Evaluating Two Methods of Ring-Opening Polymerization for Synthesizing a Degradable, Polymeric Simvastatin Prodrug

Theodora A. Asafo-Adjei, Thomas D. Dziubla[2], and David A. Puleo[1]
[1]Department of Biomedical Engineering
[2]Department of Chemical and Materials Engineering
University of Kentucky, Lexington, KY, USA

Statement of Purpose

Poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(ε-caprolactone) (PCL) are among many degradable polymers used for regenerative medicine. Their bioinertness, tunable degradation, and mechanical properties make them desirable as carriers for releasing bioactive agents. However, a limited and, at times, uncontrolled amount of drug loading remains a major disadvantage. Polymerizing the bioactive agent into its respective polymer would lift the limitation, and drug loading in the biomaterial could be controlled via molar ratios chosen for synthesis. Simvastatin is being investigated as the drug for copolymerization due to its pleiotropic properties (*i.e.*, anti-atherosclerotic, osteogenic, anti-inflammatory, and angiogenic)[1] that make it desirable for localized tissue regeneration.

Because simvastatin contains a lactone ring that may be amendable to ring-opening polymerization (ROP), the purpose of this study was to compare two ROP reactions for polymerizing simvastatin. More specifically, usefulness of an anionic ROP reaction was compared to a coordination-insertion reaction. Reactions were evaluated by monitoring the kinetics of monomer conversion to intermediate and copolymer products. Degradation was also assessed.

Materials and Methods

Simvastatin and 5 kDa monomethyl ether poly(ethylene glycol), the monomer and initiator, respectively, were used at a 100 to 1 molar ratio. The components were dried in a microvessel in nitrogen atmosphere before being submerged in a sand bath that kept the temperature of the melt at 150 ºC. The organocatalyst, triazabicyclodecene (TBD), was added, using 1 wt%. Reactions ran through for 24 hr and also underwent kinetic analysis at 0, 4, 15, and 24 hr. The same reaction conditions were used with stannous octoate at 150 and 200 ºC with analysis at 0, 4, 8, 12, 18, and 24 hr. Molecular weight (MW) and percent conversions were analyzed via gel permeation chromatography (GPC). In a pilot degradation study, the product was dissolved in dichloromethane, pipetted onto Teflon, and dried to form pellets. The pellets were put in 1 M NaOH (aq) to accelerate hydrolysis for 2 d before medium removal. The remaining product was analyzed via GPC and ultraviolet (UV) spectroscopy.

Results and Discussion

At 150 ºC, TBD polymerized a 31 kDa copolymer in 24 hr, as opposed to 9.5 kDa by stannous octoate. Stannous octoate required a higher temperature of 200 ºC to synthesize a 13 kDa copolymer. TBD was easily able to achieve the same MW at 150 ºC. As a result, stannous octoate converted simvastatin to intermediate products at a higher rate and produced more intermediates than polymer at a higher percentage (62%) than TBD. TBD yielded more of the desired product (44%) than intermediates (22%) after 24 hr (Figure 1). GPC analysis showed degradation of the crude copolymer, via TBD, with the MW decreasing from 31.1 to 23.3 kDa (Figure 2). Increased UV absorbance was seen between 220 and 240 nm, the maximum absorbance of simvastatin, within 2 d. No MW degradation was seen for the copolymer formed via stannous octoate.

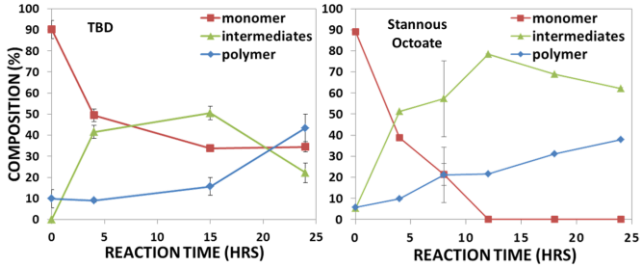

Figure 1: Percent conversion by TBD and stannous octoate

Peak	Mn	Mw	%
initial	28105	31143	9.5779
species 2	3512	6676	47.939
species 1	568	585	15.851
monomer	247	273	26.633
degraded	20990	23332	17.143
species 3	9296	9629	13.091
species 2	3157	3746	27.397
species 1	678	730	19.659
monomer	287	307	22.712

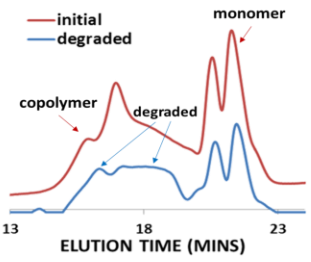

Figure 2: GPC analysis of copolymer degradation

Conclusions

Minimizing the synthesis of intermediates in simvastatin ROP is an important factor for obtaining a higher quality copolymer. Use of TBD catalyst yielded more of the desired product at a lower temperature with less intermediates compared to stannous octoate. Improved reaction control developed a copolymer capable of producing a more predictable degradation profile.

Reference

1. Sparrow C *et. al.* Arterioscler Thromb Vasc Biol. 2001; 21: 115-121.

Acknowledgements

This research was funded in part by the NIH (AR060964-02S1), and TAA was supported by an NSF IGERT fellowship (DGE-0653710).