Engineering, 522 Robotics and Manufacturing Building, University of Kentucky, Lexington, KY 40506-0108, USA.
*E-mail address:* puleo@uky.edu (D.A. Puleo).

http://dx.doi.org/10.1016/j.reactfunctpolym.2017.07.004
Received 24 February 2017; Received in revised form 7 June 2017; Accepted 21 July 2017
Available online 27 July 2017
1381-5148/ © 2017 Elsevier B.V. All rights reserved.

*block*-poly(simvastatin) (PSIM-mPEG) copolymers was also analyzed by measuring mass loss and drug release.

## 2. Experimental

### 2.1. Materials

Simvastatin was purchased from Haorui Pharma-Chem (Edison, NJ). Triazabicyclodecene, monomethyl ether poly(ethylene glycol) (mPEG), anhydrous toluene, anhydrous diethyl ether, dichloromethane (DCM), and deuterated chloroform ($CDCl_3$) were obtained from Sigma-Aldrich (St. Louis, MO). Tetrahydrofuran (THF) stabilized with 3,5-di-tert-butyl-4-hydroxytoluene (BHT) was procured from Fisher Scientific (Pittsburgh, PA).

### 2.2. Synthesis of poly(ethylene glycol)-block-poly(simvastatin)

Microscale reactions of PSIM-mPEG using stannous octoate have been previously described [9]. Macroscale reactions (2 g) were conducted using simvastatin as the monomer and mPEG (550, 2000, or 5000 Da) as the initiator. Molar ratios of 100:2 for simvastatin to mPEG 550, and 100:1 for simvastatin to mPEG 2000 or 5000 Da were used in the feed to synthesize PSIM-mPEG(550), PSIM-mPEG(2k), and PSIM-mPEG(5k), respectively. Simvastatin and mPEG were dried in a round bottom flask embedded in a silica sand bath at 120 °C for 1 h under a continuous flow of nitrogen gas. The internal bulk temperature was increased to 150 °C for an additional hour before adding 1 wt% of TBD to the homogeneous melt. Each reaction ran for 24 h.

Microscale reactions (0.4 g) were also conducted for PSIM-mPEG(550) copolymers with a TBD catalyst percentage of 0.1 or 1 wt%, a 100:1, 100:2 or 100:10 simvastatin to mPEG molar ratio, and crude samples taken at 0, 4, 12, 18, or 24 h reaction times.

Polymer dissolved in DCM was slowly added to cold diethyl ether at a 1:7 v/v ratio of DCM to ether and vacuum filtered to purify the crude PSIM-mPEG(5k) product. The purification process for PSIM copolymers with lower MW mPEG blocks involved slowly adding cold diethyl ether to the polymer in DCM solution at a 1:20 v/v ratio, followed by centrifugation and decantation of the supernatant.

### 2.3. Physico-chemical characterization

#### 2.3.1. Gel permeation chromatography (GPC)

A Shimadzu Prominence LC-20 AB HPLC system connected to a Waters 2410 refractive index detector was used to measure the weight-average molecular weights of simvastatin, mPEG (550, 2000, and 5000 Da), and the crude PSIM copolymers. Two Resipore columns in series (300 × 7.5 mm, 3 µm particle size; Agilent Technologies) were used for separation. Samples were dissolved in THF at 5 to 10 mg/ml. THF was also used as the mobile phase at a 1.0 ml/min flow rate. Polystyrene standards were used to calculate MW ranged from 160 Da to 430 kDa.

#### 2.3.2. Nuclear magnetic resonance (NMR) spectroscopy

H-NMR spectra were obtained to characterize the PSIM-mPEG(5k) copolymer and a melted mixture of simvastatin and mPEG at a 100:1 molar ratio using a 400 MHz Varian Gemini NMR instrument connected to a VnmrJ software interface. Samples weighing 5 to 7 mg each were dissolved in 1 ml of $CDCl_3$, transferred into NMR tubes, and analyzed for additional structural characterization. The number of simvastatin monomers present in the diblock copolymer was calculated by integrating the area under the peaks representing simvastatin relative to those associated with 5 kDa mPEG, of which the number of H atoms in its structure was known. With this ratio, the number of protons in the poly(simvastatin) block of the copolymer was calculated and divided by the known number of protons in simvastatin to get the number of simvastatin monomers in the diblock copolymer.

#### 2.3.3. Matrix-assisted laser desorption/ionization – time of flight mass spectrometry (MALDI–TOF MS)

Degradation products of PSIM-mPEG(5k) were analyzed using a positive ion mode Bruker Ultraflextreme MALDI-TOFMS. The procedure used for sample analysis was previously described [9].

#### 2.3.4. In vitro degradation

Films of each copolymer (10–15 mg) were made by adding a small amount of DCM to polymer to create a viscous solution (700% w/v) that was pipetted onto a Teflon sheet to dry overnight. Each film was gently shaken in 1.5 ml of phosphate-buffered saline (PBS), pH 7.4, at 37 °C. Supernatant was collected and the medium completely replaced every 12 h the first day, every other day the first week, and at 2 to 5 d for the remainder of the 44 d degradation period. The remaining samples were dried and weighed after 6 weeks to measure total mass loss.

#### 2.3.5. High performance liquid chromatography (HPLC)

A Shimadzu Prominence LC-20 AB HPLC system was used to analyze supernatants collected from the mass loss study. One Luna C18 column (150 × 4.60 mm, 5 µm particle size) was used with an isocratic mobile phase of acetonitrile and water with 0.1% trifluoroacetic acid (70:30 v/v). Absorbance was measured at 240 nm.

#### 2.3.6. Statistical analysis

Two-way ANOVA with a Bonferroni post-test was performed on the kinetic data to test effects of reaction time, catalyst percentage, and molar ratio on MW, yield, and percent composition of the copolymer. The same analysis was applied to the simvastatin amounts released during copolymer degradation. Values of $p \leq 0.05$ were deemed statistically significant. Data are plotted as mean and standard deviation.

## 3. Results and discussion

### 3.1. Polymerization Mechanism

The ROP mechanism governed by TBD is anionic. From the literature, one theorized mechanism suggests that the amidine imine nitrogen of the nucleophilic catalyst attacks the carbonyl group on the lactone ring of simvastatin to form a temporary intermediate as the acyl bond is broken. The secondary amine in the guanidine-based organocatalyst attracts the alcohols within the reaction mixture (i.e., both on mPEG and the propagating poly(simvastatin) block) via hydrogen bonding. This action propagates the PSIM block of the PSIM-mPEG diblock copolymer [8]. However, computational analysis comparing the transitional state energies of proposed TBD-mediated ROP reactions with L-lactide and methanol showed that the intermediate steps carried out via hydrogen bonding had lower energy transitional states compared to nucleophilic attraction throughout the reaction. The lower energy states due to hydrogen bonding indicated a relatively more stable mechanism [10].

In the proposed mechanism shown in Scheme 1, the amidine imine nitrogen of TBD attracts the hydrogen on the alcohol, in this case mPEG, to activate it. The activated alcohol then attacks the carbon of the carbonyl group of the lactone ring of simvastatin. The catalyst then changes orientation, subsequently hydrogen bonding to the oxygen in the C—O bond in the lactone ring, while the secondary amine remains hydrogen bonded to the oxygen in the carbonyl group. This transitional state initiates opening of the lactone ring. TBD is reformed after the hydrogen migrates away from the amidine imine to form the hydroxyl end-group of the propagating polymer [10].

### 3.2. Stannous octoate vs. TBD catalyst mediated reactions

The mole percentages of simvastatin, intermediates, and copolymer throughout the reaction using stannous octoate or TBD as a catalyst are displayed in Fig. 1. Within 24 h, a decrease in simvastatin monomer

Download English Version:

https://daneshyari.com/en/article/5209286

Download Persian Version:

https://daneshyari.com/article/5209286

Daneshyari.com