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Effect of drug loading on laser modification of polymer biodegradation

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Abstract

Biodegradable polymer is promising in drug delivery applications, while its degradation characteristics include an undesirably slow induction period of drug release. Through modifying polymer surface crystallinity, laser melting accelerates initial polymer degradation and potentially shortens the induction period of drug release. Effect of drug loading on laser modification of polymer degradation is investigated in this study. With a higher drug concentration, effect of laser melting on crystallinity and degradation modification is reduced. This is attributed to the fact that laser energy is partly absorbed by drug molecules, and less energy is available to melt the polymer matrix.

Keywords: Poly(L-lactic acid); Laser treatment; Biodegradation; Crystallinity; Drug delivery

Biodegradable polymer, poly(lactic acid) (PLA), has attracted wide attention in drug delivery applications because it allows for controlled drug release such that drug concentration in the human body is stably maintained within the effective range for 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 can hardly accommodate themselves in the crystalline region which has highly packed and densely ordered structures, while they can readily penetrate into amorphous regions [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 the drug release and effectiveness. It is essential to shorten the induction period in order to improve the drug release in polymer-based drug delivery systems.

Polymer crystallinity can be modified through thermal treatments such as melting and quenching. To shorten the induction period of drug release while keeping the subsequent release rate intact, only surface crystallinity of a polymer matrix needs to be modified and the bulk crystallinity should remain unaffected. Conventional thermal treatments are unable to meet these processing requirements. Laser surface melting, with its rapid heating and cooling rates, confines the melting depth within the polymer surface. With a reduced surface crystallinity caused by the laser treatment, pure PLA matrix (without drug loading) experiences a shorter induction period before mass loss [3,4]. The results demonstrate that laser melting can potentially be used as a novel manufacturing method to effectively modify drug release profiles in drug delivery applications. The drug loading effect on laser melting, however, has not been investigated and is the topic of this study. The drug loading is defined as the drug concentration loaded in the polymer matrix. To characterize the

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effects of drug loading and laser irradiation, polymer crystallinity is measured by the wide-angle X-ray diffraction (WAXD), and the gel permeation chromatography (GPC) is utilized to measure polymer molecular weights (MW).

1. Experiments

PLA consisting of only L-isomers, poly (L-lactic acid) (PLLA), was used in this study. 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 wt.% drug loaded polymer matrices. 100 mg matrix was thermally compressed at 185 °C and cooled in air. Semi-crystalline structures developed during the cooling process. The obtained samples are around 1 mm thick and 10 mm in diameter. Laser treatment was conducted on both sides of the sample by a KrF excimer laser (248 nm wavelength) with 25 ns pulse width. Sample crystallinity was determined by WAXD equipped with monochromatic Cu Kα 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 by GPC in chloroform at 30 °C. To separate PLLA from drug molecules for GPC measurements, precipitation of drug loaded polymer matrices in methanol followed by centrifugation was conducted. PLLA/chloroform solution with 1.5 mg/mL concentration was prepared for GPC analysis. The refractive index and differential pressure detectors were used. The schematic diagram of this experiment process is given in Figure 1.

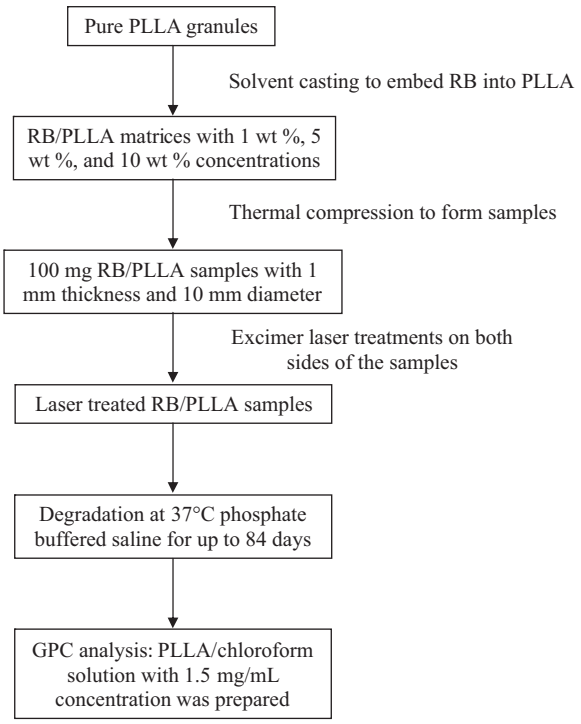

Figure 1. Schematic diagram of experimental processes in this study.

2. Results and discussion

Effect of drug loading on laser crystallinity modification studied by WAXD is depicted in Figure 2. Before the laser treatment, the crystalline peak at 16.7° is higher for the polymer matrix of higher drug concentration, suggesting a higher crystallinity. The peak reduces after the laser treatment. The crystallinity calculated based on Ref. [5] is given in Figure 3 as a function of the drug concentration. The crystallinity increases with the drug concentration and decreases after the laser treatment, as agreed with Figure 2. The addition of small drug molecules increases the free volume between polymer chains, and thus chain mobility. The enhanced chain mobility favors chain reorganization and crystallization. The amount of crystallinity decrease due to laser treatment is shown in absolute value and percentage (Figure 3). The laser treatment reduces the crystallinity because of its faster cooling rate as compared to the slow crystallization kinetics of polymer [3]. It is noted that the crystallinity decreases by a smaller amount for matrices with higher drug concentrations. This can be due to the fact that the drug molecules somewhat absorb near the laser wavelength, 248 nm. Part of the laser energy is absorbed by the drug molecules, and thus less energy can penetrate into the matrix to melt the polymer.

The effect of the laser irradiation on potential chemical modifications of polymer matrices has been considered previously [3]. 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 matrices with a thickness similar to the laser penetration depth at the wavelength used (around 100 μm) were prepared through the same thermal molding process as stated in Section 2. No modification on absorbance peak height is observed for the laser treated samples, which

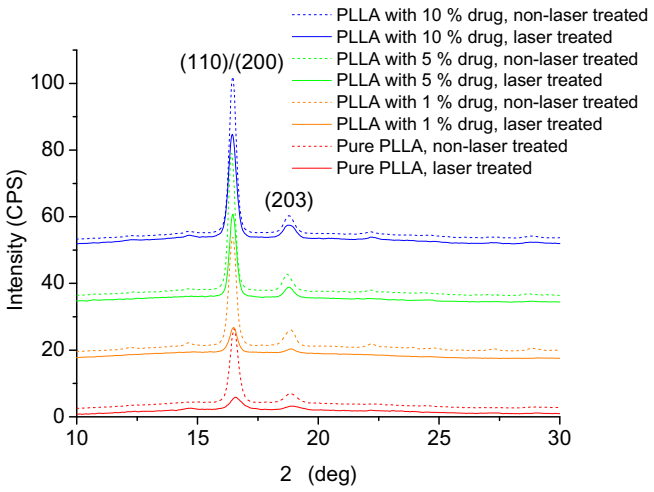

Figure 2. WAXD profiles of PLLA with different drug concentrations before and after laser treatment. Intensity of crystalline peaks decreases after laser treatment, suggesting a reduced crystallinity. Profiles are shifted in the y direction for viewing clarity.

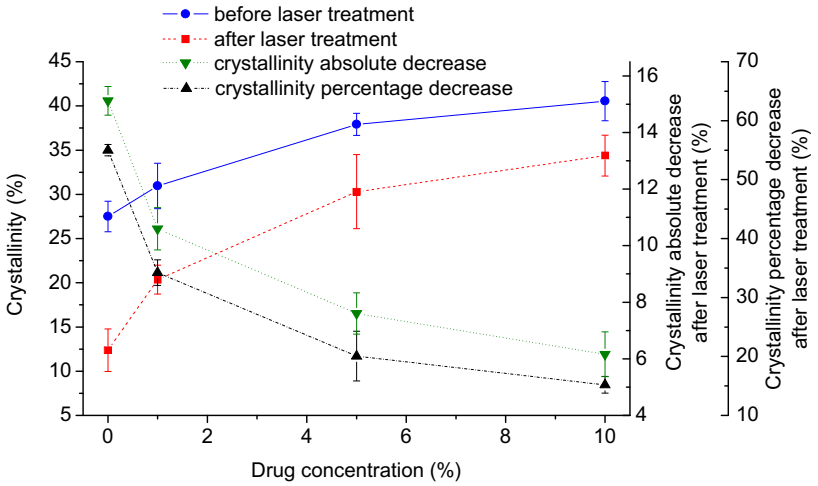

Figure 3. PLLA crystallinity before and after laser treatment as a function of drug concentration. Laser treatment reduces crystallinity, and crystallinity decreases at a smaller extent for higher drug concentrated PLLA.

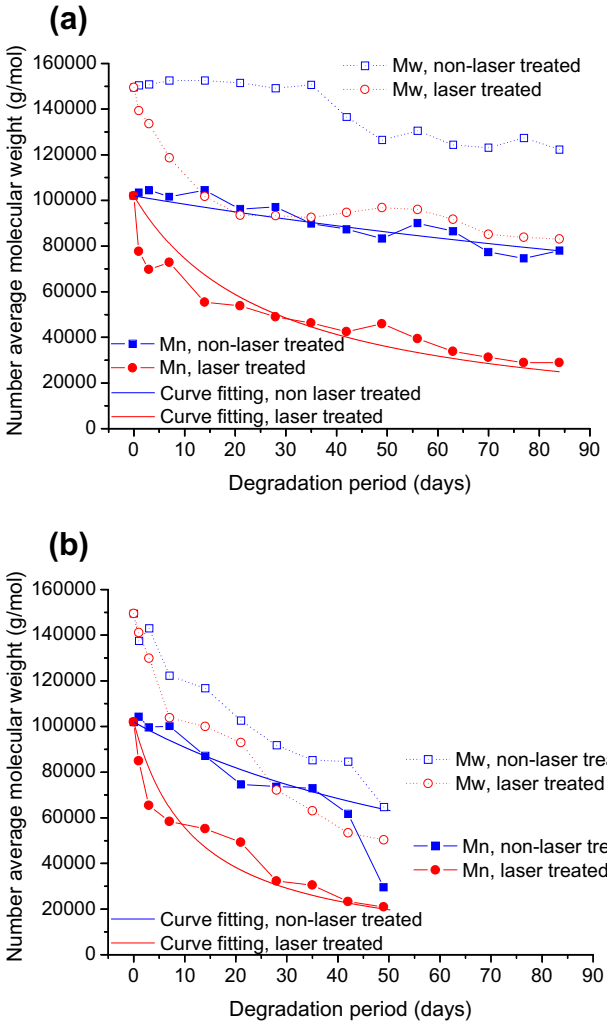

Figure 4. M_w, M_n, and fitted curves based on Eq. (1) of (a) pure PLLA matrix and (b) PLLA loaded with 1% drug.

suggests no chemical modification on the drug under the current experimental conditions.

Degradation of laser treated matrices is characterized through the MW measurement by GPC. The M_w and M_n are given in Figure 4 for pure and 1% drug loaded PLLA. In both cases, degradation occurs at an accelerated rate in the initial stage. Similarly accelerated degradation trends are observed for 5% and 10% drug loaded PLLA. It is demonstrated that reduced crystallinity by laser melting accelerates polymer initial degradation. Once the degradation of the laser melted surface layer comes to an end, the remaining polymer matrix can be seen as to the same as the non-laser treated sample. In this stage, the laser treated sample degrades at a similar rate as the non-laser treated sample, which is shown as similar MW change rate beyond the initial degradation period in Figure 4.

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

$$\frac{1}{M_n} = \frac{1}{M_n^0} + kt \tag{1}$$

where M_n^0 is the number average MW at time 0, and k is the rate constant for constant [ester] and $[\mathrm{H_2O}]$. Based on Eq. (1) the degradation rate in the initial stage can be determined through curve fitting. The fitted curves are also given in Figure 4 from which the rate constant is determined. For all samples, k increases after the laser treatment. A higher drug concentration leads to a smaller increase of k, as shown in Figure 5. The reduction trend of k as a function

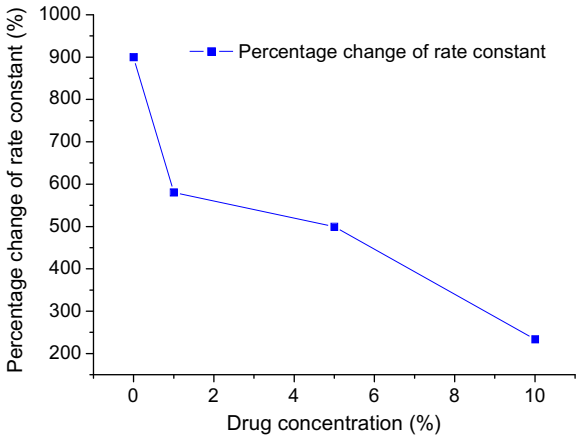

Figure 5. Percentage change of PLLA degradation rate constant caused by laser treatment as a function of drug concentration.

of the drug concentration agrees with the reduction trend of that crystallinity modification shown in Figure 3. It is suggested that drug absorbs a portion of laser energy and reduces the amount of crystallinity modification, which in turn influences the laser effect on degradation modification.

3. Conclusion

In this study, laser surface treatment has been shown to reduce the crystallinity of drug loaded polymer matrices. With a reduced surface crystallinity, the initial degradation is accelerated while degradation rate in the late stage is not affected. The effects of drug loading on laser modification of polymer crystallinity and degradation have also been investigated. With a higher drug concentration, polymer crystallinity and degradation rate are reduced less by laser melting. 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. The drug loading effect on laser modification of polymer degradation explored in the current study provides the groundwork for future investigation of laser modification of drug release from biodegradable polymers.

Acknowledgements

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