Effect of Drug Loading on Laser Modified Polymer Biodegradation

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Abstract

The biodegradable polymer such as poly(L-lactic acid) is promising in drug delivery applications because it allows for a controlled drug release over time. However, the slow polymer degradation kinetics often leads to an undesirable induction period of drug release in the early stage, during which a limited amount of drug is released. Through modifying polymer crystallinity, laser melting can accelerate polymer degradation, which potentially shortens the induction period. To apply the laser melting process on drug loaded systems, the effect of drug loading on laser modified polymer biodegradation is investigated in this study. Effect of drug loading is investigated as a function of drug concentration. Polymer crystallinity is characterized through the wide-angle X-ray diffraction method. Degradation is characterized by molecular weights from the gel permeation chromatography. It has been demonstrated that laser treatment accelerates the degradation of drug loaded polymer, and that laser modification of polymer degradation is a strong function of drug loading. With higher drug concentration, laser melting has less effect on polymer degradation modification. This is due to the fact that a portion of laser energy is absorbed by drug molecules, and less energy is available to melt the polymer matrix.

Key words: poly(L-lactic acid); laser treatment; biodegradation; crystallinity; drug release

1. Introduction

Biodegradable polymer, poly(lactic acid) (PLA), has attracted wide attention in drug

delivery applications because it allows for controlled drug release, in which drug concentration in the human body is stably maintained within the effective region over weeks or months. In drug delivery applications, drug molecules are embedded in a polymer matrix and gradually released as polymer degrades. PLA degrades via hydrolysis in a physiological environment. As a semi-crystalline polymer, PLA hydrolysis is a strong function of its crystallinity. Higher crystallinity leads to a slower hydrolytic degradation rate, because water molecules readily penetrate into the amorphous region, while hardly accommodate themselves in the crystalline region with highly packed and densely ordered structures [1,2]. Due to the slow degradation kinetics of crystalline PLA, limited amount of drug is released in the early stage of drug release period, known as the induction period. The induction period is undesirable because it delays drug release and effective period. It is essential to shorten the induction period in order to improve the drug release controlled by polymer-based drug delivery systems.

Since PLA degradation is a function of crystallinity, laser crystallinity modification has been conducted on PLA surfaces, as an attempt to modifying the degradation profiles [3]. With a reduced surface crystallinity, degradation of PLA with no drug loading occurs at a higher initial rate and experiences a shorter time period before mass loss [4]. The results demonstrate the potentiality of laser modification of polymer degradation for drug delivery systems, while the drug loading effect on laser modification of degradation requires further investigation. In this study, the effect of drug loading is considered as a function of drug concentration loaded in the polymer matrix. To characterize the effects of drug loading and laser irradiation, polymer crystallinity is measured by wide-angle X-ray diffraction (WAXD), and polymer degradation is characterized through the molecular weights by gel

permeation chromatography (GPC).

2. Experimental

PLLA from PURAC was used as received. Rhodamine B (RB), used as the model drug, was embedded into PLLA via solvent casting to prepare 1 %, 5 %, and 10 % drug loaded films. 100 mg film was thermally compressed at 185°C and cooled down in air. Crystalline phase developed during the cooling process. The obtained sample is around 1 mm thick and 10 mm in diameter. Laser treatment was conducted on both sides of the sample by a KrF excimer laser with 248 nm wavelength, 25 ns pulse width. Sample crystallinity was determined by WAXD equipped with monochromatic CuKα radiation. Polymer degradation was conducted in 37°C phosphate buffered saline (PBS), and the PBS was changed every 7 days. The weight average (M_w) and number average molecular weights (M_n) were determined in chloroform from gel permeation chromatography (GPC) at 30°C. For GPC measurements, PLLA is retrieved from the drug loaded samples by precipitation in methanol followed by centrifugation. PLLA/chloroform solution with 1.5 mg/mL concentration was prepared for GPC analysis. The refractive index and differential pressure detectors were used.

3. Results and discussion

Polymer crystallinity as a function of drug loading and laser treatment is studied by WAXD with results given in Fig. 1. The crystalline peak at 16.7° is higher for matrix with higher drug concentration, and the height reduces for all laser treated samples. The crystallinity calculated based on ref. [5] is given in Fig. 2. As agreed with Fig. 1, crystallinity increases with drug concentration and decreases after laser treatment. The addition of drug small molecules (479 g/mol) into the polymer matrix increases the free volume

between chains and enhances chain mobility. The enhanced chain mobility favors chain reorganization and crystallization. The amount of crystallinity decrease due to laser treatment is represented in terms of absolute decrease and percentage decrease, as shown in Fig. 2. Laser treatment has been shown to reduce polymer crystallinity for drug loaded and non-drug loaded matrices. Crystallinity decreases at a smaller extent for matrices with higher drug concentrations. This is because the drug molecules have an absorption peak near the laser wavelength, 248 nm. Part of laser energy is absorbed by drug molecules, and less energy penetrates into the matrix to melt the polymer.

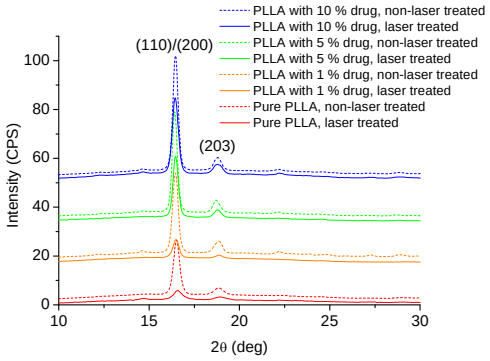


Fig. 1. WAXD profiles of PLLA with different drug concentrations before and after laser treatment. Intensity of crystalline peaks decreases after laser treatment, suggesting a reduced crystallinity. Profiles are shifted in y direction for viewing clarity.

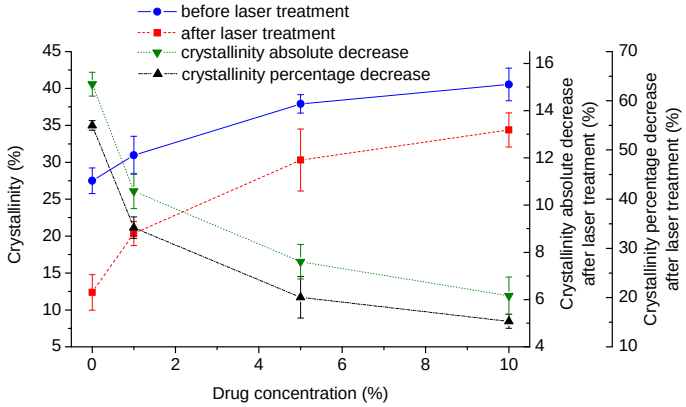
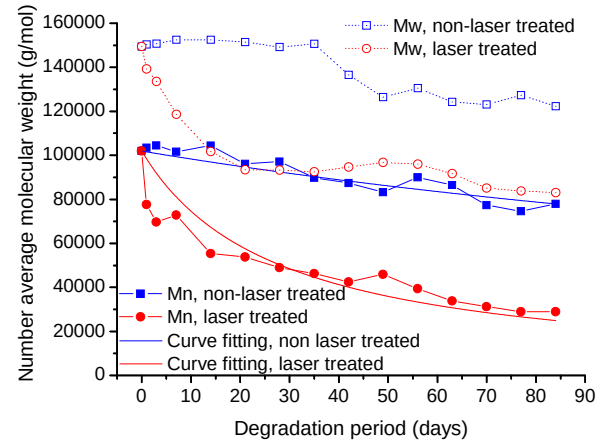
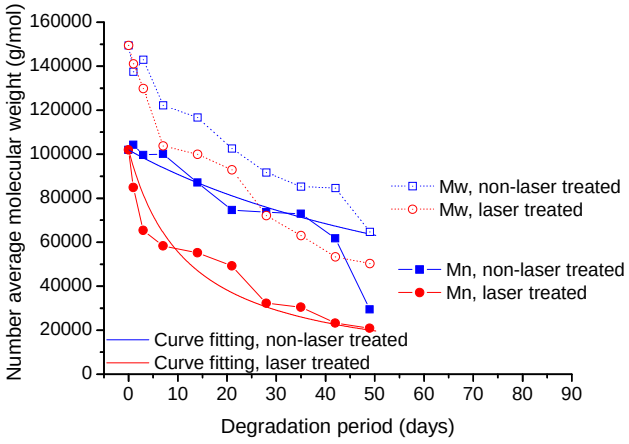


Fig. 2. PLLA crystallinity before and after laser treatment as a function of drug concentration. Laser treatment reduces crystallinity, and crystallinity decreases at a smaller extent for higher drug concentrated PLLA.

The effect of laser irradiation on potential chemical modifications of polymer matrices has been considered previously [3]. The laser energy level of 3.0 J/cm^2 induces non-measurable chemical modifications on PLLA, and is used in this study. The laser induced chemical effect on drug molecules is studied by spectrophotometry [6]. Drug loaded PLLA films with a thickness similar to laser melting depth (around 100 μm) are formed through the same thermal molding process as stated in Sec. 2. No modification on absorbance peak height is observed for the laser treated samples, suggesting no chemical modification on drug molecules.



(a)



(b)

Fig. 3. M_w, M_n, and fitted curves based on Eq. (1) of (a) pure PLLA matrix and (b) PLLA loaded with 1 % drug.

Degradation of laser treated matrices is characterized through the molecular weight measurements by GPC. The weight average and number average molecular weights are given in Fig. 3 for the pure PLLA and 1 % drug loaded PLLA. In both cases, degradation occurs at an accelerated rate in the initial stage. Similar accelerated degradation trends are observed for 5 % and 10 % drug loaded PLLA. It is demonstrated that a reduced crystallinity by laser melting accelerates polymer initial degradation. 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.

The degraded samples show a solid cross section, which suggests autocatalysis is not dominant in the current experiment conditions [4]. For the non-autocatalytic hydrolysis, PLLA chain cleavage follows the rate law given as $d[\mathrm{COOH}]/dt = k'[\mathrm{ester}][\mathrm{H_2O}]$ where [COOH], [ester], and [H_2O] are the concentrations of the carboxylic end groups, ester bonds, and water molecules, and k' is the rate coefficient [7]. Laser effect on degradation modification is significant in the initial stage [4], during which the degree of polymerization is still high, and [ester] and [H_2O] are treated as constant. [COOH] is inversely proportional to the number average molecular weight M_n, and therefore

$$M_n^{-1} = M_{n0}^{-1} + kt \qquad (1)$$

where M_{n0} are the number average molecular weight at time 0, and k is the rate coefficient for constant [ester] and [H_2O]. Based on Eq. (1) the degradation rate in the initial stage can be determined from the experimental results, with the fitted curves given in Fig. 3.

For all samples, the rate coefficients increase after laser treatment. The amount of increase, however, is smaller at higher drug concentration, as shown in Fig. 4. The

reduced amount of rate change agrees with the reduced amount of crystallinity modification when drug concentration increases, as given in Fig. 2. It is suggested that drug absorbs a portion of laser energy and reduce the amount of crystallinity modification, which in turn limits the laser effect on degradation modification.

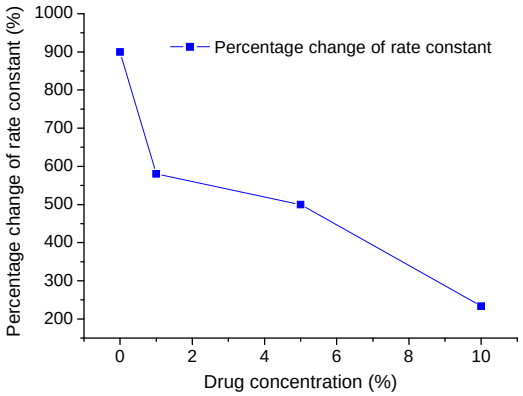


Fig. 4. Percentage change of PLLA degradation rate constant caused by laser treatment as a function of drug concentration.

4. Conclusion

In this study, laser surface treatment has been shown to reduce the crystallinity of drug loaded biodegradable polymer. With a reduced surface crystallinity, the initial degradation is accelerated for all tested samples with different drug concentrations. The effects of drug loading on laser modification of polymer crystallinity and degradation have also been investigated. It has been demonstrated that, with a higher drug concentration, the amounts of laser induced crystallinity change and degradation rate change are reduced. This is attributed to the fact that drug molecules absorb a portion of laser energy, such that less energy is available to melt the polymer matrix.

Acknowledgements

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References

[1] Tsuji H, Ikada Y. Properties and morphology of poly(L-lactide). ii. hydrolysis in alkaline solution. J Polym Sci A Polym Chem 1998;36:59-66.

[2] Chu CC. Hydrolytic degradation of polyglycolic acid: tensile strength and crystallinity study. J Appl Polym Sci 1981;26:1727-34.

[3] Hsu ST, Tan H, Yao YL. Effect of excimer laser irradiation on crystallinity and chemical bonding of biodegradable polymer. Polym Degrad Stab 2012;97:88-97.

[4] Hsu ST, Tan H, Yao YL. Effect of laser induced crystallinity modification on biodegradation profile of poly(L-lactic acid). J Manuf Sci Eng submitted.

[5] Alexander LE. X-ray diffraction methods in polymer science. New York: John Wiley & Sons, Chap. 1; 1969.

[6] Wilhelm P, Stephan D. Photodegradation of rhodamine B in aqueous solution via SiO2@TiO2 nano-spheres. J Photochem Photobio A Chem 2007;185:19-25.

[7] Pitt CG, Gu Z. Modification of the rates of chain cleavage of poly(ε-caprolactone) and related polyesters in the solid state. J Controlled Release 1987;4:283-92.

Figure Captions

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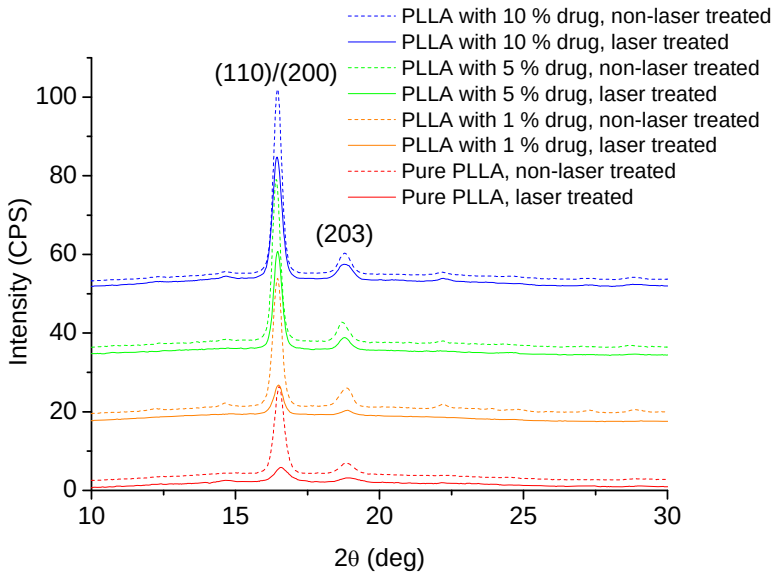

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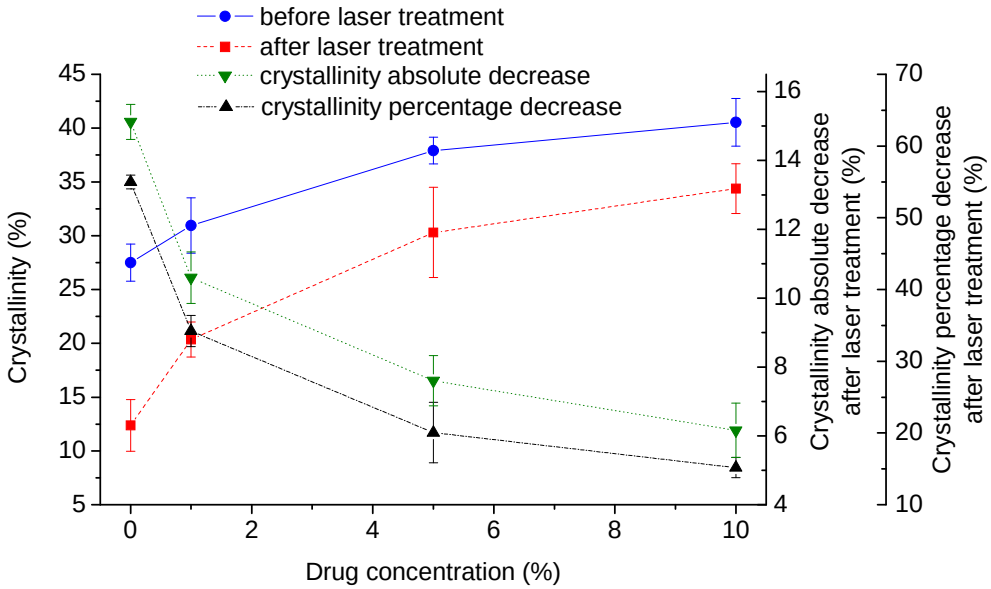

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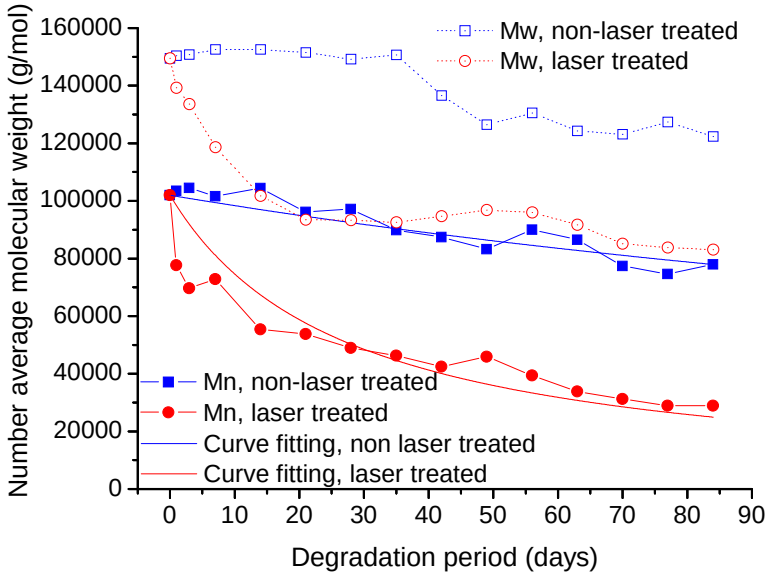
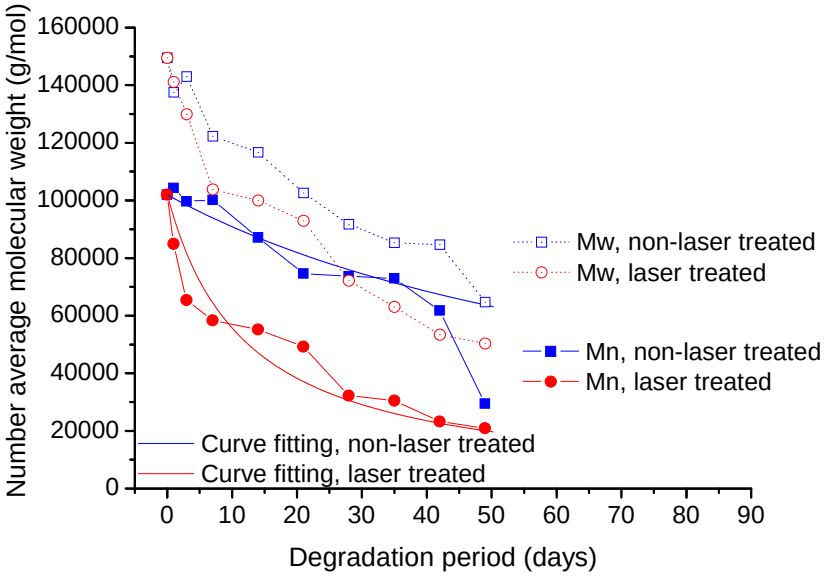


(a)



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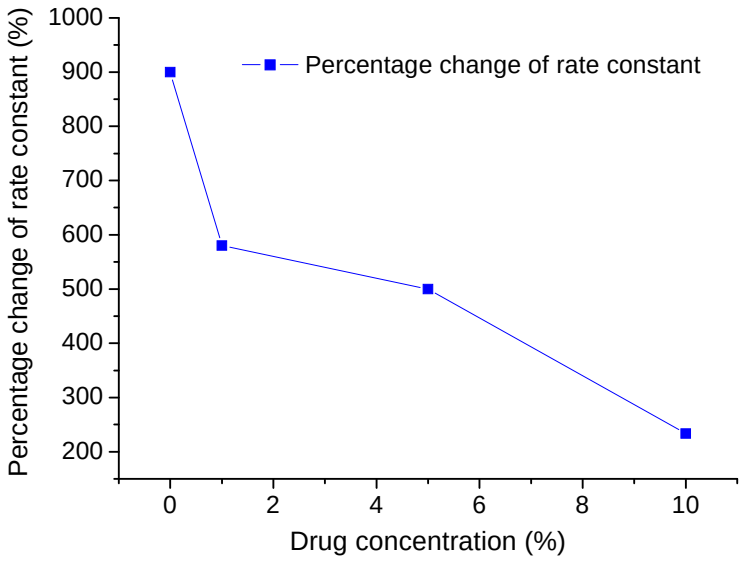

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