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Biodegradable Simvastatin-Containing Polymeric Prodrugs with Improved Drug Release

A.D. Thilanga Liyanage, Alexander J. Chen, and David A. Puleo*

F. Joseph Halcomb III, M.D. Department of Biomedical Engineering, 522 Robotics and Manufacturing Building, 143 Graham Avenue, University of Kentucky, Lexington, KY, USA

Abstract

Simvastatin was previously converted to a polymeric prodrug with higher drug loading, but the hydrophobic nature of the poly(simvastatin) component of the block copolymer led to slow release of the drug *in vitro*. In this study, we hypothesized that degradation could be accelerated by chemically modifying the polymer backbone by introducing glycolide and lactide comonomers. Copolymers were formed by ring-opening polymerization using 5 kDa monomethyl ether poly(ethylene glycol) as the microinitiator in presence of triazabicyclodecene catalyst. In addition to simvastatin, modified reaction mixtures contained lactide or glycolide. Incorporation of the less hydrophobic glycolide comonomer led to *in vitro* degradation of up to two times greater mass loss, release of up to ~7 times more simvastatin, and a 2–3 times increase in compressive modulus compared to the lactide-containing and parent polymers.

Graphic Abstract

Keywords

Polymeric prodrug; simvastatin; glycolide; controlled release; degradable polymer

*To whom correspondence should be addressed and present address: David Puleo, Ph.D., School of Engineering, P.O. Box 1848, University of Mississippi, University, MS 38677, USA, Tel: +1-915-1105, Fax: +1-915-5387, dpuleo@olemiss.edu.

Conflict of interest

DAP has an equity interest in Regenera Materials, LLC., a start-up company for commercializing novel biomaterials for tissue regeneration.

Introduction

Simvastatin was originally developed to treat high cholesterol levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase in the mevalonate pathway,¹⁻³ but this drug can also promote osteoblastic activity and inhibit osteoclastic activity, both of which are important for bone regeneration.⁴⁻⁹ Our group previously developed and characterized the physical and chemical properties of a simvastatin-containing polymeric prodrug, termed poly(simvastatin), using ring-opening polymerization (ROP).^{10,11} Simvastatin is commonly administered orally, but the higher doses needed to overcome first-pass metabolism can cause adverse muscular and hepatic effects.¹² Polymeric prodrugs enable controlled release of the drug, higher drug loading, enhanced stability, and easier processing.¹³⁻¹⁷ These biodegradable polymeric materials, or polyactives, have their drug moieties covalently bonded into the polymer backbone as monomers or conjugated to the backbone as pendant groups.¹⁸ Wang *et al.* reported synthesis of a linear polyethylene glycol (PEG), sebacic acid, and glycerol containing polyester backbone with ketoprofen side groups.¹⁹ Uhrich's group described preparation of polyesters with ibuprofen and naproxen pendant side groups.¹⁷ In a salicylic acid-containing poly(anhydride-ester), the bioactive salicylic acid moiety was chemically modified into a polymer precursor and incorporated into the polymer backbone.²⁰

In our previous work, the open ring form of simvastatin served as the monomer in the resulting polymer backbone.^{10,11} Simvastatin release was highly dependent on the monomethyl ether poly(ethylene glycol) (mPEG) initiator incorporated into the polymer backbone. The hydrophobic nature of the prodrug component of the block copolymer, however, resulted in slow release of simvastatin *in vitro*. Degradation of poly(simvastatin) is caused by the cleavage of hydrolytically labile ester bonds throughout the polymer chain. Introducing hydrophilic comonomers to increase polymer hydrophilicity is a popular approach used in the literature. The classic example is poly(lactic-co-glycolic acid) (PLGA) for which the degradation profile can be controlled by simply increasing the glycolic acid content, which renders the polymer more hydrophilic and thereby results in faster degradation rates.²¹ Ng *et al.* used glycolic acid dimer to improve the hydrolysis of ortho ester linkages without any acidic excipients.²² Copolymerization with poly(ethylene glycol) accelerates the degradation kinetics of the crystalline hydrophobic polymers poly(caprolactone) (PCL) and poly(D,L-lactic acid) (PLA).^{23,24}

The objective of the present study was to increase ability of poly(simvastatin) block copolymers to interact with water molecules to facilitate hydrolysis. Rather than introducing these moieties as pendant groups, they were incorporated directly into the existing polymer backbone as comonomers.^{25,26} In particular, glycolide and lactide were used as comonomers because of their compatibility with the ROP scheme used to synthesize poly(simvastatin). We hypothesized that these comonomers will randomly distribute in the parent polymer backbone to disrupt blocks of simvastatin monomers (Figure 1).

Experimental

Materials

All glassware was oven-dried before use and cooled under a constant stream of dry nitrogen. Simvastatin was purchased from Haorui Pharma-Chem (Edison, NJ). D,L-Lactide, triazabicyclodecene (TBD), 5 kDa monomethyl ether poly(ethylene glycol) (mPEG), anhydrous diethyl ether, dichloromethane (DCM), and deuterated chloroform (CDCl₃) were obtained from Sigma-Aldrich (St. Louis, MO). Tetrahydrofuran (THF) stabilized with 3,5-di-tertbutyl-4-hydroxytoluene (BHT) was purchased from Fisher Scientific (Pittsburgh, PA). Glycolide was obtained from Polysciences, Inc (Warrington, PA). Polystyrene Medium EasiVials (2 mL) purchased from Agilent (Santa Clara, CA) were used as the GPC standards.

Polymer synthesis

All polymers were prepared in a dry nitrogen environment following the previously published procedure.¹⁰ Briefly, copolymers were formed by ROP using 5 kDa mPEG as the microinitiator in the presence of TBD catalyst. In addition to simvastatin, modified reaction mixtures contained lactide or glycolide. For all polymerization reactions, the amounts of reagents were calculated with respect to mPEG(5k), which was kept as 1 eq. Briefly, simvastatin (100 eq) and mPEG (1 eq) were added to an oven-dried pressure vessel and sealed with a rubber septum. This was transferred to a preheated oil bath and maintained at 140 °C under continuous flow of nitrogen for 2 hours to remove moisture, after which the temperature was increased to 160 °C for 1 hour. To this homogeneous melt, 1 wt% (relative to the total weight of simvastatin and mPEG) of TBD catalyst was added. In modified reactions, glycolide or lactide (20 or 40 eq) was slowly added following the TBD catalyst. After complete addition of reactants, the rubber septum was removed, the vessel sealed with a Teflon screw cap, and the final temperature increased to 175 °C with constant stirring. Polymer reactions were terminated when the desired molecular weights were obtained. Polymers were purified by re-dissolving in DCM (1 g/mL) and precipitating two times in an excess of cold diethyl ether under vigorous stirring before being dried under vacuum and stored in a desiccator until used. The reactions showed yields around 40–45% with respect to the incorporated starting materials.

For simplicity the parent poly(ethylene glycol(5k))-*block*-poly(simvastatin) polymer is denoted by “PSim”. The lactide- and glycolide-containing modified versions are denoted by “PSimL” and “PSimG”, respectively. Depending on the equivalent amount of comonomer added to the reaction mixture, the polymer was designated as PSimL20/PSimL40 or PSimG20/PSimG40 indicating 20 eq or 40 eq of lactide or glycolide added to the reaction mixture with respect to the mPEG(5k).

Physicochemical characterization

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 number average (M_n) and weight average (M_w) molecular weights of polymeric prodrugs. 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 1 mg/mL and injected using THF as the mobile phase at a 1.0 mL/min flow rate at 40 °C. The polystyrene standards used to calculate molecular weight ranged from 162 Da to 364 kDa.

Nuclear magnetic resonance (NMR) spectroscopy—¹H NMR spectra were recorded using a Varian INOVA 400 MHz spectrometer and analyzed using MestReNova (version: 6.0.2–5475). Chemical shifts were determined relative to the CDCl₃ residual proton signal that appeared at 7.24 ppm. To deduce the structural composition, all peaks were integrated relative to the -OCH₃ protons signal in the mPEG(5k) unit, which appeared around 3.35 ppm.

Differential scanning calorimetry (DSC)—DSC analysis was conducted using a TA Instrument Model No. DSC Q100. Samples (~5 mg) were heated from –20 °C to 200 °C at a rate of 10 °C/min under nitrogen purge. Results were analyzed using TA universal analysis software. The first heating and cooling scans were used in this study. The thermograms are not shown because all four polymers tested did not show any distinct thermal transitions.

Powder X-ray diffraction (XRD)—Polymer powder was obtained after sieving via 100 µm filter and analyzed using a Siemens D500 Diffractometer to determine the relative of crystallinity of the copolymers. A 2θ angle range of 20° to 60° was used for measurement at a rate of 1°/min. Diffraction was performed at 30 mA and 40 kV. A VisxDACO software interface was used to obtain and analyze data. None of polymers synthesized exhibited distinctive peaks, indicating their amorphous nature (results not shown).

In vitro degradation and drug release—*In vitro* drug release was determined using small prodrug pellets (~15 mg) prepared by solvent casting polymer solution (600 mg/mL) on a Teflon sheet. These pellets were incubated in phosphate-buffered saline (PBS), pH 7.4, under continuous shaking at 37°C. The supernatant was collected and the medium was completely replaced by fresh PBS at pre-determined time points. After the degradation study, the remaining samples were dried and weighed to measure the mass remaining. Degradation was expressed as the percentage of mass remaining, $\{1 - (M_t/M_0)\} \times 100$.

A Shimadzu Prominence LC-20 AB HPLC system was used to analyze the supernatants collected from the degradation study. One Luna C18 column (150 × 4.60 mm, 5 µm particle size) was used with an isocratic mobile phase of acetonitrile and water containing 0.1% trifluoroacetic acid (70:30 v/v) with a flow rate of 1.0 mL/min. Absorbance was measured at 238 nm. Simvastatin standards were prepared by dissolving simvastatin in an ethanol/PBS (1:1 v/v) solvent mixture. Therefore, to ensure solubility, supernatants were diluted with ethanol to also have an ethanol/PBS ratio of 1:1 v/v.

Mechanical testing—Compression testing was performed using a Bose Electroforce 3300 mechanical testing system. Polymer disks (height 4 mm, diameter 6 mm, weight 100 mg) were prepared by compressing finely ground polymer powder under 6,000 pounds for 5 min using a Carver press. After removal from the dye, samples were incubated at 30 °C for 24 hr and subsequently at 60 °C for another 24 hr. Uniaxial compression tests were run at 5 µm/s until failure. Compressive modulus was calculated from the load-displacement data and

physical dimensions of the samples. The modulus was determined from the slope of the initial linear elastic region of each curve.

Statistical Analysis—Analysis of variance (ANOVA) was performed to test for significant differences in drug release, mass loss, and compressive modulus between polymers. If the ANOVA test results were significant, post-hoc analysis was conducted using multiple pairwise comparison with the Bonferroni adjustment. Values of $p < 0.05$ were deemed statistically significant.

Results

Molecular weight analysis

^1H NMR spectra were used to determine the relative chemical compositions of the polymers and to estimate the average number of repeating units per polymer chain or the number average molecular weight (M_n) through end group analysis. To deduce the structural composition, all peaks were integrated relative to the $-\text{OCH}_3$ protons signal in the mPEG(5k) unit denoted as letter “h” (Figure 2). The alphabetical letters assigned for the corresponding protons are the same as in our previous report on this polymer system.¹⁰ In this NMR characterization, we assumed the polymers had linear structure and similar relaxation delays.²⁷ The number of simvastatin units in the polymer backbone was calculated using the corresponding integration ratio of mPEG(5k) methoxy ($-\text{OCH}_3$) protons to the summation of “r+s” protons, which represented the high field $-\text{CH}_3$ groups in the simvastatin block.²⁸ In lactide-containing copolymers, it was difficult to assign any signals corresponding to the lactide monomer because proton signals corresponding to lactide peaks were overlapped by simvastatin proton signals. Lactide protons of methyl and methylene normally appear around 1.57 and 5.16 ppm, respectively. Due to this, the relative amount of lactide incorporated in the polymer backbone could not be readily calculated. With the glycolide copolymers, the methylene protons appeared in the 4.60–4.90 ppm range,²⁹ which was not overshadowed by corresponding simvastatin protons. Consequently, using this proton signal denoted by the letter “z”, we were able to estimate the number of glycolide monomers incorporated in the polymer backbone. According to the ^1H NMR estimation, the parent polymer PSim had 22 simvastatin units and the 20 eq. lactide copolymer PSimL20 had 21 simvastatin units (Figure 2). The 20 and 40 eq. glycolide copolymers, PSimG20 and PSimG40, showed 21 and 29 simvastatin units and 14 and 26 glycolide units, respectively (Figure 2). Compared to PSimG20, the proton signal of PSimG40 corresponding to the glycolide monomer was relatively broader.

Using these values, M_n were deduced from the ^1H NMR estimations. For our calculations, we assumed the molecular weight (M_n) of the mPEG unit as 5000 g/mol, each simvastatin repeating unit in the polymer backbone as 418 g/mol, and the glycolide repeating unit as 116 g/mol. These yielded M_n of 14 kDa for PSim, 15 kDa for PSimG20, and 20 kDa for PSimG40. Because the number of lactide monomers in the polymer backbone could not be determined from ^1H NMR, we did not estimate the M_n for PSimL20.

Polymer molecular weights estimated from GPC are shown in Figure 3. The M_w of PSim, PSimL20, PSimG20, and PSimG40 were 25, 21, 20, and 22 kDa, respectively. All four

polymers showed a polydispersity index of approximately 1.6. For PSim, the M_n estimated by GPC (15kDa) was in good agreement with that estimated from ^1H NMR (14 KDa). For both glycolide copolymers, the ^1H NMR estimated M_n (15 kDa for PSimG20 and 20 kDa for PSimG40) were higher compared to the molecular weights estimated by GPC (12 kDa and 13 kDa, respectively). Although our microinitiator mPEG(5k) had an estimated molecular weight of 5 kDa, GPC analysis indicated M_n of 7 kDa and M_w of 7.8 kDa. Using the GPC calculated PSim M_w , we estimated 41 simvastatin monomers attached within the parent polymer backbone by deducting the M_w value of mPEG to provide the molecular weight of the poly(simvastatin) block, which could then be divided by the molecular weight of simvastatin.

***In vitro* degradation and drug release**

PSimG40 showed a burst release of $\sim 1.5\ \mu\text{g}$ of simvastatin in the first 24 hr, whereas the other polymers exhibited lower or negligible burst (Figure 4a). Maximal release occurred for the two glycolide-containing copolymers by day 7, after which release decreased. This was more prominent for the higher glycolide copolymer. The lactide copolymer, PSimL20, and parent polymer, PSim, both released their maximum amount of simvastatin, $\sim 1\ \mu\text{g}$, on day 5, after which release was sustained throughout the 38 day study.

All polymers synthesized showed two distinct kinetic behaviors corresponding to the two phases (biphasic) observed in the instantaneous profiles (Figure 4a). The parent polymer PSim released only $\sim 0.3\ \mu\text{g/d}$ during the first 13 days and $\sim 0.2\ \mu\text{g/d}$ between days 13 to 38. PSimL20 showed a slight improvement compared to the parent polymer PSim, releasing $\sim 0.4\ \mu\text{g/d}$ during the first 13 days and $\sim 0.2\ \mu\text{g/d}$ between days 13 to 38. PSimG40 released simvastatin at $\sim 2.3\ \mu\text{g/d}$ during the first 13 days but only $\sim 0.7\ \mu\text{g/d}$ between days 13 to 38, and PSimG20 $\sim 0.8\ \mu\text{g/d}$ during the first 13 days but $\sim 0.2\ \mu\text{g/d}$ between days 13 to 38.

As reflected in the cumulative release profiles (Figure 4b), cumulative amounts of 6.7, 8.5, 16.2, and $48.2\ \mu\text{g}$ of simvastatin were released from PSim, PSimL20, PSimG20, and PSimG40, respectively. Compared to the parent polymer PSim, the modified glycolide copolymers of PSimG20 and PSimG40 released 2.4 and 7.2 times more simvastatin during this time period. Cumulative drug release from the variant polymers, PSimG20 and PSimG40, was significantly different from the parent polymer PSim ($p < 0.05$), but release from PSim and PSimL20 was similar. Cumulative release was also significantly different between PSimG40 and PSimG20 ($p < 0.05$).

During the 38 days of our study, an average total mass loss of 17, 18, 24, and 30% occurred for PSim, PSimL20, PSimG20 and PSimG40, respectively (Figure 5). There was a significant difference in mass loss between the parent polymer PSim and the variant polymers PSimG20 and PSimG40 ($p < 0.05$) but no significant difference between PSimL20. Both PSimG20 and PSimG40 showed significantly greater mass loss compared to PSimL20 ($p < 0.05$).

Mechanical Testing

The parent polymer PSim had the lowest compressive modulus and PSimG40 the highest, with PSimL20 and PSimG20 having intermediate values (Figure 6). Comparing PSimG20

and PSimG40, doubling the glycolide content in the polymer backbone resulted in a modulus approximately two times larger. There was a significant difference in compressive modulus between PSim and both glycolide copolymers PSimG20 and PSimG40 ($p < 0.05$). Also, the compressive modulus of PSimG40 was significantly larger than that for the other two copolymers PSimG20 and PSimL20 ($p < 0.05$). The compressive moduli of PSimL20 and PSimG20 were statistically similar.

Discussion

As happens with other polyesters, degradation of poly(simvastatin) copolymers occurs via cleavage of the hydrolytically labile ester bonds. The hydrophobic nature of the prodrug component of the block copolymer, however, leads to slow release of simvastatin.^{10,11} In present study, we accelerated degradation by chemically modifying the polymer backbone by introducing relatively more hydrophilic (i.e., less hydrophobic) glycolide and lactide comonomers. Degradation of the polymer backbone highly depends on the chemistry of the polymer backbone and can be tuned by careful choice of monomers.³⁰ For example, reactivity of the extremely slow-degrading PCL was improved by modifying the polymer backbone with PLGA and PLA.^{31,32}

Compared to lactide and simvastatin, glycolide is expected to be more reactive in ROP due to less steric crowding.^{33,34} When considering this effect, the monomers used would show the order of reactivity as glycolide > lactide > simvastatin. At the beginning of polymerization, more reactive monomer will be incorporated into the polymer backbone at the expense of the less reactive monomer. Consequently, the concentration of more reactive monomer in the reaction mixture (in our case, lactide or glycolide) decreases more quickly than that of the less reactive simvastatin.³³ Because simvastatin is less reactive, it was introduced into the reaction mixture at higher concentration compared to the comonomers (100 eq) to yield a higher probability for incorporating simvastatin units into the initial polymer backbone. After consumption of the highly reactive monomer (lactide or glycolide), chain growth would result from addition of simvastatin units. Figure 7 schematically illustrates the predicted monomer arrangement in the polymer chains.

Although glycolide is far more reactive than lactide in ROP,³⁵ all of the glycolide monomers in the reaction mixture were not incorporated into the main polymeric chain. According to the ¹H NMR estimation for PSimG20, even though 20 units of glycolide were added to the reaction mixture, the polymer backbone contained only 14 units. When we doubled the glycolide content in the polymer reaction mixture (40 units), the PSimG40 polymer backbone contained only 26 units, roughly double the glycolide content in PSimG20. One explanation is that the highly reactive glycolide monomers initiated several low molecular weight oligomers that were removed in our extensive purification steps. Further, compared to PSimG20, the proton signal corresponding to the glycolide monomer in PSimG40 was relatively broad, which may be due to the more scattered distribution of glycolide monomers in the parent polymer backbone creating relatively different chemical environments. In contrast, PSimG20 may have had more localized distribution of glycolide content (Figure 7), resulting in relatively narrow ¹H NMR signal.

We were able to estimate the M_n of the PSim and PSimG polymers from both ^1H NMR and GPC. Values for PSim and PSimG20 were in good agreement to the two estimates, but for PSimG40, the GPC estimated M_n (13 kDa) was lower compared to that from ^1H NMR (20 kDa). The latter difference may be due to the overestimated integrals due to the signal overlapped and non-uniform base line. Broadness of the signals due to overlap and the non-uniform baseline created some ambiguity during integration, meaning M_n values calculated from ^1H NMR were rough estimates. Additionally, these estimations are true only for linear polymers, but the presence of additional hydroxyl groups in simvastatin may lead to side reactions and branched structures. The ^1H NMR estimations relied on assumptions of a linear polymer backbone and all protons in the polymer backbone having similar chemical environment to result in similar relaxation times. Again, it is unclear whether these copolymers are truly linear, and the chemical environment of the monomers can be drastically different depending on the monomer distribution (e.g., Figure 7). We have previously conducted kinetics studies,^{10,11} and will carry out others in the future, but elucidating the detailed structure of these molecules is challenging.

As predicted, both glycolide-containing copolymers showed improved simvastatin release compared to the parent polymer. Furthermore, doubling the number of glycolide monomers (i.e., PSimG20 vs. PSimG40) enabled water molecules to penetrate the polymer more readily and thereby facilitate ester hydrolysis. According to the literature, increasing the glycolic acid portion of PLGA renders the polymer more hydrophilic and thereby results in faster degradation rates.³⁶ This is also reflected in the rapid simvastatin release observed for PSimG40 compared to PSimG20. According to the ^1H NMR, compared to PSimG20, PSimG40 showed a broader glycolide signal. This may be due to the higher number of glycolide comonomers randomly clustered along the polymer backbone (e.g., Figure 7), which would enhance water intake, hydrolysis, and simvastatin release. After the clustered glycolide segments are broken down, the simvastatin-containing polymer backbone again becomes more hydrophobic, similar to the parent polymer, thereby reducing simvastatin release. Additionally, the high content of glycolide in the polymer backbone can eventually generate more glycolic acid due to the hydrolysis, which will autocatalyze the hydrolysis of ester linkages in the polymer backbone. Hydrolysis of the ester bond within the simvastatin block itself cannot be ruled out. This will be limited, however, due to the steric crowding caused by the adjacent six-membered ring and the two methyl groups, which will shield the ester bond in simvastatin. In contrast, ester linkages in the glycolide or lactide comonomer portions are readily accessible for protons to induce hydrolysis. Regardless, side products due to the hydrolysis of simvastatin can be generated. This may be a reason for low molecular weight peaks in some polymers. Both PSim and the lactide-containing copolymer, PSimL20, showed similar simvastatin release profiles, with PSimL20 finally releasing 8.5 μg of simvastatin compared to 6.7 μg for PSim. Since all of the poly(simvastatin) copolymers synthesized had similar molecular weights, the resulting simvastatin release was intrinsic to the comonomers introduced into the polymer backbone.

Incorporation of lactide and glycolide comonomers improved the mechanical properties, i.e., increased the compressive modulus, compared to the parent polymer PSim. Compression of all of these copolymers containing significant hydrophobic blocks leads to increased intra- and intermolecular repulsion. Differences with the lactide and glycolide copolymers,

however, may be due to hydrogen bonding between the carbonyl of lactide and glycolide comonomers and the hydroxyl group of simvastatin (Figure 8).³⁷ Increasing the comonomer content increased the number of hydrogen bonding sites. Both PSimG20 and PSimL20 had comparable compressive modulus but increasing (doubling) the glycolide content from PSimG20 to PSimG40 doubled the modulus. The higher glycolide content leads to increased intra- and intermolecular stabilization by hydrogen bonding in the uncompressed state, which provides greater resistance to deformation during mechanical testing. Improvement of compressive modulus in the presence of H-bonding is well documented in current literature.^{38,39} For example, the higher compressive modulus of poly(p-phenylene terephthalamide) (PPTA) is attributed to sheet-like hydrogen bonding,^{40,41} and a bidirectional network of hydrogen bonds leads to the properties of poly{2,6-diimidazo[4,5-b:4'5'-e]pyridinylene-1,4(2,5-dihydroxy)phenylene} (PIPD).^{42, 43}

Conclusion

In present study, release of simvastatin from a polyactive was improved by chemically modifying the polymer backbone using more hydrophilic comonomers. When we incorporated 40 eq or 20 eq of glycolide into the initial reaction mixture, the resulting polymer released 7.2 or 2.4 times more simvastatin, respectively, compared to the parent polymer. The more hydrophobic lactide-containing copolymer did not show significant improvement in simvastatin release. Rather than being homogeneously distributed along the polymer backbone, comonomers likely were clustered, resulting in biphasic release kinetics (i.e., faster in comonomer regions and slower in simvastatin regions). Overall, properties of the copolymers were intrinsic to the amount of comonomers incorporated into the polymer backbone. Future studies will investigate the effects of release kinetics on poly(simvastatin)-stimulated bone formation.

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Figure 1.

Proposed chemical structures of poly(ethylene glycol(5k))-*block*-poly(simvastatin) (left) and poly(ethylene glycol(5k))-*block*-poly(simvastatin)-*ran*-poly(lactide/glycolide) (right).

Figure 2.

¹H NMR spectra of poly(simvastatin) copolymers in CDCl₃ at room temperature: a) PSim, b) PSimL20, c) PSimG20, and d) PSimG40. (# ; residual dichloromethane)

Figure 3.
GPC chromatograms of poly(simvastatin) copolymers with their respective M_n and M_w shown.

Figure 4.
 (a) Instantaneous and (b) cumulative release of simvastatin from poly(simvastatin) copolymers during incubation in PBS, pH 7.4. Data are mean $\pm$ standard deviation (n=3).

Figure 5. Percentage mass remaining after incubation of poly(simvastatin) copolymers in PBS, pH 7.4, for 38 days. Data are mean $\pm$ standard deviation (n=3).

Figure 6. Compressive modulus of poly(simvastatin) copolymers. Data are mean $\pm$ standard deviation (n=3).

Figure 7. Schematic representations of glycolide-containing poly(simvastatin) block copolymers. The higher reactivity of glycolide compared to simvastatin leads to mPEG(5k) initially reacting with glycolide. Further, a larger content of glycolide in the reaction mixture for PSimG40 results in a more random distribution throughout the chain as glycolide and simvastatin compete for incorporation into the backbone.

R: -CH₃ for lactide copolymer (PSimL); R: -H for glycolide copolymer (PSimG)

Figure 8.

Schematic illustration of possible packing arrangement of glycolide- or lactide-containing poly(simvastatin) copolymers. Red dashed lines represent hydrogen bonding between polymer backbones.