

A MONTE CARLO SIMULATION STUDY OF THE EFFECT OF CHAIN LENGTH ON THE HYDROLYSIS OF POLY(LACTIC ACID)*

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Abstract The intrinsic relationship between molecular chain length and the probability of chain reaction during poly(lactic acid) (PLA) hydrolysis was investigated by Monte Carlo simulation. The chain reaction rate was calculated by introducing a power function of different molecular chain lengths. The hydrolysis of both amorphous and extended-chain crystal PLA was selected as the model system. It is found that, the chain reaction probability was proportional to the chain length with a power of 0.4 for amorphous PLA and 0.7–1 for extended-chain crystal PLA, respectively. These results indicate that PLA with longer chain length usually exhibits larger reaction rate than that with shorter length. Comparing the hydrolysis of the two kinds of PLA, the competition between longer and shorter chains in the different condensed structures is different.

Keywords: Monte Carlo; Simulation; Chain length; Poly(lactic acid); Hydrolysis; Molecular weight distribution.

INTRODUCTION

Degradation property of poly(lactic acid) (PLA) is of great importance in the application as biomedical materials^[1]. Many factors contribute to the degradation of PLA, and the degradation rate of PLA has been widely studied^[2, 3]. There into, the time evolution of the weight-average molecular weight was a key point^[4–6]. Studying the competition of molecules is a way to investigate the evolution of weight-average molecular weight.

Up to now, there are few studies focusing on the competition of PLA with different chain lengths. On the view of the physical properties of molecules, two molecules with different molecular weights are different. PLA molecules, owing to their same structure but slight differences in molecular weight, have close properties, it is unbelievably hard to separate them by experimental methods. Materials of PLA are composed of a large amount of PLA molecules with different molecular weights. It is obvious that the molecules with different molecular weights are bound to exhibit different abilities during reactions. Unfortunately, due to limitations of experimental methods, the effect of molecular weight on the degradation is scarcely reported. In contrary, computer simulation can easily record each chain in the reaction system^[7, 8]. It can be used to investigate the competition of chains during hydrolysis.

Computer method based on suitable mathematic tactics, such as Monte Carlo algorithm^[9], is promising to be the major way overcoming the experimental limitations to study the effect of molecular weight on the PLA degradation rate. Model for the variation in the molecular weight distribution during degradation is mainly conducted to study the location of fracture on the molecular chain. Models^[10–12], usually adopted, including unzipped scission, random scission, central cut and Gaussian scission, only succeeded in simulating some degradation under special conditions^[13]. Emsley *et al.*^[11] investigated the changes of the molecular weight

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distribution curves of the production of linear polymer after the random scission and central scission. Mohammadi *et al.*^[14] discussed the effect of molecular weight on the degradation rate by investigating the amorphous PLA degradation. Tayal *et al.*^[15] found that there were discrepancies between the simulation result and the experiment in the polysaccharide degradation.

The major cause of the discrepancies between the simulation and the experiment, apart from the complexity of the fracture, could be ascribed to the effect of the molecular weight on the reaction probability of the chain. Hence, in this paper, we assume that the ability of the chain participating in the reaction varies continuously with the chain of different molecular weights, and the reaction rate is associated with the molecules with different molecular weights by an appropriate function. This study on the effect of chain length helps to analyze the reaction mechanism of the hydrolysis of the biodegradable PLA.

MODELS AND MONTE CARLO ALGORITHM

Modeling

Materials

According to Kricheldorf and Sumbel's method^[16], L-poly lactide (PLLA) was prepared *via* ring opening polymerization of L-lactide. The thin PLLA film was prepared by molten tableting.

The thickness of the tablets (18 mm × 30 mm) was $25 \pm 5 \mu\text{m}$. PLLA films was placed between glass sheets, melted at 200 °C for 3 min and quenched under liquid nitrogen to get amorphous PLLA films.

Each of the PLLA films (18 mm) was placed between two Teflon sheets and then sealed in a glass tube^[17]. The sealed PLLA films were melted at 200 °C for 5 min, and then annealed at 160 °C for 600 min to be crystallized, after that they were quenched by liquid nitrogen. To obtain the extended-chain crystal PLLA or to remove the chains in the amorphous regions, hydrolysis of the crystallized films was carried out in 100 mL phosphate buffer solution (PBS, 0.15 mol/L, pH = 7.4, 97 °C) for 40 h. After the hydrolysis, the films were rinsed with distilled water and dried for 7 days under reduced pressure at room temperature.

Hydrolysis experiments

PLLA films were placed in 100 mL, 0.15 mol/L Phosphate Buffered Saline (PBS) solution (pH = 7.4, 37 °C) for predetermined periods of time, the buffer solution was changed every month^[18]. After hydrolysis, the residual amorphous PLLA films were washed with distilled water and dried for 7 days under reduced pressure at room temperature. The PLLA crystalline residues were collected by centrifugation (Xiangyi centrifuge, TG16-WS) at 11000 r/min for 30 min and washed with distilled water followed by drying under reduced pressure at room temperature for at least 7 days.

Molecular weight measurements and remaining weight tests

Molecular weight and molecular weight distribution of PLLA at different hydrolysis time were measured *via* gel permeation chromatography (GPC, Waters 1515), column temperature 40 °C, in chloroform, using polystyrene as a standard sample.

The remaining weights were calculated as the following:

$$\text{Remaining weight (\%)} = 100 \times W_b / W_a \quad (1)$$

where W_a and W_b are the weight of the films before and after hydrolysis, respectively. The weights of these materials were measured by Sartorius electronic balance.

Degradation rate of PLLA

The scission of PLLA chains during hydrolysis could be regarded as the self-catalysis ester bond scission of the unzipped acid, seen as follows^[19]:

$$d[\text{COOH}]/dt = k'[\text{COOH}][\text{H}_2\text{O}][\text{ester}] \quad (2)$$

[COOH] denotes the concentration of carboxyl groups. Assuming $[\text{H}_2\text{O}]$ [ester] is constant and $[\text{COOH}] \propto M_n^{-1}$,

we can convert equation (2) to

$$M_{n,t} = M_{n,0} \exp(-kt) \quad (3)$$

$M_{n,t}$ and $M_{n,0}$ denote the molecular weight at time t and 0. $k = k'[\text{H}_2\text{O}][\text{ester}]$, so:

$$\ln M_{n,t} = \ln M_{n,0} - kt \quad (4)$$

If the molecular weight was determined, the degradation rate k could be calculated *via* this equation.

Monte Carlo Algorithm

Model of chain-length-independence

The scission reaction of PLA could be modeled by the Monte Carlo chemical kinetics model^[20] (Gillespie model^[9]). Simulating a reaction process is to identify one of the reactants in the system participating in a certain chemical reaction at a certain time. Suppose all PLA molecules with different chain length participate in degradation reaction at the same time. A chain cleavage of the μ -th type of ester bonds occurs if:

$$\sum_{i=1}^{\mu-1} P_i < r_1 \sum_{i=1}^M P_i < \sum_{i=1}^{\mu} P_i \quad (5)$$

In which r_1 is uniformly distributed random numbers within (0, 1), and M is the total number of the different types of ester bonds. P_i is the probability of the i reaction. The corresponding time step length of the chain cleavage is calculated by

$$dt = \frac{1}{\sum_{i=1}^M P_i} \ln\left(\frac{1}{r_2}\right) \quad (6)$$

r_2 is another uniformly distributed random number within (0,1). The probability of the reaction P is described below:

$$P(k_s, n_u) = k_s n_u \quad (7)$$

k_s is denoted as the microscopic rate constant of the reaction, n_u is the number of molecules involved in each reaction, u represents the number of chain units of these molecules between the interval $1 \leq u \leq u_{\max}$. The values of the microscopic rate constants are difficult to determine. When the reaction is a first-order reaction:

$$k_s = K \quad (8)$$

k_s is the microscopic rate constant, K is the macroscopic reaction rate constant. According to the value of macro reaction rate constant K , the value of k_s are approximately obtained.

This model executes one chain cleavage at each time step. The calculation follows:

- (i) Calculate three scission reaction probabilities with random scission $P(k_{rs}, n_u)$, central scission $P(k_{cs}, n_u)$, and unzipped scission $P(k_{zs}, n_u)$ by Eq. (7), respectively.
- (ii) Selecting a chain to occur a specific scission by Eq. (5). The number of the molecules is recalculated after the scission. When the random scission occurs, a random unit on the selected chain is broken. Relatively, the specific unit is chosen to break on the selected chain when the central or unzipped scission is occurred.
- (iii) Set a time step dt by Eq. (6) and update time $t = t + dt$.
- (iv) Return to step (i).

This model ignores the chain length affection.

Model of chain-length-dependence

To scale the difference in reaction rates between long chains and short chains, we assumed a parameter R called molecular weight reaction index, and it defines that the reaction rate is proportional to the molecular weight with the R -th power. For example, molecules of molecular weight m and n , the chain reaction probability of the

former is $(m/n)^R$ times that of the latter. This model can be applied to any kinds of degradation by modifying the parameter R for the domain of any real number. When R is a positive number, the probability of long chains is larger than that of the short chains, vice versa. If R becomes zero, it means that the molecules with different molecular weights have the same reaction probability in the reaction. If R becomes one, the reaction probability is linear proportion to the molecular weight.

Using Gillespie's method, the probability of all the reactions is described as follows:

$$P'(k_s, n_u) = k'_u m_u^R n_u \quad (9)$$

$$k_s = k' \times m_u^R \quad (10)$$

k'_s defines the micro reaction rate constant by equation (10). m_u means the molecular weight of the u -th chain. R is the molecular weight reaction index. Molecular weight can be considered as the number of chain units. u was defined as the number of chain units of the u -th chain. So for PLA, there is:

$$m_i = u \times 72 + 18 \quad (11)$$

Calculate steps are similar to the model of chain-length-independence, using Eq. (9) instead of Eq. (7). The model with the effect of molecular weight for the PLA hydrolysis will be obtained.

Evaluation of the Results

A match function $C(R, k, t)$ is defined in order to evaluate the matching degree between the simulation results and the experimental GPC ones:

$$C(R, k, t) = \sqrt{\frac{\sum_{i=1}^N [n_{u,\text{exp}}(t) - n_{u,\text{simu}}(R, k, t)]^2}{N}} \quad (12)$$

Here, k is the microscopic reaction rate constant in unit of day^{-1} ; t is the reaction time in unit of day; N means the maximum number of the chain units at time t ; $n_{u,\text{exp}}(t)$ and $n_{u,\text{simu}}(R, k, t)$ means the number of units on the u -th chain at time t in the experiment and the simulation results, respectively. The larger the difference between the experiment and the simulation results, the larger the value of the $C(R, k, t)$. The absolute value of the $C(R, k, t)$ is related to the number of selected examples during the normalization process. So, here the relative value of the $C(R, k, t)$ is discussed, instead of the absolute value. In the simulation of PLLA hydrolysis, the molecular weight reaction index R is set, and the reaction rate constant k is a variable. The minimum value of the $C(R, k, t)$ in time t will be found. The golden section method is used to optimize, and the convergence precision $\varepsilon = (\text{minimum region}) \times 10^{-3}$.

Realize

The simulation program was coded in C++ language, and run on a Pentium4 3.2GHz, 1G memory computer with Windows XP.

RESULTS AND DISCUSSION

Simulation of Amorphous PLLA Hydrolysis

The experimental results of the degradation of amorphous PLLA in water are shown in Fig. 1. The degradation rate constant calculated via Eq. (4) demonstrates that the degradation rate constant k is not a constant and increases from $2.83 \times 10^{-3} \text{ day}^{-1}$ (first year) to $4.03 \times 10^{-3} \text{ day}^{-1}$ (the third year); both values are close to the data reported by Cha^[19] ($6.73 \times 10^{-3} \text{ day}^{-1}$) and Tsuji^[18] ($5.20 \times 10^{-3} \text{ day}^{-1}$). Although there was a recrystallization process in the hydrolysis, the crystal region had a little effect on the hydrolysis of amorphous PLLA^[18]. So the simulation model has ignored the crystal region affection.

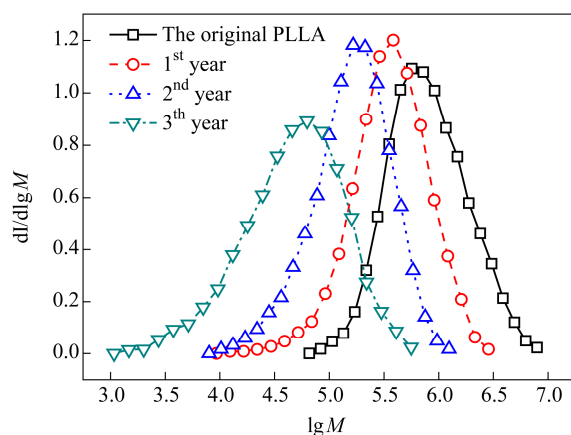


Fig. 1 The molecular weight distribution curves of amorphous linear PLLA after degraded in PBS

The hydrolysis of amorphous PLLA was first simulated using the model without considering the difference in the chain length of PLLA (chain-length-independence). According to the research of Emsley^[11] and Bose^[10], the shape of the molecular weight distribution curve of the hydrolysis products would be affected by the scission mode of the linear chain. The simulation adjusted the reaction rate constant of the two scission modes k_{rs} and k_{cs} (numerical interval $[1 \times 10^{-4}, 1 \times 10^{-2}] \text{ day}^{-1}$). Selecting the minimum value of $C(0, k, 1095)$ in this range of the reaction rate constant, the molecular weight distribution curves of experiment and simulation are shown in Fig. 2(a). It can be found that there is a notable discrepancy between the curves of the experiment and simulation, and the discrepancy cannot be reduced by adjusting the model parameters of the scission mode. The results imply that the actual situation of PLLA hydrolysis is not independent of the chain length, and the model of chain-length-independence is not applicable.

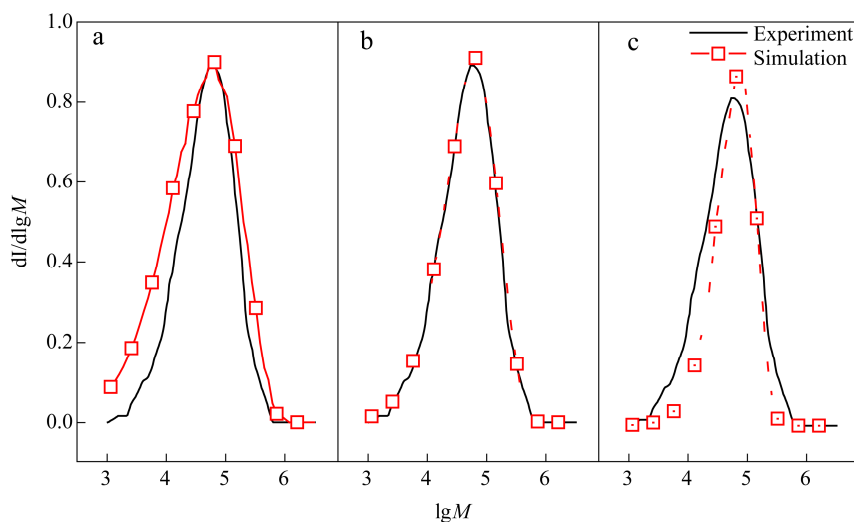


Fig. 2 Molecular distribution curves of amorphous PLA after hydrolysis for 1095 days with (a) $R = 0$, (b) $R = 0.4$, and (c) $R = 1$

(a) $k_{rs} = 3.896 \times 10^{-3} \text{ day}^{-1}$, $k_{cs} = 2.741 \times 10^{-3} \text{ day}^{-1}$; (b) $k_{rs} = 3.792 \times 10^{-3} \text{ day}^{-1}$, $k_{cs} = 2.687 \times 10^{-3} \text{ day}^{-1}$; (c) $k_{rs} = 3.225 \times 10^{-3} \text{ day}^{-1}$, $k_{cs} = 2.216 \times 10^{-3} \text{ day}^{-1}$

Using the model of chain-length-dependence, the resulting molecular weight distribution curves of amorphous PLLA after hydrolysis for 1095 days with different R values are shown in Fig. 2. When the reaction probability is proportional to or does not relate to the molecular chain length, a notable discrepancy between the

simulation and experimental results occurs. When $R = 0.4$, the simulation results are very consistent with the experimental results, meaning that the reaction rate correlates with the molecular chain length. The longer the molecular chain is, the greater the probability of the reaction occurs. In the calculation of $C(R, k, t)$, k is a variable but it changes little, and can be approximately regarded as a constant. While the time t is a fixed parameter, therefore the $C(R, k, t)$ is simplified as $C(R)$.

According to the definition, the smaller the value of the function $C(R)$ is, the better the matching degree. A series of R values had been invited to simulate the hydrolysis. The values of $C(R)$ are shown in Fig. 3. The minimum value of $C(R)$ was obtained by using the molecular weight reaction index $R = 0.4$ in the whole amorphous PLLA hydrolysis process. According to the Eq. (10) of the reaction rate, there is:

$$k_{\text{long}}/k_{\text{short}} = (m_{\text{long}}/m_{\text{short}})^{0.4} = [(u_{\text{long}} \times 72 + 18)/(u_{\text{short}} \times 72 + 18)]^{0.4} \quad (12)$$

The subscripts long and short mean the long chain and the short chain, respectively. Here m is the molecular weight of the chain, and u is the number of units in the chain. When the molecular weight is large enough, the above equation can be converted to:

$$k_{\text{long}}/k_{\text{short}} \approx (u_{\text{long}}/u_{\text{short}})^{0.4} \quad (13)$$

The long chains have a faster reaction rate than the short ones. In the early stage of the hydrolysis process, the $C(R)$ value varied little with the change of R values, suggesting a weak influence of the R value on the hydrolysis reaction. With the increase of the hydrolysis time, the influence of R increased gradually.

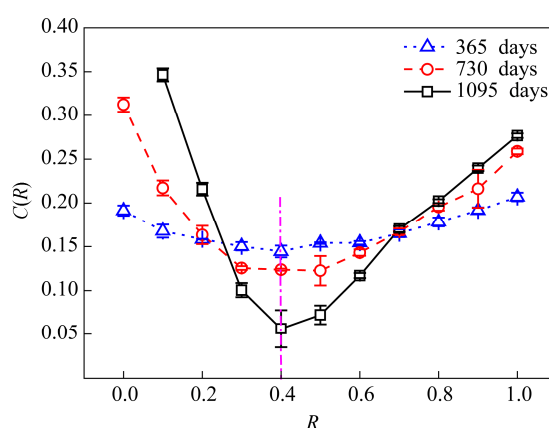


Fig. 3 $C(R)$ values with different R values of the amorphous PLA hydrolysis simulation at 3 periods

The Simulation of Extended-chain Crystallite PLA Hydrolysis

The extended-chain crystal PLLA has a unique condensed structure. It was considered that the hydrolysis of extended-chain crystal PLLA was dominated by the unzipped scission mode, because the cleavage reaction does not occur in the crystal region^[21]. The experiment results of molecular weight distribution curves are shown in Fig. 4. The model of chain-length-independence was used to simulate the hydrolysis of extended-chain crystallite PLLA with the degradation reaction in the presence of random scission k_{rs} , central scission k_{cs} and unzipped scission k_{zs} (numerical interval $[1 \times 10^{-7}, 5 \times 10^{-1}]$ day⁻¹). The molecular weight distribution curve with the minimum value of $C(R)$ is shown in Fig. 5. It was found that the reaction rates of random scission and central scission were very small. Therefore, the hydrolysis of extended-chain crystal PLLA could be approximately considered as unzipped scission mode only. As is seen in Fig. 5, there was still some discrepancy between simulation and experiment. This motivated us to introduce the chain-length-dependent reaction rate to the simulation.

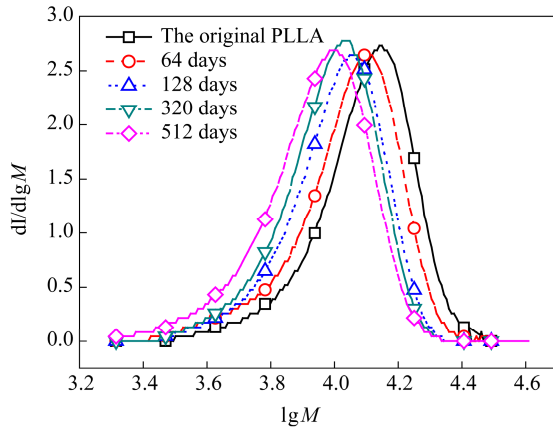


Fig. 4 The molecular weight distribution curves of extended-chain crystal PLLA after degradation in PBS

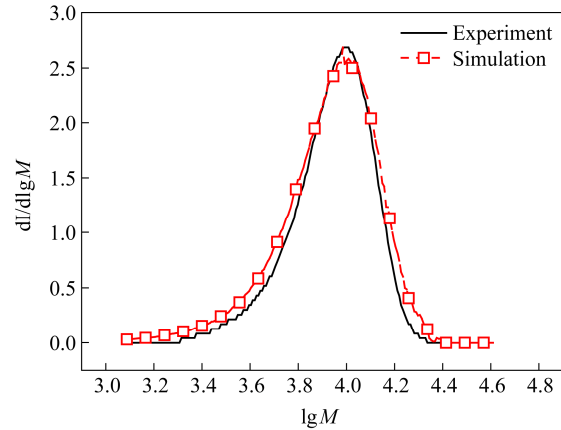


Fig. 5 Molecular weight distribution curves of experiment results and simulation results of extended-chain crystal PLLA hydrolysis after 512 days with the parameter $R = 0$ ($k_{rs} = 2.267 \times 10^{-7} \text{ day}^{-1}$, $k_{cs} = 1.259 \times 10^{-7} \text{ day}^{-1}$, $k_{zs} = 1.146 \times 10^{-1} \text{ day}^{-1}$)

Using the model of chain-length-dependence, the resulting molecular weight distribution curves of extended-chain crystal PLLA after hydrolysis for 512 days with different R values are shown in Fig. 6. Comparing the case of the hydrolysis of the amorphous PLLA, the influence of R is weak in extended-chain crystal PLLA. When $R = 0.7$, the minimum value of $C(R)$ was obtained.

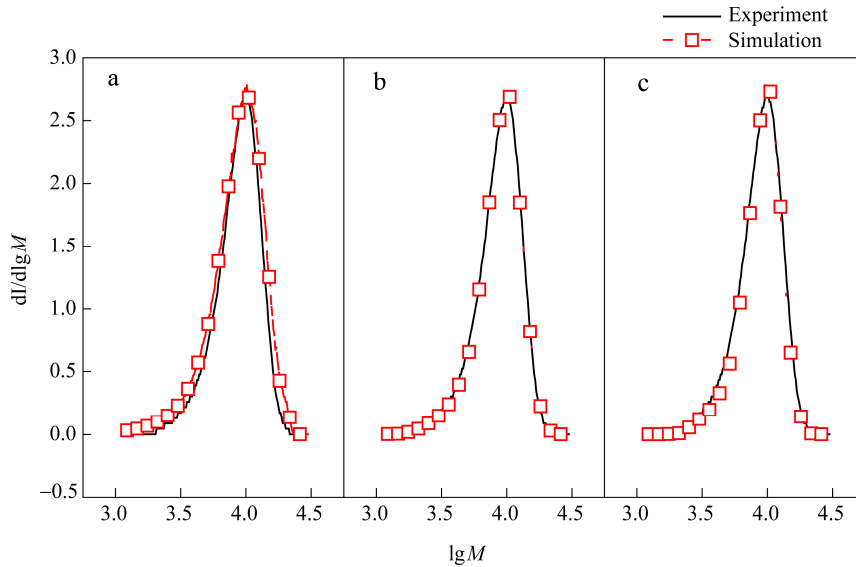


Fig. 6 Molecular weight distribution curves of extended-chain crystallites PLA hydrolysis after 512 days with (a) $R = 0$, (b) $R = 0.7$, and (c) $R = 1$
(a) $k_{zs} = 1.249 \times 10^{-1} \text{ day}^{-1}$; (b) $k_{zs} = 9.468 \times 10^{-2} \text{ day}^{-1}$; (c) $k_{zs} = 8.998 \times 10^{-2} \text{ day}^{-1}$

The match function $C(R)$, which quantifies the matching degree of molecular weight distribution between simulation and experiment, is shown in Fig. 7 as a function of R for PLLA degraded over a period of 512 days. During each period, there exists a best molecular weight reaction index, shown in Fig. 8. As the hydrolysis time increased, the R value decreased. The relationship between reaction probability and the chain length changed from directly proportional to unrelated. The reaction rate constants between different molecules were directly proportional to their molecular weight ratio with 1-st to 0.7-th power. It can be found from the result of the

simulation in which R was a positive real number, the chains with the larger molecular weight were more inclined to degrade in the hydrolysis process. And R decreased it indicated that the influence of molecular weight reduced. The reaction probabilities of the chains changed and became closed to each other as the hydrolysis proceeded.

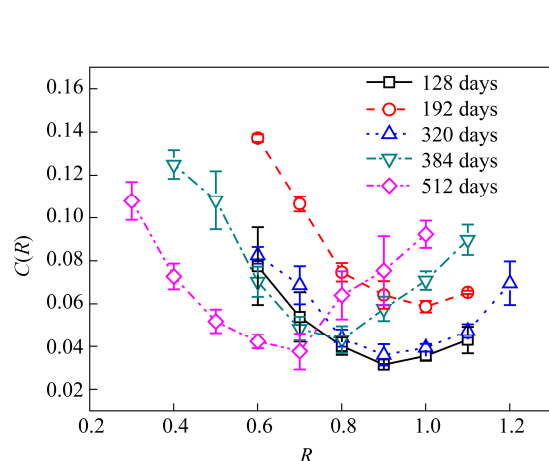


Fig. 7 $C(R)$ values with different ' R ' values of the extended-chain crystallite PLLA hydrolysis after different hydrolysis time

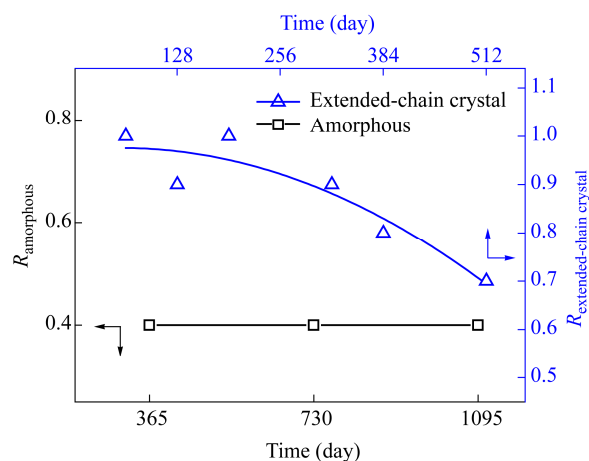


Fig. 8 The best ' R ' values of the extended-chain crystallite PLLA and amorphous PLLA hydrolysis in different hydrolysis time

When the hydrolysis reaction occurs, PLA chains must be in contact with water molecules. In the case of the crystalline PLLA, which has a compact crystalline region where water molecules cannot go into, the scission will occur on the surface of the regions. The extended-chain crystal PLLA is full of the chain ends on the surface of the regions. That is why the material degrades in an unzipped scission mode. In the experimental study, the PLLA was prepared by pre-degradation to remove the amorphous region of the PLLA. In the pre-degradation process, the PLA chains rearranged^[17], and the crystalline thickness increased^[22]. The defects developed easily on the surface at 97 °C. The chain scissions mainly occurred in these defects on the surface. After a time period of hydrolysis, the lengths of the chain ends outside the crystalline become the same, which caused the morphology of materials to be more regular and homogeneous. The probabilities of various molecules were likely to become closer. Therefore, the molecular weight reaction index decreased.

The results of hydrolysis of the extended-chain crystal PLLA are completely different from that of the amorphous PLLA. Figure 8 shows that the best molecular weight reaction index decreases along the extended-chain crystal PLLA hydrolysis, on the contrary, the index does not change in the amorphous PLLA hydrolysis. In the hydrolysis of amorphous PLLA, the reaction probabilities of the chains with different lengths will not change as the hydrolysis extended. Therefore, the molecular weight reaction index stays constant.

CONCLUSIONS

Monte Carlo simulation was successfully applied to investigate the hydrolysis behaviors of both amorphous PLLA and extended-chain crystal PLLA using molecular weight reaction index model. In both cases, excellent agreement between simulation and experiment was obtained by modulating the value of molecular weight reaction index, introduced to take into account a chain-length-dependent degradation rate. In the hydrolysis process of amorphous PLLA, the molecular weight reaction index is equal to 0.4, and it remains unchanged as the hydrolysis goes on. In the hydrolysis process of the extended-chain crystal PLLA, the molecular weight reaction index changed with the variation of the hydrolysis time, from 1.0 to 0.7, indicating that the reaction abilities of molecules with different molecular weights tended gradually to be the same.

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