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A simplified theory of crystallisation induced by polymer chain scissions for biodegradable polyesters

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ABSTRACT

A simplified theory for the crystallisation of biodegradable polyesters induced by polymer chain scissions during biodegradation is presented following a theory developed by Han and Pan. The original theory is greatly simplified so that it becomes very straightforward to use and the number of material parameters is significantly reduced. Furthermore it is demonstrated that the spherulite structure widely observed in polymers can be taken into account using the theory. The simplified theory is fitted to the experimental data of poly-L-lactic acids (PLLAs) obtained from literature. It is shown that the simplified theory is equally able to fit the data as the original one. It is also shown that the theory can fit degradation data for PLLAs of different initial degrees of crystallinity with spherulite structures.

1. Introduction

Bioresorbable polymers such as poly-L-lactic acid (PLLA) have been widely used for various temporary interventions inside the human body. Fixation screws, drug-eluting stents and tissue engineering scaffolds are some typical examples. These bioresorbable polymers have been the subject of extensive experimental testing giving details on average molecular weight, crystallinity and mechanical properties as functions of time. A clear degradation pathway has been established [1–10]. Water diffuses into the devices relatively quickly and then the polymer chains react slowly with water molecules (hydrolysis) leading to chain cleavage. The chain scissions provide the polymer chains with extra mobility so that they crystallise leading to a gradual and significant increase in the degree of crystallinity. It is very important to be able to predict how crystallinity changes during the degradation process because crystallinity affects both the degradation rate and mechanical properties of the devices [3,7,11]. Pan and his co-workers summarised the existing experimental observations and understanding into a set of mathematical models for polymer degradation [12–14]. In particular they developed a theory for chain scission induced crystallisation [12,13] by extending the classical Avrami theory [15–17]. Their original theory, however, involves both differential and integrational equations which are difficult to use. The objective of this paper is to show that the theory can be greatly simplified. The integration equation can be eliminated and the number of material parameters in the theory can be reduced. Furthermore it is shown that the spherulite structure widely observed in semi-crystalline bioresorbable polymers can be taken into account in the theory.

2. A simplified theory for crystallisation induced by polymer chain scission

In the model developed by Han and Pan [12,13], the rate of polymer chain scission due to hydrolysis reaction is given by

$$\frac{dR_s}{dt} = k_1 C_e + k_2 C_e \left(\frac{C_{ol}}{1 - X_c}\right)^{0.5} \tag{1}$$

in which R_s (mol m^{-3}) is the molar number of scissions per unit volume, k_1 (day^{-1}) and k_2 ([mol^{-1} m^3]$^{0.5}$ day^{-1}) are the reaction constants for the non-catalytic and auto-catalytic hydrolysis reactions respectively, C_e (mol m^{-3}) is the molar concentration of ester bonds in the amorphous polyester chains, and X_c is the degree of crystallinity (volume fraction). Water is assumed to be abundant hence its concentration does not appear in the rate equation. The polymer chains have a distribution in length. In order to make the model traceable, Wang and Pan [14] made a key simplification in their original model – the polymers chains are divided into two

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groups: long polymer chains that are water insoluble and cannot diffuse, and short chains, referred to as oligomers, that are water soluble and can diffuse. In the degradation model, this distinction is important because the oligomers can diffuse away to reduce the local acidity and reduce the degradation rate. On the other hand the actual distribution of the chain length does not have a major effect on the degradation rate. If a chain scission occurs near either end of the chain, then an oligomer is produced. The molar number of ester bonds in oligomers per unit volume, C_{ol} (mol m^{-3}), is calculated based on the concentration of scissions according to the following empirical relation [12,13]:

$$\frac{C_{ol}}{C_{e0}} = \alpha\left(\frac{R_s}{C_{e0}}\right)^{\beta} \tag{2}$$

in which α and β are empirical parameters (no units), and C_{e0} (mol m^{-3}) is the initial value of C_e. The values of α and β can be adjusted to reflect the probability of scissions creating oligomers, thereby allowing the model to be suitable for degradation ranging from end scission to random scission. For crystallisation, Han and Pan [12,13] assume that each chain scission has a probability of nucleating a crystal which gradually grows to a maximum size. Because crystals are nucleated at different times of the degradation process, the current degree of crystallinity is history dependent for which an integrational equation over time is required. In fact the individual crystals are all nano-sized [18] and the time taken to form these crystals are much shorter than the typical time taken by the hydrolysis reaction. In the current paper, it is assumed that each chain scission has a probability, p (no units), of nucleating a crystal which immediately grows to a finite volume of V_c (m^3). The extended degree of crystallinity, X_{ext} (volume fraction), which assumes the crystals do not impinge on each other, is then given by

$$X_{ext} = p\eta_A R_s V_c \tag{3}$$

in which η_A is Avogadro's constant (mol^{-1}). Following the Avrami theory [15–17], we assume that the actual and extended degrees of crystallinity are related by

$$\frac{dX_c}{dX_{ext}} = X_{max} - X_c \tag{4}$$

in which we have introduced a maximum degree of crystallinity, X_{max} (volume fraction), as a model parameter. Finally following Han and Pan [12,13] the consumption of amorphous polymer chains by the oligomer production and crystallisation leads to

$$\frac{dC_e}{dt} = -\frac{dC_{ol}}{dt} - \frac{\omega dX_c}{dt} \tag{5}$$

in which ω is the inverse molar volume (mol m^{-3}) of the crystalline phase. The number-averaged molecular weight (g mol^{-1}) is given by

$$M_n = \frac{(C_e + \omega X_c)M_0}{N_{chains0} + (R_s - (C_{ol}/m))} \tag{6}$$

in which $N_{chains0}$ (mol m^{-3}) is the initial molar concentration of the polymer chains, M_0 (g mol^{-1}) is the molar mass of a lactic acid unit, and m (no units) is the average number of repeating units of the oligomers. The term on the top of Eq. (6) is the total weight of the crystalline and amorphous phases in the calculation unit excluding oligomers due to the assumption that oligomers are too small to be measured experimentally. The term on the bottom is the total number of polymer chains excluding oligomers in which $(R_s - (C_{ol}/m))$ is the number of new chains produced by chain scission excluding oligomers. Eqs. (1)–(6) completely define the simplified model for simultaneous degradation and crystallisation of polyesters. Here the oligomer diffusion is ignored in order for us to focus on the new elements of the crystallisation theory. The diffusion equation used by Pan et al. [12–14] can be readily added to the above equations to accommodate oligomer diffusion.

In the original model by Han and Pan [12,13], the changing rate of molar concentration of nucleation sites, N (mol m^{-3}), is calculated as

$$dN = -\xi N\, dt - \frac{N}{1 - X_c}\, dX_c + p\, dR_s \tag{7}$$

The extended degree of crystallinity is given by

$$X_{ext} = \int_0^t \alpha_0 r_{max}^3 \left(1 - e^{(G/r_{max})(t-\tau)}\right)^3 \xi N(\tau)\eta_A\, d\tau \tag{8}$$

in which crystal growth is integrated from the time since their nucleation, τ (day), to the current time t (day). The model parameters ξ (day^{-1}), λ (no units), α_0 (no units), r_{max} (m), and G (m day^{-1}) have been removed in the simplified theory. The actual and extended degrees of crystallinity are related by

$$\frac{dX_c}{dX_{ext}} = \left[\left(1 - \frac{C_{ol}}{C_{e0}}\right) - X_c\right]^{\lambda} \tag{9}$$

A minor correction is made in Eq. (9) to that used by Han and Pan to ensure mass conservation.

3. Validation of the theory using data obtained by Weir et al.

Weir et al. [4,5] carried out a set of degradation experiments for PLLA in phosphate buffer solution (PBS) with pH 7.4 at three temperatures: 37 °C, 50 °C, and 70 °C. Compression-moulded samples of 0.8 mm in thickness were used. Measurements of average molecular weights, mass loss, crystallinity, and thermal and mechanical properties were taken at various follow-up times during degradation. Weir et al. [4,5] found that their molecular weight data can be fitted to a hydrolysis model using a single activation energy despite testing at temperatures on both sides of the glass transition temperature. This was later confirmed by Han et al. [13] who fitted both the molecular weight and crystallinity data to the original model. Here the following parameters are assumed to be temperature dependent according to Arrhenius relation:

$$k_1 = k_{10}e^{-(E_{k_1}/RT)}, \quad k_2 = k_{20}e^{-(E_{k_2}/RT)},$$
$$G = G_0 e^{-(E_G/RT)}, \quad \xi = \xi_0 e^{-(E_\xi/RT)}, \quad X_{max} = X_{max0}e^{-(E_{X_{max}}/RT)} \tag{10}$$

in which k_{10} (day^{-1}), k_{20} ([mol^{-1} m^3]$^{0.5}$ day^{-1}), G_0 (m day^{-1}), ξ_0 (day^{-1}), and X_{max0} (no units) are pre-exponential constants, E_{k1}, E_{k2}, E_G, E_ξ, and E_{Xmax} (all J mol^{-1}) are the corresponding activation energies, R (J K^{-1} mol^{-1}) is the gas constant and T (K) is the absolute temperature.

In order to quantitatively indicate how well a model can fit the experimental data, a root mean square error is used in the following discussion which is defined as

$$\text{RMSE} = \sqrt{\frac{\sum (x_i - y_i)^2}{n}} \tag{11}$$

where x_i are the calculated values from the model, y_i are the measured values, and n is the number of data points.

Fig. 1 shows the best fit between our theories and the experimental data obtained by Weir et al. [4,5]. The solid lines represent

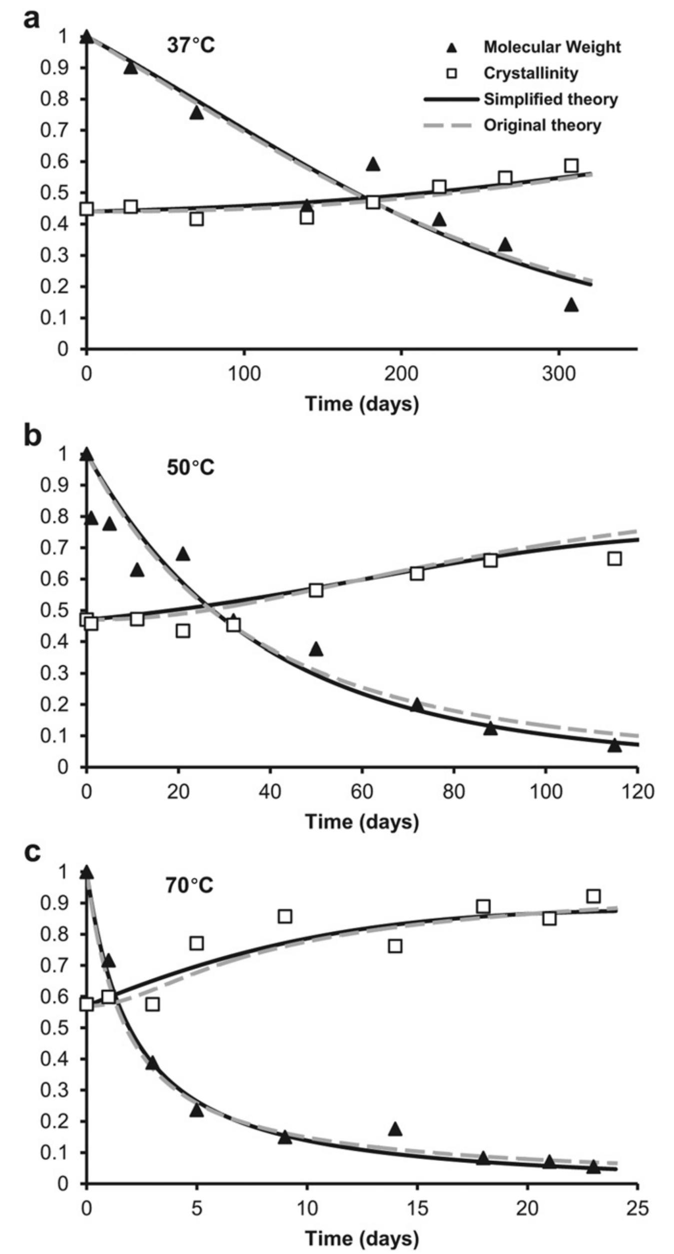

Fig. 1. Normalised number-average molecular weight and crystallinity as a function of hydrolysis time. Experimental data points [4,5] (discrete symbols) are plotted for three temperatures: (a) 37 °C, (b) 50 °C, and (c) 70 °C. Simplified and original models are shown as solid and dashed lines respectively.

the simplified theory, the dashed lines represent the original theory and the discrete symbols represent the experimental data. It can be observed from Fig. 1 that the simplified theory works with similar accuracy to that of the original one. For the degree of crystallinity, RMSE = 0.0425 for both theories. For the normalised molecular weight, RMSE = 0.0678 and 0.0688 for the original and simplified theories respectively. The initial conditions for the numerical calculations are $X_c = X_{c0}$; $C_e = C_{e0}(1-X_{c0})$; and X_{ext}, R_s, C_{ol}, t, $N = 0$. The model parameters used in the fitting are provided in Table 1. X_{c0}, $N_{chains0}$, C_{e0} and M_0 are all initial properties of the polymer before degradation which are taken from Weir et al. [4,5]. The inverse molar volume of the crystalline phase, ω, is taken as the same as that of the amorphous phase. V_c is the volume of a polymer crystal which was estimated from the literature [18]; for simplicity, V_c is taken to equal $a_0^* r_{max}^3$ from the original model. The values of $\alpha = 28$ and $\beta = 2$ represent a probability of scissions producing oligomers when the polymer degradation is assumed to occur by random scission [13]. m is the average degree of polymerisation of the oligomers which is taken as 4 since it is generally believed that short chains with less than 8 degree of polymerisation become water soluble and mobile [19]. The best fit is achieved by setting the activation energies such that non-catalytic degradation is more dominant at high temperatures and auto-catalytic degradation is more dominant at low temperatures. This is supported by existing experimental data [20,21] in which hollow specimens resulted from degradation at 37 °C but not at 60 °C. The zero activation energy for G and very large value of G_0 in the original theory reflect that crystals grow very fast growth which reassures the validity of the simplified model.

4. The effect of spherulite structure

When amorphous PLLA is annealed, crystallinity gradually increases producing a typical spherulite microstructure. The spherulites contain crystal lamellae which are connected to each other by amorphous regions [18], hereon referred to as inter-lamellae amorphous regions. If the annealing process is ended before spherulites have grown to engulf the entire volume of the polymer then in addition to the inter-lamellae amorphous phase inside spherulites, there is a fully amorphous phase outside spherulites [3,11]. The two different amorphous phases are likely to vary in many ways due to, for example, the constraints put on the inter-lamellae amorphous phase by the nearby crystal lamellae. Tsuji et al. [3] suggested that the inter-lamellae amorphous regions may have an increased density of terminal carboxyl and hydroxyl groups which are excluded from the crystalline region during crystallisation (annealing). This indicates that the free amorphous regions and the inter-lamellae amorphous regions may degrade at different rates. To account for this difference, the simplified theory is applied to the volume occupied by the spherulites and the amorphous phase outside the spherulites separately using two different sets of parameters. Using "/in" and "/out" subscript suffixes to indicate the phases inside and outside the spherulites

Table 1
Model parameters that were used to fit the experimental data. Values were the same for the simplified and original model unless otherwise stated.

T (°C)	X_{c0}	$N_{chains0}$ (mol m^{-3})	C_{e0} (mol m^{-3})	M_0 (g mol^{-1})	ω (mol m^{-3})	α	β	m
37	0.448	7.85	17300	72	$=C_{e0}$	28	2	4
50	0.470	7.50						
70	0.575	7.50						

Parameters that varied between the models

		Original model	Simplified model
λ		3	–
α_0		$4\pi/3$	–
r_{max}	(nm)	10	–
p		1	0.01
E_G	(kJ mol^{-1})	0	–
E_ξ	(kJ mol^{-1})	130	–
E_{k1}	(kJ mol^{-1})	145	145
E_{k2}	(kJ mol^{-1})	65	75
E_{Xmax}	(kJ mol^{-1})	–	7.5
G_0	(m day^{-1})	1.0×10^{100}	–
ξ_0	(day^{-1})	1.1×10^{18}	–
k_{10}	(day^{-1})	6.5×10^{18}	6.0×10^{18}
k_{20}	([mol^{-1} m^3]$^{0.5}$ day^{-1})	1.3×10^6	7.0×10^7
X_{max0}		–	12.2
V_c	(nm^3)	–	4.19×10^3

respectively, and f_s (no units) to represent the volume fraction of the spherulites, we have

$$X_c = X_{c/in} f_s + X_{c/out}(1 - f_s) \tag{12}$$

$$R_s = R_{s/in} f_s + R_{s/out}(1 - f_s) \tag{13}$$

$$C_{ol} = C_{ol/in} f_s + C_{ol/out}(1 - f_s) \tag{14}$$

and

$$M_n = \frac{\left[f_s\left(C_{e/in} + \omega \cdot X_{c/in}\right) + (1 - f_s)\left(C_{e/out} + \omega \cdot X_{c/out}\right)\right] M_0}{N_{chains0} + (R_s - (C_{ol}/m))} \tag{15}$$

Variables without "/in" or "/out" suffixes represent average values for the whole polymer. Tsuji et al. [3] tested the degradation behaviour of PLLA samples of different initial degrees of crystallinity. PLLA films, 25–50 μm thick, were hydrolysed in PBS, pH 7.4, at 37 °C for 36 months. Five sets of films were tested with initial degrees of crystallinity of 0.00, 0.02, 0.30, 0.45 and 0.54; they are identified as PLLA0, PLLA15, PLLA30, PLLA45, and PLLA60 respectively to reflect annealing times of 0, 15, 30, 45 and 60 min at 140 °C. A distinctive spherulite structure was observed in their semi-crystalline PLLA samples. Tsuji et al. [3] fitted their molecular weight data to a simple model for auto-catalytic hydrolysis without taking into account its interaction with crystallisation. Different values of the reaction constant, k, had to be used for different periods of the degradation which in fact indicates that the model is invalid.

Fig. 2 shows the fitting between our simplified theory and the experimental data for molecular weight and degree of crystallinity. The overall RMSE is 0.0424 and 0.0370 for the normalised molecular weight and degree of crystallinity respectively. In the fitting the auto-catalytic hydrolysis rate, k_2, was the only parameter that was set at different values for the amorphous volumes inside and outside the spherulites. The best fit was obtained by setting k_2 inside the spherulites to be six times faster than that in the free amorphous regions, which suggests that the amorphous chains entrapped by the spherulites degrade in a more auto-catalytic manner than those outside the spherulites. This is consistent with the finding by Tsuji et al. [3] that the higher the initial degree of crystallinity, the faster their PLLA samples degraded. Table 2 provides all the parameters used in the fitting. It was found that when PLLA is annealed at 140 °C for sufficient time to allow spherulites to consume the entire volume, the crystallinity is approximately 0.55 [10,11] which was taken as the initial crystallinity inside the spherulites ($X_{c0/in}$). A same crystal limit, X_{max}, was used for polymer volumes inside and outside the spherulites. Setting $\alpha = 28$ and $\beta = 2$ implies oligomers are produced at the rate they would be if random scission occurred during the degradation [13]. The values of $N_{chains0}$ and f_s are derived from the measurement by Tsuji et al. [3]. The following initial conditions were used for the numerical calculation: $X_{c/in} = X_{c0/in}$; $X_{c/out} = X_{c0/out}$; $C_{e0/in} = C_{e0/out} = C_{e0}$; $C_{e/out} = C_{e0/out}$; $C_{e/in} = C_{e0/in}(1 - X_{c0/in})$; and $X_{ext/in}$, $X_{ext/out}$, $R_{s/in}$, $R_{s/out}$, $C_{ol/in}$, $C_{ol/out} = 0$. In the fitting k_1, $k_{2/in}$, $k_{2/out}$, p, and X_{max} are the parameters that were adjusted. It can be observed from Fig. 2 that the simplified theory is able to fit the experimental data for all five different films using a same set of parameters except for the auto-catalytic hydrolysis constants $k_{2/in}$ and $k_{2/out}$.

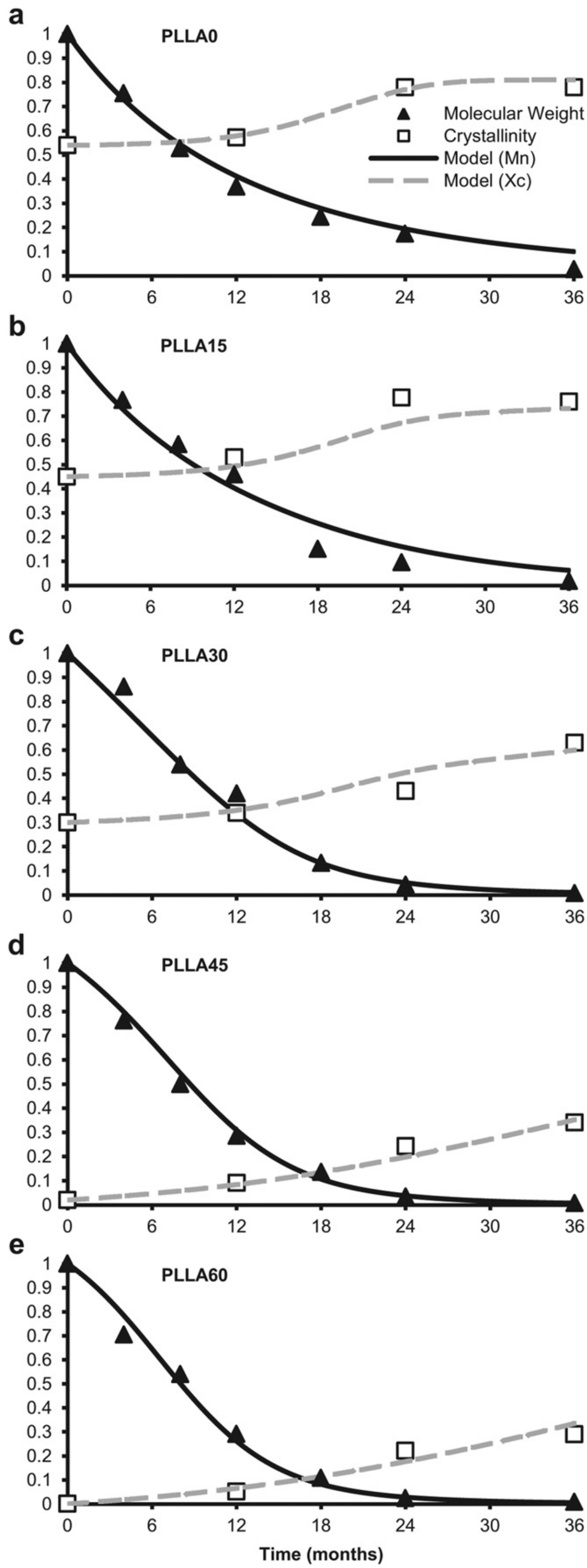

Fig. 2. Normalised number-average molecular weight (solid lines) and crystallinity (dashed lines) as a function of time for PLLA with different initial degrees of crystallinity of (a) $X_c = 0.00$, (b) $X_c = 0.02$, (c) $X_c = 0.30$, (d) $X_c = 0.45$, (e) $X_c = 0.54$. The discrete symbols are experimental data obtained by Tsuji et al. [3] while lines represent the fitting using the simplified model.

Table 2
Model parameters that were used to fit the experimental data.

Test ID	$N_{chains0}$ (mol m^{-3})	$k_{2.in}$ ([mol^{-1} m^3]$^{0.5}$ day^{-1})	p	M_0 (g mol^{-1})	m	f_S	$X_{c0,in}$	$X_{c0,out}$
PLLA0	2.31	53×10^{-5}	0.01	72	4	0	0.55	0
PLLA2	2.29					0.36		
PLLA30	2.42					0.55		
PLLA45	2.49					0.82		
PLLA54	2.13					0.98		
C_{e0} (mol m^{-3})	ω (mol m^{-3})	$k_{2.out}$ ([mol^{-1} m^3]$^{0.5}$ day^{-1})	k_1 (day^{-1})	α	β	X_{max}	V_c (nm^3)	
17,300	$=C_{e0.TOTAL}$	9.0×10^{-5}	1.1×10^{-5}	28	2	0.82	4.19×10^3	

5. Conclusion

The following conclusions can be drawn from this study:

- When modelling chain cleavage induced crystallisation in biodegradable PLLAs, it can be assumed that the crystal growth occurs much faster than the hydrolysis reaction.
- In semi-crystalline PLLAs, the amorphous polymer chains entrapped by the spherulites degrade much faster than the free amorphous polymer chains outside the spherules.
- Based on the above understanding, a simplified model proposed in this paper is able to fit experimental data of both molecular weight and crystallinity to a good accuracy.

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