Analysis of Molecular Weight Growth and Degradation of a Simvastatin Polymeric Prodrug

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

Statement of Purpose

Bioresorbable polymers are currently used to aid in tissue regeneration (e.g. poly (lactic-co-glycolic acid) (PLGA) and poly (lactic acid) (PLA)) due to their biocompatibility, adjustable degradation kinetics, and mechanical strength. However, their role in promoting tissue healing is solely passive through encapsulation of drugs, and/or conjugating drug molecules via linkers to polymer backbones. As a result of passive loading, they can often be limited in the amount of payload they carry. Alternatively, one can develop polymers composed entirely of the active agent, thereby greatly increasing the inherent loading potential. For instance, simvastatin is a well-known hypolipidemic prodrug that possesses osteogenic, anti-inflammatory, and angiogenic properties[1] which prove desirable for a bioactive polymeric drug delivery system. Goals of the present studies were to identify the potential to create a poly (simvastatin) system for controlled release applications. Polymerization conditions were evaluated by monitoring molecular weight (MW) growth of the copolymer at different temperatures while degradation capabilities of the resultant polymers were also assessed.

Materials and Methods

Simvastatin, the monomer, and 5 kDa poly (ethylene glycol) methyl ether (mPEG), the initiator, were dried at a 100 to 1 molar ratio while being purged with nitrogen. The components were heated at 130 °C for 1 hr and then melted at 150, 200, 215, 230, 240, or 250 °C for 1hr before 1 wt% of stannous octoate, dissolved in toluene, was added as catalyst. Reactions continued under nitrogen purge for 24 hrs. Samples of the reaction mixture were taken at increasing time points throughout synthesis. Gel permeation chromatography (GPC) was used to obtain the weight-averaged molecular weight and polydispersity (PDI) of the product throughout the reaction. Infrared spectroscopy (IR) was used to characterize the products functional groups. To demonstrate copolymer hydrolysis, the product was dissolved in EtOH before adding to 0.1 M NaOH (aq) and heated for 2 hrs[2]. Absorbance at 240 nm was measured throughout heating by ultraviolet spectroscopy (UV).

Results

GPC results showed increasing trends of polymer growth onto mPEG as temperature increased (Figure 1). At 150 °C, the temperature used for the initial procedure of copolymer synthesis, showed minimal growth of the poly (simvastatin) block after 24 hrs. Products of polymerization at 200, 215 and 230 °C achieved MWs of 13.6, 31.6, and 23.5 kDa respectively with PDIs of 1.3, 2.6, and 1.9 respectively. The large PDIs may have indicated branching due to the secondary hydroxyl group of simvastatin acting as a second source of initiation. Extended hyperbranching was observed for the high MW final products of reactions at 240 and 250°C with large PDIs of 4.8 and 6.8, respectively. The IR spectrum of the diblock copolymer showed characteristics from both mPEG and simvastatin components, and a carbonyl shift from 1704 to 1722 cm^{-1} which indicated new ester bond formation. In Figure 2, the turbid copolymer solution cleared, and its absorbance decreased in 2 hrs, which indicated at least partial degradation.

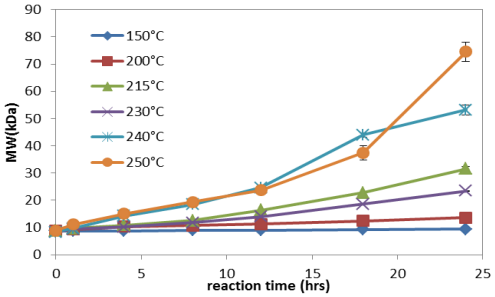

Figure 1. Poly (simvastatin) MW growth on mPEG

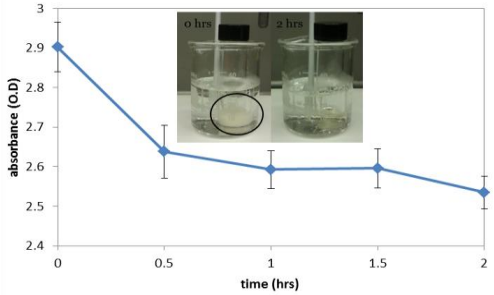

Figure 2. Time course of copolymer hydrolysis

Conclusions

A simvastatin-based copolymer can prove to be a very suitable polymeric drug delivery system for bone growth. Successful MW growth of poly (simvastatin) above 200 °C after 24 hrs and observed copolymer hydrolysis capability showed its potential for increasing the weight percent of simvastatin in the material and degradation. Branching and transesterification reactions causing polydispersity were minimized between 200 and 230 °C. However, polymers obtained with greater polydispersity may prove to be useful for faster copolymer degradation.

References

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Acknowledgements

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