JOURNAL OF Applied Polymer SCIENCE

Effect of Drug Loading and Laser Surface Melting on Drug Release Profile from Biodegradable Polymer

Shan-Ting Hsu, Y. Lawrence Yao
Department of Mechanical Engineering, Columbia University, New York, NY
Correspondence to: S-T Hsu (E-mail: sh2852@columbia.edu)

ABSTRACT: The biodegradable polymer such as poly(L-lactic acid) is promising in drug delivery applications because it allows for drug release in a controlled manner. In a polymer-based drug delivery system, drug release is controlled by polymer degradation and drug loading concentration. In this study, effect of drug concentration on drug release profile is investigated through polymer crystallinity, chain mobility, and polymer degradation, as characterized by the wide-angle X-ray diffraction, differential scanning calorimetry, and gel permeation chromatography, respectively. The addition of drug has been shown to accelerate polymer degradation and drug release rate. With a low drug concentration, the slow polymer degradation kinetics results in an induction period of drug release, during which a limited amount of drug is released. The induction period is undesirable because it delays drug release and effectiveness. Since drug release is controlled by polymer degradation, which is a function of polymer crystallinity, laser surface melting is conducted to reduce polymer surface crystallinity and modify its degradation. The effect of laser crystallinity modification on drug release is investigated. A numerical model is also implemented based on hydrolysis and diffusion mechanisms to investigate the effects of drug loading and laser surface melting on polymer degradation and drug release process. It has been demonstrated that laser treatment shortens the induction period of drug release while keeps the release rate unmodified, as desired in drug delivery applications.
 J. Appl. Polym. Sci. 130: 4147–4156, 2013

KEYWORDS: biodegradable polymer; biomedical applications; drug delivery; laser irradiation; surface treatment

Received 25 February 2013; accepted 1 June 2013; Published online 12 July 2013
DOI: 10.1002/app.39664

INTRODUCTION

Poly(lactic acid) (PLA) is of interest in drug delivery applications due to its biocompatible and biodegradable properties. In such applications, drug molecules are embedded in a polymer matrix and released into the human body, with release profiles controlled by polymer degradation. The advantages of using biodegradable polymers for drug delivery are demonstrated by the controlled drug release over time. With controlled release, drug concentration in the human body is stably maintained within the effective level.[1] The prolonged drug effective period reduces drug taking frequency and improves the life quality of patients.

In a physiological environment, PLA degradation occurs via hydrolysis, in which water breaks the ester bonds in PLA, leading to chain scission and producing shorter chains with carboxylic (—COOH) groups and alcohol (—OH). Hydrolysis rate is proportional to molar concentrations of water molecules and ester bonds.[2] Hydrolysis may become autocatalytic if carboxylic end groups remain in the bulk. During autocatalyzed hydrolysis, the reaction rate depends on the concentration of carboxylic end groups as well.[3] PLA hydrolysis is also affected by crystallinity, because water molecules are readily accommodated in the amorphous region, while hardly in the crystalline region with highly packed and densely ordered structures.[4] A higher water concentration increases hydrolysis rate, which is, therefore, higher in the amorphous region.[5] The slow degradation kinetics of crystalline PLA leads to an induction period of drug release, during which a limited amount of drug is released. The induction period is undesirable because it delays drug release and effectiveness. Since PLA degradation is a function of crystallinity, laser melting has been conducted on PLA surface to reduce its crystallinity, as an attempt to modify its degradation.[6] With a reduced surface crystallinity, PLA degrades faster and experiences a shorter time period before mass loss.[7] The results demonstrate the potentiality to shorten the induction period of drug release through laser crystallinity modification.

Drugs are typically small molecules. Blending of small molecules into polymer increases chain mobility because small molecules

Additional Supporting Information may be found in the online version of this article.

render extra free volume between chains, known as plasticization.[8] Plasticization leads to a reduced glass transition temperature (T_g) and melting temperature (T_m).[9,10] Plasticization also increases PLA crystallinity, because mobile chains are easy to reorganize themselves to an ordered state.[11] PLA with higher crystallinity exhibits a slower degradation, which in turn slows down drug release. The combined effects of modified chain mobility and crystallinity by drug loading on drug release are not clear and require further investigation.

In addition to polymer degradation, drug is also released during the initial burst period. A mechanism of initial burst is the rapid dissolution of the drug molecules near the polymer matrix surfaces.[12] The drugs on surfaces are quickly dissolved into the release medium, leaving behind a vacant space with no polymer molecules. The vacant space can connect with each other, forming channels which allow for further drug diffusion into the release medium.[13] This process leads to the initial burst release, and has less correlation with polymer degradation. As drug releases, water molecules will diffuse into the matrix. Since water concentration determines the hydrolysis rate, water diffusion into the polymer matrix is expected to affect polymer degradation. It has been pointed out that, drug release profile is composed of up to four phases: initial burst, induction period, degradation controlled release, and terminal release phase.[14] On immersion into the release medium, the polymer matrix begins to be hydrated by the surrounding liquid environment, leading to the initial burst, phase 1. After phase 1, drug release is then controlled by polymer degradation. Before polymer chains degrade into chain segments with molecular weights small enough, drugs are held in the polymer matrix and cannot release, which accounts for the induction period as demonstrated in phase 2. Once chain segments with small enough molecular weights are formed, drugs can be released, as observed in phase 3. By the end of the release period, release occurs at a reduced rate, phase 4, as a result of longer diffusion path length of the drug located in the bulk center.

Accordingly, drug release from a polymer system is complicated by multiple factors, including polymer crystallinity, polymer mobility modified by drug loading, and the vacant space left behind after drug release. Investigation of the combined effects is prerequisite to better control the drug release profiles. By considering these combined effects, the objective of this work is to investigate the effects of drug loading on polymer degradation and drug release, as well as the modification of drug release profiles through laser surface melting. Polymer degradation is characterized by the molecular weight of polymer matrix measured from the gel permeation chromatography (GPC). Effect of drug loading on polymer matrix is characterized by its crystallinity and thermal properties from the wide-angle X-ray diffraction (WAXD) and differential scanning calorimetry (DSC). The amount of drug release in a release medium is determined by spectrophotometry. A numerical model is developed to capture polymer degradation and drug release processes.

NUMERICAL MODEL

Simulation is conducted to investigate the effect of drug loading and laser treatment on polymer degradation and drug release profiles. Laser energy absorbed by PLLA generates heat and is governed by the heat equation.[6,7] The process of polymer degradation and drug release is captured by a phenomenological model. In the model, PLLA matrix is assumed to be composed of nine species: nondegraded amorphous chains, degraded amorphous chains in stages 1, 2, and 3, crystalline chains, degraded crystalline chains, monomers, water molecules, and drug molecules, with details given in literature.[7,15]

Degradation of amorphous and crystalline chains is considered separately. During degradation, the concentration of nondegraded amorphous chain is expressed as

$$\frac{dC_0}{dt} = -\gamma_0 C_0 C_w - \gamma_0 C_0 C_w C_m^n - \kappa_0 \frac{dC_c}{dt} \tag{1}$$

where C_0, C_c, and C_w are the molar concentrations of monomers in the nondegraded amorphous chains, nondegraded crystalline chains, and water molecules, respectively. The dissociation of the acid end groups n is assumed to be unity. Values of γ_0, ε_0, and κ_0 are the phenomenological rate constants, accounting for non-autocatalysis, autocatalysis, and crystallization due to hydrolysis of nondegraded amorphous chains. Degradation of amorphous chains experiences three stages before monomers are generated.[16] The concentration of monomers in each stage is expressed as

$$\frac{dC_i}{dt} = \left(\gamma_{i-1} + \varepsilon_{i-1} C_m^n\right) C_{i-1} C_w - \left(\gamma_i + \varepsilon_i C_m^n\right) C_i C_w - \kappa_i \frac{dC_c}{dt} \tag{2}$$

where $i = 1$, 2, and 3, representing degradation stages 1, 2, and 3. C_i is the molar concentration of the monomers in stage *i*. γ_i, ε_i, and κ_i are the phenomenological rate constants accounting for non-autocatalysis, autocatalysis, and crystallization in stage *i*. Hydrolysis of stage 3 generates monomers which have high mobility to diffuse. Assuming Fick's second law for monomer diffusion, which predicts the change of monomer concentration with space and time, the molar concentration C_m of the monomers with high mobility is modeled by

$$\frac{dC_m}{dt} = \left(\gamma_3 + \varepsilon_3 C_m^n\right) C_3 C_w + \nabla \cdot \left(D_{m,\mathrm{eff}} \nabla C_m\right) \tag{3}$$

where $D_{m,\mathrm{eff}}$ is the effective monomer diffusivity as a function of matrix porosity induced by degradation. The pores are defined as regions in a polymer matrix with a molecular weight low enough to allow drug to release. $D_{m,\mathrm{eff}}$ is then expressed as $D_{m,\mathrm{eff}} = D_m \varepsilon(r, z, t)$ where D_m is the monomer diffusivity via pores, and $\varepsilon(r,z,t)$ is the matrix porosity from 0 to 1. Assuming the molecular weights which form the pores follow a normal distribution, $\varepsilon(r,z,t)$ is given as[17]

$$\varepsilon(r, z, t) = 1 - \frac{1}{2}\left[\mathrm{erf}\left(\frac{M_w(r, z, t) - M_{\mathrm{wp}}}{\sqrt{2\sigma^2}}\right) + 1\right] \tag{4}$$

where σ^2 accounts for the variation of degradation. $M_w(r,z,t)$ is the molecular weight at location (r,z) and time t. M_{wp} is the average molecular weight at which pores start to form, allowing the diffusion of small molecules such as monomers and drug molecules.

Degradation of crystalline chains is assumed to be a one-step process, in which chain scission only occurs on the fold surfaces

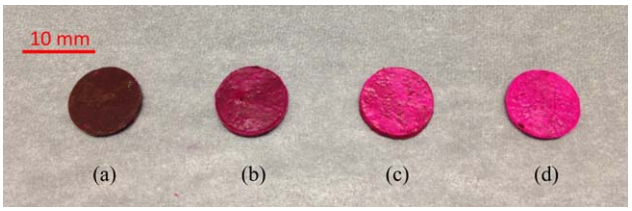

Figure 1. Non-laser treated PLLA matrices loaded with 5% drug (a) before degradation and drug release, and degraded and released for (b) 35, (c) 49, (d) 70 days. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of lamellae, generating the crystalline region composed of the integral folds the crystalline chains. Crystal degradation is thus given as

$$\frac{dC_c}{dt} = (\kappa_0 + \kappa_i)\frac{dC_c}{dt} - \gamma_c C_c C_w - \varepsilon_c C_c C_w C_m^n \quad (5)$$

where $(\kappa_0 + \kappa_i)$, γ_c, and ε_c are the phenomenological rate constants accounting for crystallization of amorphous chains during their degradation, non-autocatalysis, and autocatalysis of crystalline chains, respectively.

Drug concentration within a matrix during polymer degradation is as a function of space (r,z) and time t, and is calculated from Fick's second law as[18]

$$\frac{\partial C_d(r,z,t)}{\partial t} = \nabla\left(D_{d,\text{eff}}\nabla C_d\right) \quad (6)$$

where C_d is the concentration of drug molecules, $D_{d,\text{eff}}$ is the effective diffusivity accounting for the porosity during polymer degradation and drug release period.

Drug molecules located in the layer below matrix surface are subjected to initial burst. The layer accounting for initial burst is thicker for higher drug loading concentration. It is assumed that in the layer from the matrix surface S to a depth of $S-d_{ib}$, drug is subject to initial burst and the matrix porosity ε is unity. In the bulk from matrix center to $S-d_{ib}$, drug release is a function of porosity generated by polymer degradation, such that $D_{d,\text{eff}} = D_d\varepsilon(r,z,t)$ where D_d is drug diffusivity via pores, and $\varepsilon(r,z,t)$ is the matrix porosity from 0 to 1 as expressed in eq. (4). Due to fast water diffusion into PLLA matrix as compared to the slow PLLA hydrolysis kinetics,[19] water concentration, C_w, is assumed to be saturated over the degradation and drug release period, and loss of monomer and drug is replaced by water molecules in simulation.

Solutions of thermal analysis are used as the initial conditions to solve the coupled eqs. (1–5) to capture degradation profiles. Release of embedded drug is simulated based on eq. (6). Appropriate units are used for the phenomenological rate constants so that concentration change is expressed in mole per volume per time. Rate constants are selected to capture experimental results. The equations are solved through the finite element method in a two-dimensional axisymmetric model using COMSOL Multiphysics 4.1. In the spatial domain, the 1 mm by 5 mm matrix is immersed in a 10 mm by 10 mm aqueous medium. Laser treated area covers both sides of the matrix domain, which is initially composed of drug molecules, nondegraded crystalline and amorphous chains with crystallinity determined experimentally. Monomers generated during degradation diffuse into the surrounding medium. The simulation time domain corresponds to experiment time span.

MATERIALS AND METHODS

PLLA granules from PURAC were used as received. Rhodamine B (RB) from Sigma Aldrich was used as the model drug. To assure homogeneous drug loading, RB was loaded into PLLA by solvent casting. Two grams of PLLA granules were dissolved in 45 mL dichloromethane by sonication for 1.5 h. During sonication, 20, 100, 200, and 400 mg RB powder was dissolved in the PLLA solution to prepare 1%, 5%, 10%, and 20% drug concentrations, respectively. The solution was cast in a covered Petri dish at 25°C for 72 h, and a drug loaded PLLA film was left behind. One hundred milligrams of the film was thermally compressed under 5.7×10^4 Pa at 185°C for 1 h, and cooled down in air. The cooling process lasts for around 2 h to reach room temperature, allowing for polymer crystallization. Sample crystallinity and thermal properties were determined by WAXD and DSC. The WAXD system is equipped with monochromatic CuKα radiation with wavelength $\lambda = 0.15418$ nm at 40 kV and 30 mA. For DSC measurement, around 5 mg matrix was heated from 50 to 200°C at a rate of 5°C/min under a nitrogen gas flow. To study the effect of laser treatment on shortening the drug release induction period, the 1, 5, and 10% drug loaded matrices were treated on both sides by a KrF excimer laser with a 248 nm wavelength, 25 ns pulse width, and 3.0 J/cm^2 fluence.[7]

Drug release tests were conducted such that each sample was placed in a vial and fully immersed in 10 mL phosphate buffered saline (PBS) with a pH of 7.4. The drug release period lasts for up to 84 days. Vials were placed in water bath at 37°C, and the PBS was changed every 7 days. The amount of released drug was monitored by spectrophotometry. The RB absorbance at 552 nm was recorded and a function of concentration. After drug release, samples were rinsed with distilled water and dried in vacuum for 2 days. To characterize polymer degradation, the

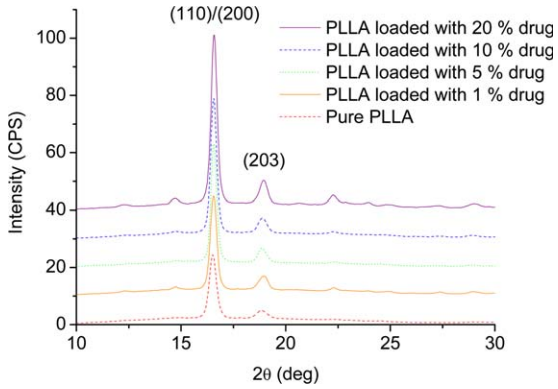

Figure 2. WAXD profiles of PLLA with different drug loading concentrations. Intensity of crystalline peaks increases with drug concentration, suggesting a higher crystallinity. Profiles are shifted in y direction for viewing clarity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

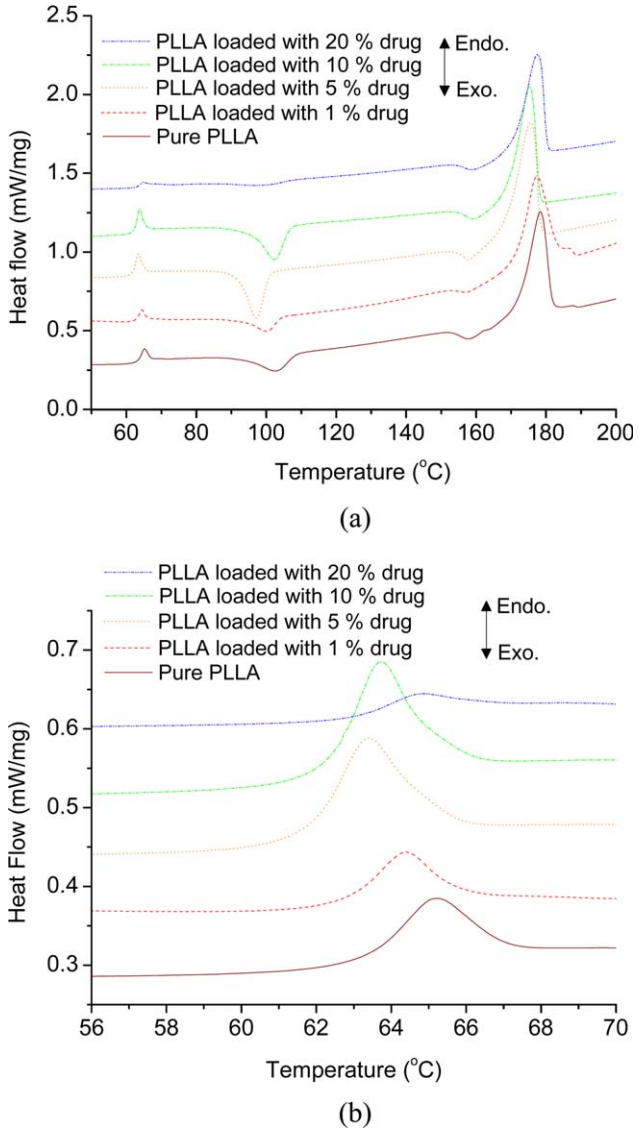

Figure 3. DSC thermograms of pure PLLA and PLLA loaded with 1, 5, 10, and 20% drug (a) heating from 50 to 200°C and (b) around the glass transition temperature. The heating rate is 5°C/min. Profiles are shifted in *y* direction for viewing clarity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

weight average molecular weight (M_w) and number average molecular weight (M_n) were determined in chloroform by GPC at 30°C. For GPC measurements, the samples were purified to remove RB. The drug loaded PLLA were dissolved in chloroform, and methanol was added to the solution to precipitate PLLA. The mixture was separated by centrifugation to collect the precipitated PLLA. The PLLA/chloroform solution with a concentration of 1.5 mg/mL was prepared for GPC measurements. The GPC was calibrated with polystyrene standards, and the refractive index and differential pressure detectors were used.

RESULTS AND DISCUSSION

PLLA were loaded with RB for drug release tests. The PLLA matrices loaded with 5% drug before and after different drug release periods are shown in Figure 1. The obtained PLLA matrix has 1 mm thickness and 10 mm diameter. The matrix color becomes lighter with longer drug release period. The color change indicates a less amount of drug molecules embedded in the matrix after the controlled release. Effects of drug loading on polymer matrix properties, as well as effects of drug concentration and laser treatments on drug release profiles, are discussed in the following sections.

Effect of Drug Loading on Chain Mobility and Polymer Crystallinity

The addition of drug molecules in polymer chains changes the free volume between chains, affecting chain mobility and crystallization. Crystallinity of the resulted polymer matrices is characterized by WAXD, with results given in Figure 2. The 16.7° WAXD crystalline peak becomes more prominent for the samples loaded with higher concentrated drug. Crystallinity, calculated based on the WAXD profile,[20] is given in Figure 5, in which the crystallinity calculated from DSC results is also shown and is discussed later. Figure 5 shows that crystallinity increases with the increasing drug concentration. As the free volume theory predicts, the introduction of plasticizers facilitates chain movements, which tends to increase the number and size of crystallites.[21] Therefore, during the cooling process of thermal molding, PLLA loaded with a higher concentrated drug has higher mobility and is ended up with higher crystallinity.

The crystals developed in PLLA matrices influence chain mobility. To investigate the combined effect of drug loading and polymer crystallinity, the thermal properties of the drug loaded matrices are characterized by DSC. The DSC thermograms of the PLLA matrices are given in Figure 3(a). The thermograms demonstrate that the PLLA experience the glass transition at around 60–65°C, cold crystallization at around 95–105°C, and melting at around 160–190°C. The occurrence of cold crystallization is because at a temperature higher than T_g, polymer chains gain extra mobility when compared to their initial status below T_g, which allows chain crystallization to achieve a more energetically stable state. A weak exotherm is demonstrated at around 160°C, which is slightly lower than the onset temperature of melting. The exotherm is generated because a part of

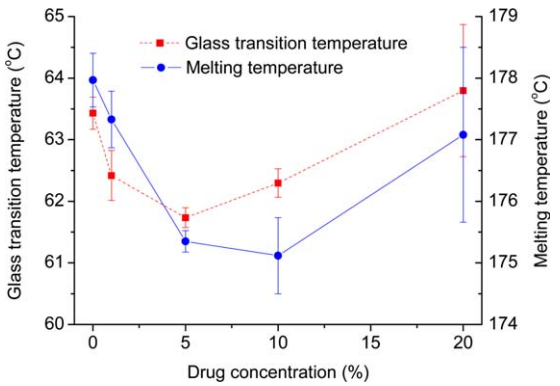

Figure 4. Glass transition temperature and melting temperature of drug loaded PLLA matrices as a function of drug concentration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

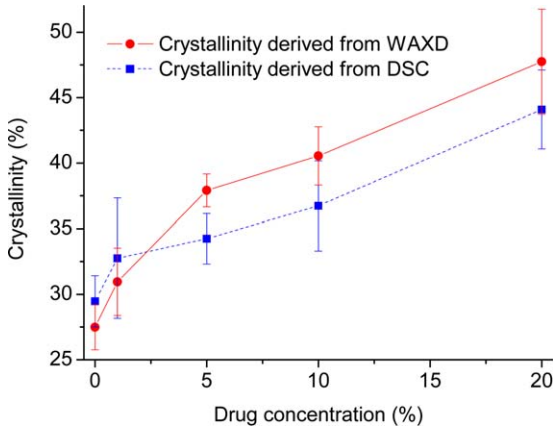

Figure 5. Crystallinity as a function of drug loading concentration obtained from WAXD and DSC. Crystallinity increases with drug concentration based on both measurements. The error bar represents the standard deviation of 3 data points. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

polymer chains start to melt at that temperature, which increases chain mobility and induces the crystallization. The melting peak then begins right after the exotherm. The initial crystal and the crystal developed during the two crystallization processes of DSC scanning are melted, generating the melting peak.

The thermograms around T_g is given in Figure 3(b). Both T_g and T_m shift with drug concentrations. The values of T_g and T_m are plotted as a function of drug concentration in Figure 4. When the drug concentration is below 5%, T_g and T_m reduce with an increasing drug concentration. The reduction of T_g and T_m suggests an increased chain mobility due to the plasticization effect. However, at high drug concentration (above 5%), an opposite trend is observed. T_g and T_m increase with an increasing drug concentration, suggesting reduced chain mobility. The reduced chain mobility is a result of high crystallinity in the samples with high drug concentration, Figure 5. High crystallinity limits chain movement and thus increases T_g and T_m.

In addition to the WAXD, sample crystallinity is also derived from the DSC. The crystallinity x of the PLLA matrices is evaluated according to the following equation.

$$x=(\Delta H_m+\Delta H_c)/\Delta H_{m0} \quad (7)$$

where ΔH_m is the melting enthalpy represented by the melting peak shown in Figure 3, ΔH_c is the total crystallization enthalpy represented by the two crystallization exotherms in Figure 3,

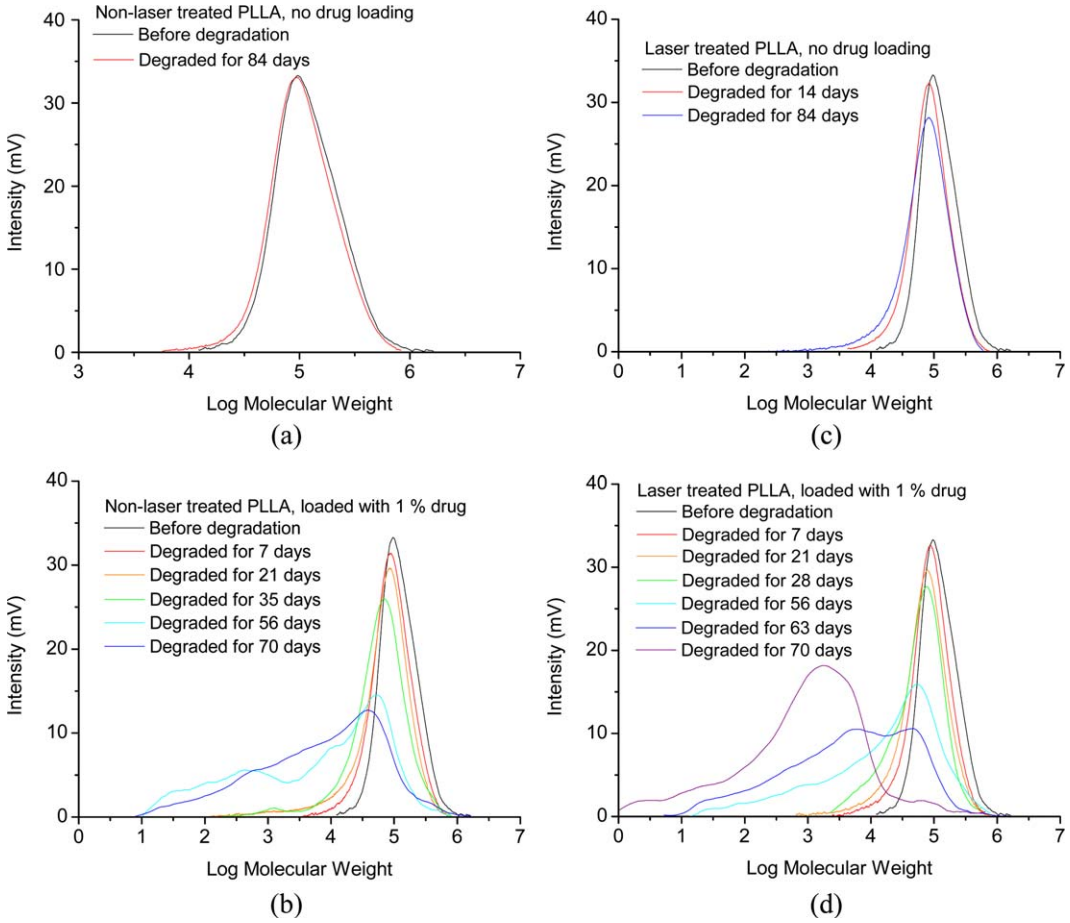

Figure 6. GPC profiles of the (a) non-laser treated pure PLLA matrix, (b) non-laser treated PLLA matrix loaded with 1% drug, (c) laser treated pure PLLA matrix, and (d) laser treated PLLA matrix loaded with 1% drug, as a function of degradation and drug release period. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Applied Polymer SCIENCE

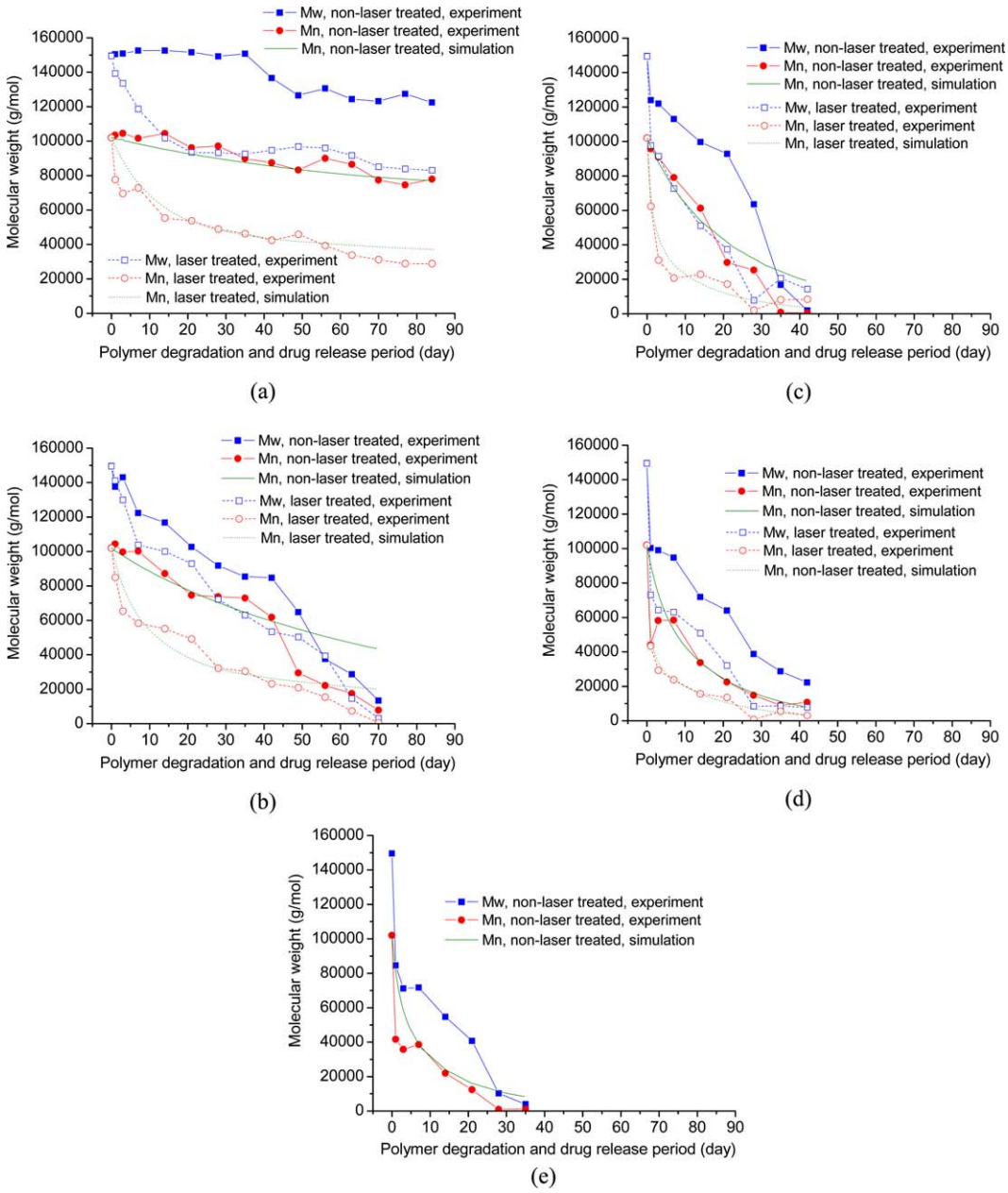

Figure 7. Number average and weight average molecular weights of (a) pure PLLA and PLLA loaded with (b) 1%, (c) 5%, (d) 10%, (e) 20% drug with polymer degradation and drug release period. For pure PLLA and PLLA loaded with 1, 5, and 10% drug, effect of laser melting on degradation is also studied. Laser melting accelerates initial degradation rate for all treated matrices. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and ΔH_{m0}, 93 J/g, is the melting enthalpy of PLLA crystals with infinite crystal thickness such that the crystallinity is 100%.[22] The calculated crystallinity is given in Figure 5. Crystallinity increases with drug concentration, which agrees with the crystallinity derived from the WAXD results.

Effect of Drug Concentration on Drug Release

Drug loading affects polymer degradation and the resulted drug release profiles. Effects of drug concentration on polymer degradation and drug release profiles are investigated and discussed in this section.

Polymer Degradation during Drug Release. Effect of drug concentration on polymer degradation is characterized by the molecular weight through the GPC. GPC profiles of non-laser treated and laser treated samples are given in Figure 6 for pure PLLA and 1% drug loaded PLLA. Minor change of GPC profile is observed for the pure PLLA, suggesting insignificant degradation over time. The GPC profiles of drug loaded PLLA shift left, demonstrating a decrease of molecular weight as a result of degradation. Bimodal distributions are observed in the late stage for the drug loaded PLLA, because the preferential chain scission on the lamella fold surfaces generates integral folds of

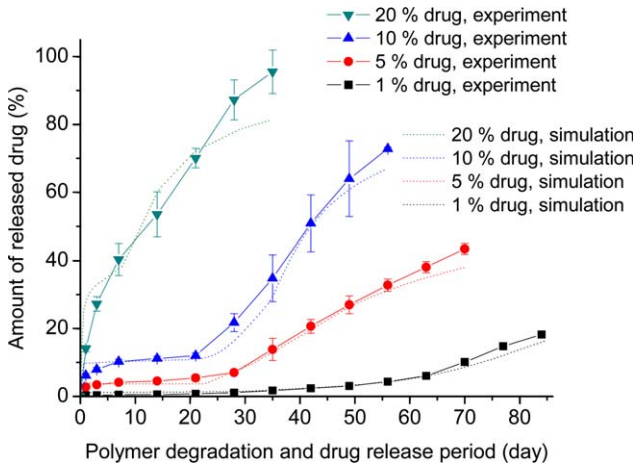

Figure 8. Drug release profiles of PLLA with different drug loading concentrations. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

crystalline chains.[7] For 5, 10, and 20% drug loaded PLLA, the GPC profiles also shift left with time and the bimodal distributions are observed. The broadened profiles are a result of widened distribution of chain length, leading to a larger polydispersity index.[7] The profiles shift left at a higher rate with a higher drug concentration, suggesting a faster degradation.

The molecular weights determined from GPC and simulation are given in Figure 7. The molecular weights decrease insignificantly for the non-laser treated PLLA with no drug loading, which agrees with Figure 6(a). As shown in Figure 7(b), drug loading accelerates degradation rate because of the enlarged free volume by drug small molecules favors water diffusion into the matrix and hydrolysis. The model drug, RB, also induces an acid environment and accelerates polymer degradation. In addition, polymer degradation is accelerated by the initial burst occurring on the first several days. It is observed that 10 and 20% drug loaded PLLA significantly degrades in the first 3 days, Figure 7(d,e), which corresponds to the initial burst period, as will be discussed in Figure 8. During the initial burst period, drug on the matrix surface is released, and the space initially occupied by drug molecules becomes vacant. The vacant space favors water diffusion and accelerates hydrolysis in the first 3 days. The accelerated hydrolysis generates a structure with higher porosity, and favors subsequent water diffusion and hydrolysis. The degradation profiles are captured numerically, in which the molecular weight experiences a rapid initial drop followed by degradation at a slow rate. In the late stage, the simulation curve of molecular weight tends to level off, while the experimental data demonstrate a more significant decrease. A possible reason is that, due to significant amount of drug release in the late stage, polymer matrix disintegrates, which is experimentally observed as cleavage and holes on the degraded samples. Effects of macroscale morphology changes are not numerically considered.

It is observed that polymer degradation accelerates with higher drug concentration, and is not a function of chain mobility as revealed in Figure 4. Chain mobility, therefore, plays a less important role in determining polymer degradation under the current test conditions. Instead, due to the enlarged free volume and the vacant space after drug release, as well as the acid environment induced by drug loading, drug release is a strong function of drug loading concentration.

Drug Release. Drug release is measured by spectrophotometry. The model drug, RB, has a characteristic absorbance peak at 552 nm. The peak height is a function of concentration. To determine the relationship between the peak height and RB concentration, the RB/PBS solution with different concentrations are prepared and measured by spectrophotometry. The absorbance profiles are a function of solution concentration, as given in the Supporting Information Figure S1. A linear relationship between absorbance at 552 nm and RB concentration in PBS is described

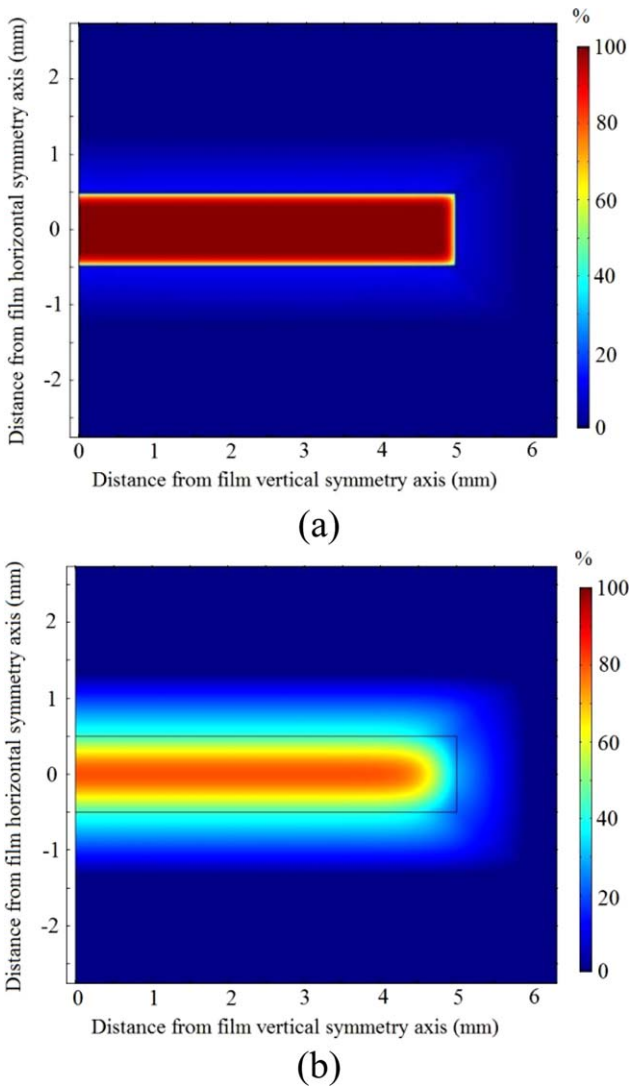

Figure 9. Simulated spatial distribution of drug concentration in non-laser treated PLLA loaded with 5% drug after release for (a) 30 and (b) 70 days. Drug concentration is represented as a percentage of initial value. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

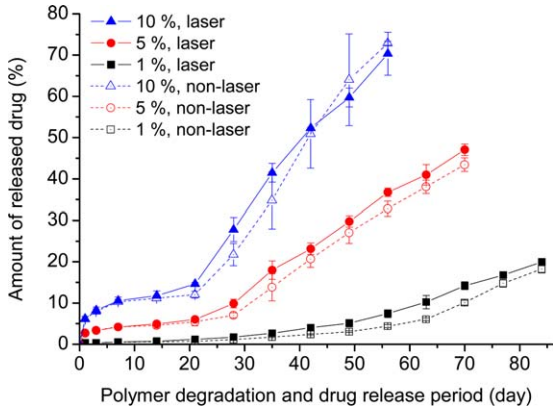

Figure 10. Drug release profiles of laser treated and non-laser treated matrices. Through laser melting, the induction period of drug release is shortened. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

by $A=0.058c_{RB}-0.017$, where A is the RB absorbance at 552 nm and c_{RB} is the RB concentration in μmol/L.

The drug release profiles are given in Figure 8, in which the y-axis is the amount of released drug as a percentage of the initial drug. Simulation results are also provided. A higher release rate is observed in matrix with higher drug concentration, as discussed in Figure 8. Drug release profiles are a strong function of drug concentration. For low drug concentration, drug release begins with an induction period during which a limited amount of drug is released. For medium drug concentration, the release profiles begin with an initial burst, followed by an induction period. As the drug concentration increases, the initial burst is more significant and the induction period is shorter. With a higher drug concentration, the space occupied by the drug molecules has higher opportunity to connect with each other, forming channels which allow for fast drug release and water diffusion. Therefore, degradation is accelerated, leading to a short induction period. At 20% drug concentration, no induction period is observed. The higher degradation rate causes a higher drug release rate as shown in Figure 8.

The model captures physical phenomena obtained experimentally, including initial burst, induction period, and subsequent release. Deviation between simulation and experiment is observed in the late stage of release period. In simulation, the drug release rate slows down at the end. This stems from the different diffusion time for drug located near the surface and in the center. As given in Figure 9, the spatial drug distribution is simulated for the PLLA with 5% drug after the end of induction period (30 days) and in the end of drug release (70 days). Drug release starts on the matrix surface. Because of the shorter path length, drug diffusion requires shorter time. The drug molecules located in the matrix center, on the other hand, are released in the late stage. Due to the longer path length of diffusion to the surface, they are released at a slower rate. Experimentally drug release in the late stage is accelerated by matrix disintegration. The cleavage and holes generated during this period enlarge the matrix contact area with the release medium and accelerate drug release, which accounts for the deviation between simulation and experiment in the late stage.

Laser Modification of Drug Release Profile

It has been shown in previous section that at low drug concentrations (1, 5, and 10%), drug release experiences an induction period, which is undesirable. Laser treatment has been conducted on these matrices in our previous study.[23] It has been demonstrated that laser treatment reduces polymer crystallinity and accelerates polymer initial degradation. The GPC profiles of laser treated PLLA are given in Figure 6(c) for pure PLLA and Figure 6(d) for 1% drug loaded PLLA. In both cases, GPC profiles shift left, suggesting the occurrence of degradation. The comparison between non-laser treated pure PLLA, Figure 6(a), and laser treated pure PLLA, Figure 6(c), demonstrates the effect of laser crystallinity modification on polymer degradation. A reduced crystallinity by laser melting accelerates polymer degradation. For laser treated 1% drug loaded PLLA, Figure 6(d), the GPC profiles shift left within a shorter period as compared to non-laser treated counterpart, Figure 6(b), suggesting an accelerated degradation.

Based on the GPC measurements, the M_w and M_n are calculated with the results given in Figure 7, in which simulated M_n is also given. An accelerated degradation induced by laser melting is demonstrated for all laser treated PLLA matrices with and without drug loading. As clearly shown in Figure 7, laser treatment accelerates the initial degradation of polymer matrices, because laser melted material, with a lower crystallinity, degrades at a higher rate. Once the degradation of laser melted material comes to the end, the matrix can be seen as composed of a structure similar to the non-laser treated matrix. At this later stage, therefore, the laser treated matrix degrades at a rate similar to the non-laser treated matrix. It should be noticed that the drug loaded matrices have been methanol precipitated to remove embedded drug molecules for GPC measurements. The precipitation process may lose a fraction of low molecular

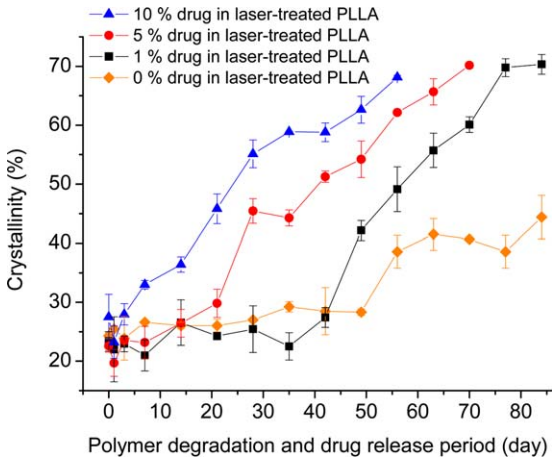

Figure 11. Crystallinity of laser treated PLLA loaded with 1, 5, and 10% drug as a function of polymer degradation and drug release period. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

weight polymers. The observed molecular weights after degradation, therefore, might over-estimate the real molecular weights.

Drug Release. Drug release from laser treated PLLA is investigated with results given in Figure 10, in which the non-laser treated results are also provided for comparison. The induction period is defined as a period after which the drug release rate increases. It is demonstrated that the induction periods of laser treated matrices have been shortened. For 1% drug loaded PLLA, the induction period is shortened by around 2 weeks, from day 63 to day 49. For 5% drug loaded PLLA, the induction period is shortened by around 1 week, from day 28 to day 21. For 10% drug loaded PLLA, the induction period is shortened by around 1 week, from day 21 to day 14.

The shortened induction period is because of the accelerated initial degradation induced by laser melting. By comparing Figures 7 and 10, it can be observed that the induction period comes to the end when the measured M_n reduces to around 20,000 g/mol. The time period for the molecular weight to reduce to the critical value reduces after laser treatment, which in turn shortens the induction period of drug release. The induction period shortens at a smaller extent for matrix loaded with a higher drug concentration (10%), which is because drug molecules absorbs laser energy and reduces the portion of laser energy to melt polymer, as demonstrated and discussed our previous study.[23]

It has been noticed that both drug loading and laser surface melting accelerates polymer degradation. However, the accelerated degradation by drug loading and laser surface melting shows different profiles. Drug loading accelerates overall degradation of the bulk, and gives a higher degradation rate until the end of degradation. Effect of laser melting, on the other hand, is limited within a layer below matrix surface, and keeps the bulk intact. Laser melting, therefore, only accelerates the initial degradation, while the degradation in the later stage remains unchanged. Therefore, effects of drug loading and laser treatment lead to distinct drug release profiles. Drug loading results in a shorter induction period of drug release and a higher drug release rate. Laser surface melting shortens the induction period of drug release, but keeps the subsequent drug release rate similar to the non-laser treated sample, which is desired since drug release rate needs to be maintained within a specific range for the drug to be nontoxic and effective.

Polymer Crystallization during Drug Release. Crystallinity of laser treated PLLA over the degradation and drug release period is monitored using the WAXD, with results given in Figure 11. Crystallinity increases with polymer degradation and drug release period. Crystallization is a result of polymer chain degradation, because degraded chains have smaller molecular weights and thus a higher mobility. With enough mobility, the degraded chains reorganize into the crystalline state, which is energetically stable. It is noticed that the crystallinity increases with a similar pattern of the drug release profiles as shown in Figure 10. Namely, crystallinity increases after an induction period, within which crystallinity increase is limited. The induction period is shorter for PLLA loaded with higher drug concentration. The similarity between crystallinity change and drug release profiles is also observed for the non-laser treated PLLA. This phenomenon is attributed to the fact that drug release and crystallinity increase are both determined by polymer degradation. It is also noticed that, for the laser treated PLLA, the induction periods of crystallinity change are shorter than those of the non-laser treated PLLA.

Water can hardly penetrate into polymer crystalline region, and thus higher crystallinity can retard drug release. However, based on Figures 10 and 11, drug release does not slow down as the crystallinity increases. This is because drug release and polymer degradation left behind a porous structure. The pores accelerate water diffusion and hydrolytic degradation, even if the crystallinity increases. The effect of higher crystallinity to slow down degradation and drug release is, therefore, canceled out and does not dominate during the drug release process. In addition, drug release profiles are expected to be a function of matrix shape, since matrix geometry determines water diffusion paths, and, therefore, polymer degradation and crystallization behaviors. Combined effects of laser treatment and matrix shape require further studies.

CONCLUSIONS

The effects of drug loading concentration and laser surface melting on PLLA biodegradation and drug release have been investigated. It has been shown that PLLA biodegradation is a strong function of drug loading, with a higher drug concentration leading to faster degradation. The accelerated degradation caused by drug loading is attributed to the porous structure in the polymer matrix after drug release. The porous structure favors water diffusion into the matrix and accelerates hydrolytic degradation. The accelerated biodegradation reduces the induction period of drug release and increases the drug release rate. Drug loading also influences chain crystallinity and mobility, while both factors do not dominantly determine PLLA biodegradation and drug release in the current study.

Laser melting reduces surface crystallinity of PLLA matrix, which accelerates polymer degradation in the early stage and shortens the induction period of drug release. Laser treatment only melts a layer below matrix surface and keeps the bulk intact. Therefore, after laser melted material degrades at a higher rate, polymer degradation proceeds at a rate similar to the non-laser treated samples. Similar polymer degradation rate results in similar drug release rate after laser treatment. Accordingly, laser crystallinity modification has been shown to reduce the induction period of drug release, while keep the drug release rate unmodified, which is desired in drug delivery applications.

ACKNOWLEDGEMENTS

Financial support from NSF under CMMI-1030536 is acknowledged. WAXD measurements were carried out at MRSEC, Columbia University. GPC measurements were carried out at the Center for Functional Nanomaterials, Brookhaven National Laboratory, which is supported by the U.S. Department of Energy, Office of Basic Energy Sciences, under Contract No. DE-AC02–98CH10886.

REFERENCES

1. Amass, W.; Amass, A.; Tighe, B. *Polym. Int.* **2008**, *47*, 89.
2. Pitt, C. G.; Gu, Z. *J. Controlled Release* **1987**, *4*, 283.

3. Lyu, S.; Schley, J.; Loy, B.; Lind, D.; Hobot, C.; Sparer, R.; Untereker, D. *Biomacromolecules* **2007**, *8*, 2301.
4. Chu, C. C. *J. Appl. Polym. Sci.* **1981**, *26*, 1727.
5. Tsuji, H.; Ikada, Y. *J. Polym. Sci. Part A: Polym. Chem.* **1998**, *36*, 59.
6. Hsu, S.-T.; Tan, H.; Yao, Y. L. *Polym. Degrad. Stab.* **2012**, *97*, 88.
7. Hsu, S.-T.; Tan, H.; Yao, Y. L. J. *Manuf. Sci. Eng.*, accepted.
8. Flory, P. J. *J. Am. Chem. Soc.* **1940**, *62*, 1057.
9. Ljungberg, N.; Wesslen, B. *J. Appl. Polym. Sci.* **2002**, *86*, 1227.
10. Xiao, H.; Lu, W.; Yeh, J. *J. Appl. Polym. Sci.* **2009**, *113*, 112.
11. Yeh, J.; Huang, C.; Chai, W.; Chen, K. *J. Appl. Polym. Sci.* **2009**, *112*, 2757.
12. Lao, L. L.; Venkatraman, S. S.; Peppas, N. A. *J. Biomed. Mater. Res. A* **2009**, *90*, 1054.
13. Spenlehauer, G.; Vert, M.; Benoit, J.-P.; Chabot, F.; Veillard, M. *J. Controlled Release* **1988**, *7*, 217.
14. Rothstein, S. N.; Federspiel, W. J.; Little, S. R. *J. Mater. Chem.* **2008**, *18*, 1873.
15. Wang, Y.; Pan, J.; Han, X.; Sinka, C.; Ding, L. *Biomaterials* **2008**, *29*, 3393.
16. Stephens, C. H.; Whitmore, P. M.; Morris, H. R.; Bier, M. E. *Biomacromolecules* **2008**, *9*, 1093.
17. Rothstein, S. N.; Federspiel, W. J.; Little, S. R. *Biomaterials* **2009**, *30*, 1657.
18. Saltzman, W. M.; Langer, R. *Biophys. J.* **1989**, *55*, 163.
19. Lyu, S.; Untereker, D. *Int. J. Mol. Sci.* **2009**, *10*, 4033.
20. Alexander, L. E. X-Ray Diffraction Methods in Polymer Science; Wiley: New York, **1969**; Chap. 1.
21. Marcilla, A.; Beltran, M. In Handbook of Plasticizers; Wypych, G., Ed.; ChemTec Publishing: Toronto, **2004**; Chap. 5.
22. Fischer, E. W.; Sterzel, H. J.; Wegner, G. *Kolloid-Z. u. Z. Polym.* **1973**, *251*, 980.
23. Hsu, S.-T.; Yao, Y. L. *Manuf. Lett.*, submitted.