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Texture Induced by Molecular Weight Dispersity: Polymorphism within Poly(L-lactic acid) Spherulites

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 Electronic Supplementary Information

Abstract Poly(L-lactic acid) (PLLA) has drawn much attention due to its excellent medical and pharmaceutical applications for decades. As a semi-crystalline polymer, morphology and crystal structure of PLLA greatly determine its properties. Here, we demonstrate, for PLLA films, a non-conventional texture featuring two types of spherulites emerging in pairs to form a distinct nested structure where a small spherulite (~10 μm) is embedded in a large one (100 μm to 300 μm). In addition to the size, the molecular weight and polymorph are different in the large and small spherulites. Crystallographic α -form and relatively low molecular weight are identified in the large spherulites, while *meta*-stable α' -form and relatively high molecular weight in the small ones. These differences suggest that the polydisperse PLLA polymers fractionate during film formation and the high-molecular-weight fraction crystallizes into the small spherulites with *meta*-stable structure because of its complicated polymer entanglement and high viscosity. In contrast, the rest of polymers crystallize into the large spherulites with the thermodynamically stable polymorph. Furthermore, this texture exhibits accelerated PLLA degradation initiated from the small spherulites, which is distinct from the typical PLLA spherulites. Insights provided by this work may lead to new texture-properties relationship associated with polydispersity of molecular weight.

Keywords PLLA; Spherulite; Polymorphs; Molecular weight

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INTRODUCTION

Poly(L-lactic acid) (PLLA) is well known as a biodegradable and biocompatible material that can be used in the biomedical field as surgical suture materials, drug release devices, tissue engineering scaffolds and so on.^[1–4] As a semi-crystalline thermoplastic polymer, the crystallization of PLLA often results in spherulites,^[5–8] and the properties of the crystals including mechanical and thermal properties are significantly influenced by its morphology and crystal structure.^[9–12] Moreover, polymorphism has been found and PLLA has complicated crystallization characteristics that four different crystal forms have been discovered depending on the preparation conditions.^[13–16] Efforts have been made to study the crystallization behavior of PLLA and its effects on the structures and properties, including the structural feature of single-crystal,^[13,17–19] thermal behavior of different crystal modifications^[20–24] as well as degradation performance of crystals under various conditions.^[25–27] These studies promote the in-depth understanding of the PLLA crystallization.

Very recently, a new texture inside spherulites of a semi-

crystalline polymer, poly(ϵ -caprolactone) (PCL), has been reported by our group.^[28,29] The PCL spherulites exhibit a spatial distribution of the degree of crystallinity, with lower crystallinity at the spherulite center. Also, the PCL spherulites exhibit non-uniform melting behavior, with the spherulite centers starting to melt at a lower temperature. Interestingly, non-uniformity of the degradation property within the PLLA spherulites was found previously by Cam *et al.*^[30] who noticed that erosion started from the center by hydrolysis when swelling the PLLA spherulites in a NaOH solution. Based on this non-uniform property within the PLLA spherulites as well as the rich crystallization behavior of PLLA, we envision that the PLLA spherulites might exhibit undetected textures featuring non-uniform crystalline structures. In this work, we examine the PLLA spherulites and report an unprecedented PLLA texture where two polymorphs coexist with one embedded in the other. Further, the formation mechanism for this texture is discussed and it is attributed to the molecular-weight-dependent crystallization kinetics.

EXPERIMENTAL

PLLA Spherulite Film Preparation

PLLA (M_n = 38 kDa, PDI = 1.38, Polymer Source) was dissolved in

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chloroform (HPLC, Ourchem) at 100 °C for 8 h with a concentration of 50 g/L. Subsequently, the solution was filtered (polytetrafluoroethylene, LABMAX, pore size of 0.22 μm). And then the solution was spin-coated at room temperature on a silicon wafer (2000 r/min for 60 s) to obtain PLLA films. Next, the films were melted at 200 °C for 30 min and the molten films were transferred quickly to a hot stage of 120 °C for isothermal crystallization (1 h). Finally, the PLLA spherulites with average diameter about 200 μm were obtained.

Characterization

Raman spectra were collected through the Raman microscopy (Renishaw inVia) with 532 nm excitation wavelength. The Raman mapping measurement was performed at room temperature and temperature-controlled Raman measurement was examined upon a hot stage (Linkam THMS600). For the measurement under increasing temperatures, the PLLA samples were kept at each temperature for 10 min before measurement. The line scanning was executed with a step of 2 μm across the spherulite center.

To characterize the crystallographic structures, PLLA spherulites and amorphous films were prepared on the silicon wafer (15 mm $\times$ 15 mm) and the X-ray diffraction (XRD) was examined (Shimadzu XRD-7000 using a Cu target). The scanning rates of 1 and 2 ($^{\circ}$)/min for the scanning 2θ angle range from 10 $^{\circ}$ to 25 $^{\circ}$ and 5 $^{\circ}$ to 90 $^{\circ}$ were adopted, respectively.

For the characterization of molecular weight, solutions were prepared by dissolving the films in tetrahydrofuran (99.5%, Sigma-Aldrich) with a concentration of 2 mg/mL. After being filtered, the solution was detected by gel permeation chromatography (GPC) at 40 °C and a flow rate of 1.0 mL/min (Breeze 2 HPLC system). Polystyrene with the narrow molecular weight distribution was used as the standard reference. The value of molecular weight of PLLA was calculated from Mark-Houwink Equation.^[31]

RESULTS AND DISCUSSION

Texture: One Spherulite Embedded in the Other

PLLA spherulites were prepared through the isothermal crystallization (120 °C) to avoid temperature change that might lead to the crystal transformation in spherulites or the annealing effect in the melt crystallization.^[32,33] The obtained PLLA crystalline films exhibit the typical morphologies of spherulites (Figs. 1a and 1b). Interestingly, they are clearly distinct from the conventional polymer spherulites, in the sense that two Maltese crosses instead of one emerge in pairs, as shown in the polarizing optical microscopy (POM) images (Fig. 1b). The two Maltese crosses indicate that two spherulites coexist with one embedded in the other. These two types of spherulites with different sizes are termed as large and small spherulites. The diameter of the small spherulites embedded is about 10 μm , while that of the large spherulites ranges from 100 μm to 300 μm . In addition to the morphology of two spherulites nested together, morphology of one spherulite exists rarely (13 out of 238 in 4 films), with diameters of about 200 μm (Fig. 1e).

Identification of the Nested Large and Small Spherulites

The structures of the nested large and small spherulites are identified. First, we examine the spectra collected from the

large and small spherulites, respectively. Laser confocal Raman spectrometry (LCRS) was selected because of its powerful capability in the polymer structure analysis.^[34,35] More importantly, the detected region of LCRS can reach down to about one micron, enabling the examination for the small spherulites (diameter: about 10 μm). For a pair of large and small spherulites, Raman spectra for the carbonyl groups (C=O) stretching mode^[36–38] were collected at three positions marked in Fig. 1(c), with position 2 locating at the small spherulite and positions 1 and 3 at the large one. Clearly, two distinct Raman characteristics can be recognized (Fig. 1d). For positions 1 and 3, multiple bands at 1749, 1763 and 1773 cm^{-1} are shown, which is consistent with the most common polymorph (α -form) of PLLA crystal.^[36,37] In contrast, single band at 1760 cm^{-1} exhibits for position 2, suggesting that the large and small spherulites are associated with two distinct Raman features. This correlation is further reconfirmed by one supporting evidence. Line scanning along the radial direction of the spherulites indicates that the single-peak spectrum appears only for the region inside the small spherulite while the multiple-peak feature of the α -form emerges exclusively for the large spherulite (Fig. S1 in the electronic supplementary information, ESI). For comparison, the spherulites without small spherulite in the same film were also examined through Raman mapping measurement. Only multiple-peak signal was detected (Fig. 1f and Fig. S2 in ESI), indicating that this type of spherulite is composed of α -form crystals. Therefore, we conclude that polymorphism is the reason to observe the non-conventional nested large and small spherulites. The large spherulite is assigned to the α -form of PLLA crystal while the polymorph for the small spherulite is subsequently examined.

There are four different PLLA crystal modifications named as α , α' , β , γ -form.^[39,40] The α -form with a 10₃ helical chain conformation is the most common and stable phase of PLLA crystallizing from the melt or solution.^[41,42] The α' -form crystals of pseudohexagonal form are obtained at temperature lower than 120 °C. They are considered as conformationally disordered α -crystals and have a lower chain packing density, slightly increased lattice spacings as well as lower specific enthalpy of melting compared to the α -form. Under slowly heating, the irreversible transformation from α' -form into stable α -form is a significant thermodynamic phenomenon of PLLA.^[15,43–45] The β -form is known to take a 3₁ helical conformation defined as metastable and frustrated structure. The β -form can be mainly produced by stretching the melt or solution-spin PLLA fibers at a high temperature and a large drawing ratio.^[20,46–47] Interestingly, the PLLA modified chemically with supramolecular unit can crystallize into β -form from the cold or melt crystallization without using the external forces.^[48] The γ -form was reported to form through epitaxial crystallization on a hexamethylbenzene substrate.^[13]

In the region of 1700–1800 cm^{-1} in the Raman spectrum, the four polymorphs exhibit varied features for the carbonyl groups (C=O) stretching mode.^[36–38] For the α -form crystal, the carbonyl band splitting is due to interactions and coupling between carbonyl groups.^[43] Similarly, for γ -form, intermolecular interactions, such as the hydrogen bonding, cause band splitting into two bands.^[49] With regard to α' - and β -form, because of the weak interactions of carbonyl,^[43,49] the

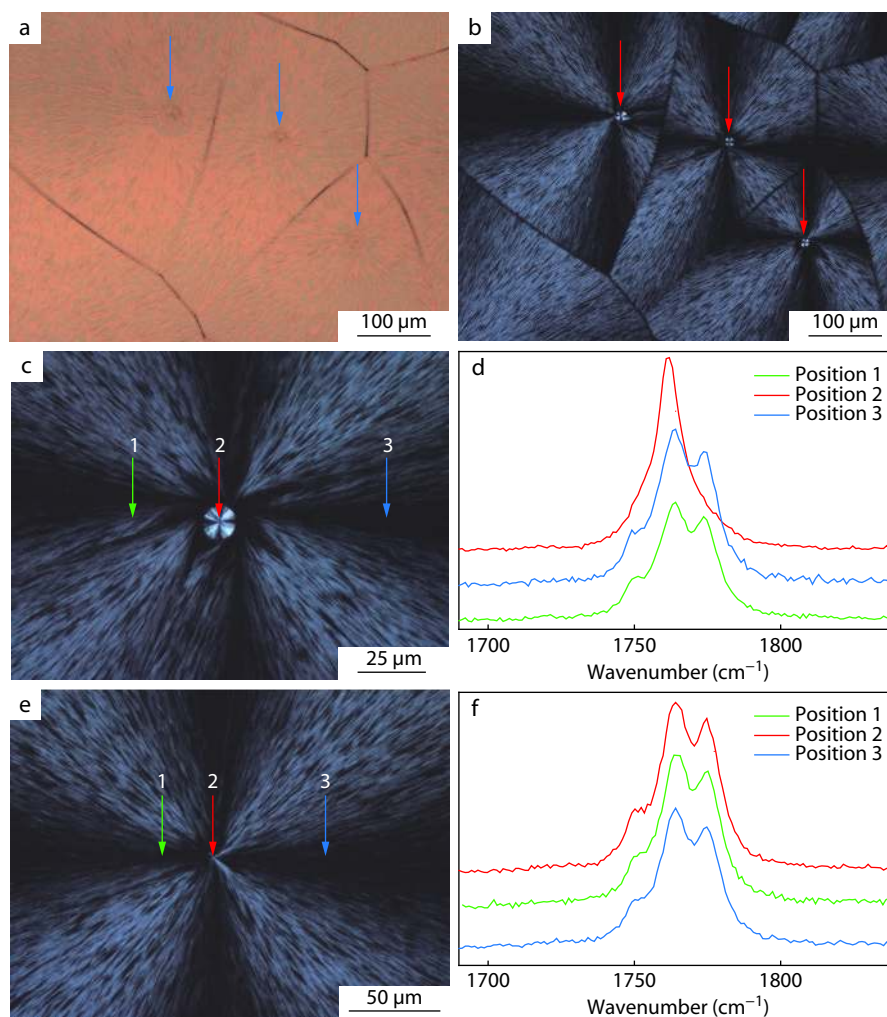


Fig. 1 Micrographs and Raman spectra of PLLA spherulites. (a, b) Optical microscopy (OM) and POM images of PLLA spherulites, with the small spherulites highlighted by arrows. (c) A POM image for the region examined by Raman spectrometer, with the three detected positions highlighted by arrows of red, green, and blue colors. (d) Raman spectra collected at the three positions highlighted in part c. (e) A POM image of a region without the small spherulite, with the three detected positions highlighted by arrows. (f) Raman spectra collected at the three positions highlighted in part e.

carbonyl stretching band of 1760 cm^{-1} could maintain the single peak profile like the red curve in Fig. 1(d). Therefore, we expect that the small spherulites are composed of either α' -form or β -form crystals. Next, the small spherulites are assigned as the α' -form in three steps.

First, the melting behavior of the small spherulites was examined. As previously reported,^[47,50] the melting temperature (T_m) is about 180, 175, and $155\text{ }^{\circ}\text{C}$ for the α -, β -, and α' -form, respectively. Heating between 155 and $175\text{ }^{\circ}\text{C}$ should cause the melting of the α' -form but not the β -form. Therefore, the PLLA spherulite films were heated at $165\text{ }^{\circ}\text{C}$ for half an hour. Compared to the sample before heating, the small spherulites in the heated films melt as shown by the POM image (Figs. 2a and 2b). This thermal behavior indicates that the small spherulites are not the β -form crystals. Instead, they might be the α' -form crystals.

Second, a direct evidence for the α' -form is from the XRD measurement for the PLLA films. The diffraction at 2θ value of 16.7° exhibits as an asymmetric band with a shoulder

(Fig. 2e), indicative of two peaks overlapping together. By fitting the band using Voigt function,^[51,52] the two diffraction peaks are located at 16.5° and 16.7° , respectively. Interestingly, the shoulder disappears once the small spherulites are selectively removed. By etching the PLLA films in hot *p*-xylene at $105\text{ }^{\circ}\text{C}$ for 15 s, the small spherulites were entirely dissolved away while the large spherulites were not (Figs. 2c and 2d). The XRD pattern for the etched films shows that the peak at 16.7° is symmetric without a shoulder (Fig. 2f). The distinct XRD patterns for the pristine and etched films (Figs. 2e and 2f) suggest that the diffraction peak at the shoulder (16.5°) is from the small spherulites, while the peak at 16.7° is from the large spherulites. These two diffraction peaks are consistent with the previous reports for the α' - and α -form crystals with 16.4° (α') and 16.7° (α) peaks representing the $\{110\}$ and $\{200\}$ diffraction.^[15,53] The peak for the α' -form (16.5°) is not exactly identical to the reported value at 16.4° and the reason is attributed to its weak diffraction due to the relatively small volume proportion for the α' -form

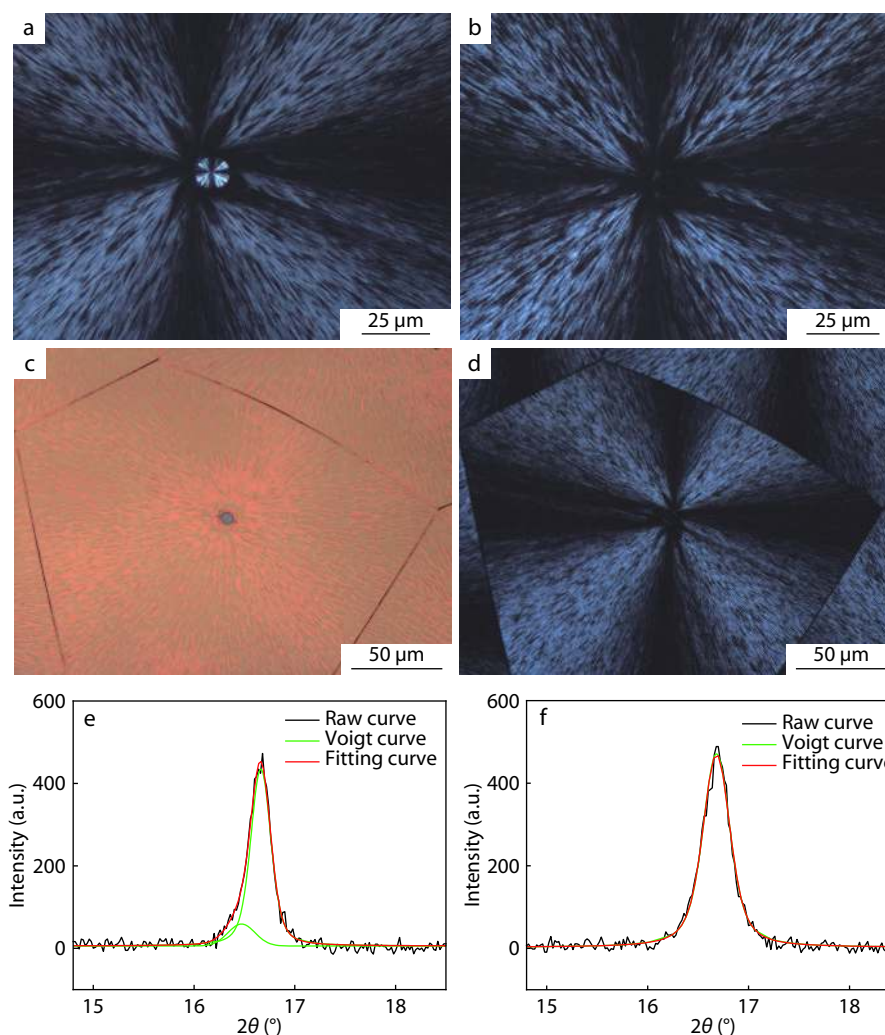


Fig. 2 Melting behavior and XRD patterns of PLLA spherulites. (a, b) POM images of PLLA spherulites (a) before and (b) after heating at 165 °C for 30 min. (c, d) OM and POM images of a film after etching in *p*-xylene at 105 °C for 15 s, with the pristine small spherulite selectively etched away. (e, f) XRD patterns of PLLA spherulite films (e) before and (f) after etching, with the raw XRD curves (black) fitted by the Voigt function (red) and decomposed into peaks (green).

spherulites. Therefore, we conclude that the small spherulites are the crystals in α' -form.

Finally, another supporting evidence for the α' -form is from the phase transition occurring in the small spherulites during heating. The phase transition from α' -form to α -form PLLA crystals between 150 and 160 °C on slow heating has been reported by researchers.^[18,21,54,55] We monitored the evolution of Raman spectra (1600–1900 cm^{-1}) collected from the small spherulites at increasing temperatures with a 2 °C interval. Clearly, the spectrum kept as a single band below 156 °C and transformed to multiple bands consistent with the α -form crystal above 158 °C (Fig. 3). Besides, the spectrum maintained the multiple bands when cooling the film. Therefore, the phase transition from α' -form to α -form PLLA crystals occurs in the small spherulite during heating.

Based upon the analysis on Raman spectra, XRD patterns, and the thermal behavior, we conclude that, in the nested spherulites, the central small spherulites are composed of α' -form crystals and the external large spherulites are identified

as the α -form crystals. We note that the films are semi-crystalline and amorphous structures exist in the spherulites in addition to the α - and α' -form crystals.

Formation Mechanism of the Texture

After identifying the large and small spherulites, we proceed to investigate their formation mechanism. There were two steps to prepare the crystals. First, PLLA films were obtained by spin coating. Second, the films were molten at 200 °C and were transferred quickly to a hot stage of 120 °C for isothermal crystallization. The large and small spherulites should form during the isothermal crystallization instead of the spin coating. As supporting evidences, there is no Maltase cross extinction observed in the spin-coated films and no XRD peak could be found for the films either (Figs. S3 and S4 in ESI).

One possible mechanism is that the two types of spherulites with different polymorphs form under different crystallization conditions. Previously, nested spherulites were reported for isotactic polypropylene,^[33,56] poly(trimethylene terephthalate),^[57] and poly(1,4-butylene adipate) (PBA) crystal-

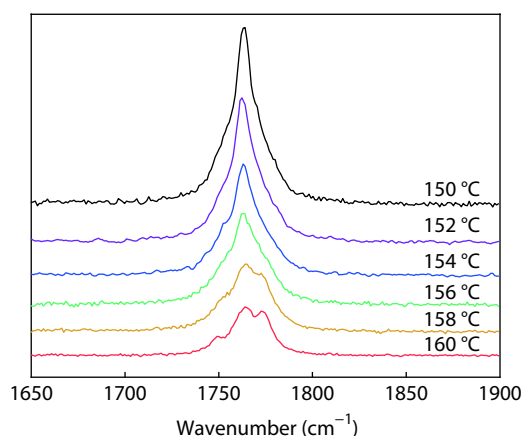


Fig. 3 Raman spectra recording the phase transition of the small spherulite under increasing temperatures. Single band was detected under 156 °C and transformed to multiple bands at 158 °C.

lized sequentially under varied crystallization temperatures.^[58] Nevertheless, isothermal crystallization at 120 °C was used in the current work and the crystallization condition for the two spherulites was kept identical. Therefore, varying crystallization condition is not the reason for the formation of two spherulites with varied polymorphs. Interestingly, Liu *et al.*^[59] reported a similar 3-layered nested spherulites containing two polymorphs with a sequence of “stable/meta-stable/stable forms” for PBA crystallized isothermally. And the formation of the nested structure was attributed to the competition between the growth rates of the stable and meta-stable crystalline modifications.

Because the crystallization conditions for the large and small spherulites were identical, their different polymorphic structures should have originated from the crystallizing molecules themselves. We first removed the PLLA molecules in the small spherulites and examined the residual large spherulites. As described above, the small spherulites are α' -form crystals where molecules pack more loosely^[15,43] than the large spherulites in α -form. And solvents diffused more easily into the small spherulites to etch them away, as observed by the POM images (Figs. 2c and 2d). Subsequently, we measured the number-average molecular weight (M_n), weight-average molecular weight (M_w), and polymer dispersity index (PDI) by GPC for PLLA spherulite films before (I) and after (II) etching (Table 1, Fig. S5 in ESI). Clearly, M_n , M_w , and PDI all decrease after etching and M_w decreases more than M_n . These data indicate that the part etched away has higher molecular weight. In other words, the high-molecular-weight components are partially concentrated into the small spherulites. Therefore, the molecules in the large and small spherulites are different in terms of molecular weight.

Based on the above observations, we propose a mechanism by which the two spherulites nest together, as depicted in Fig. 4. (1) As the PLLA solution is spin-coated into an amorphous film, fractional precipitation induces the local concentrating of the high-molecular-weight component. (2) During the isothermal crystallization, spherulites nucleate preferentially from the high-molecular-weight components.^[60–63] Complicated entanglement and high viscosity of

Table 1 Comparison of molecular weight before (I) and after (II) etching away the small spherulites from the PLLA films. Five sets of comparison are listed.

No.	PLLA	M_n (kDa)	M_w (kDa)	PDI
1	I	28.3	38.0	1.34
	II	27.8	36.5	1.31
2	I	27.9	37.7	1.35
	II	26.9	35.5	1.32
3	I	27.4	36.6	1.34
	II	26.9	34.8	1.29
4	I	29.4	40.0	1.36
	II	28.7	38.8	1.35
5	I	27.9	36.6	1.31
	II	27.0	35.1	1.30

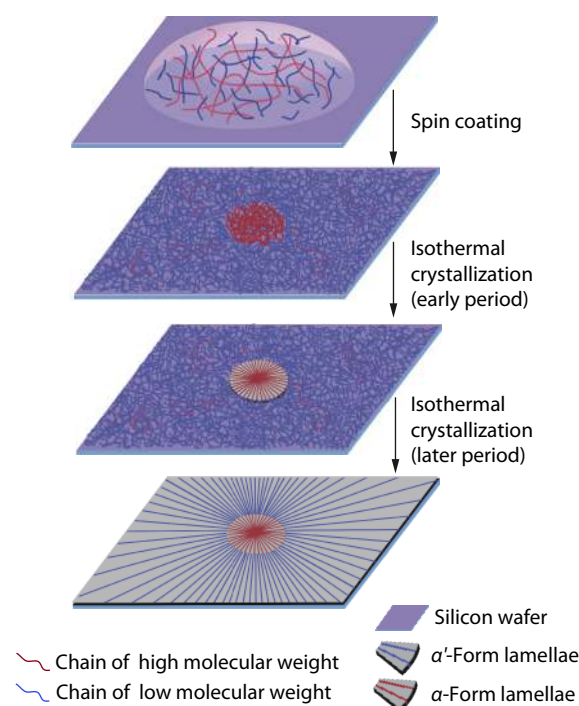


Fig. 4 A schematic representation of the formation mechanism for the PLLA nested spherulites. For clarity, polydisperse PLLA molecules were simplified into double components (high- and low- molecular-weight chains).

these molecules make the structural adjustment and diffusion of polymer chains difficult during crystallization. Consequently, the less ordered crystalline polymorph, α' -form PLLA crystals, forms as the small spherulites.^[15,64,65] (3) With the growth of spherulite, the high-molecular-weight component consumes and the lower-molecular-weight component with lower viscosity crystallizes into the stable α -form PLLA crystals. Eventually, morphology of two spherulites nested together emerges. There are two supporting evidences to verify the proposed mechanism.

First, the formation processes of the nested spherulites were monitored *in situ* using POM, indicating that the small and large spherulites formed in sequence. For a typical nested structure, its formation process is shown in Fig. 5. Initially, a small spherulite formed (Fig. 5a), and its diameter

gradually increased (Fig. 5b). Six minutes later, the external large spherulite started to form at the edge of the small spherulite (Fig. 5c, red ovals). Subsequently, the external spherulite continued to enlarge, resulting in the nested spherulites (Figs. 5d–5f).

Second, as the molecular weight is reduced, the small spherulites tend not to form. We reduced the molecular weight by thermal decomposition.^[66] Before isothermal crystallization, the spin-coated amorphous films were melted at varied temperatures for half an hour and the molecular weight of the polymers decreased with the increase of temperatures, as measured by GPC (Fig. 6a). During the subsequent isothermal crystallization, the size of the large spherulites was measured. In addition, the amounts of the nested spherulites and the conventional spherulites without an in-

ternal small spherulite were both measured to calculate the proportion of the nested spherulites. Interestingly, with the increase of temperatures for thermal decomposition, the size of large spherulites increased and the proportion of nested spherulites decreased dramatically (Fig. 6b). Below 210 °C, average diameter of the large spherulites is about 200 μm , the small spherulites are commonly observed, and the proportion of the nested spherulites is more than 90%. In sharp contrast, above 240 °C, the average diameter reaches a maximum of about 2500 μm and the small spherulites do not form. This trend is consistent with the proposed mechanism above (Fig. 4). When the molecular weight decreases, the nucleation density of the spherulites decreases and their size becomes larger because the nucleation is more difficult for the short polymer chains.^[63,67] In addition, the short polymer

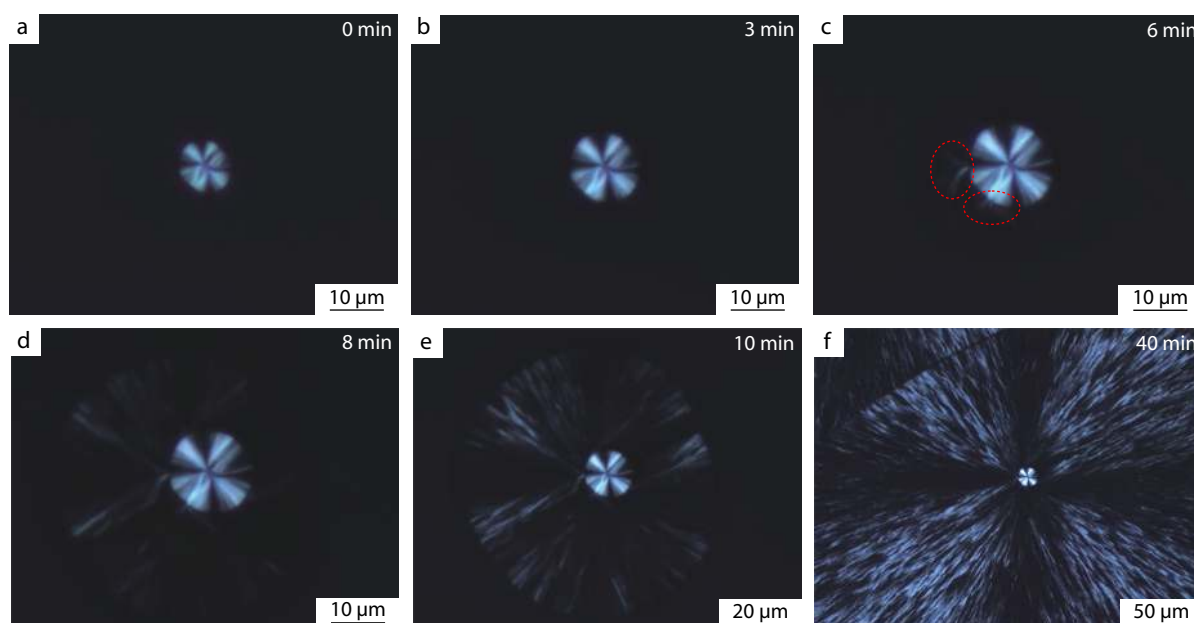


Fig. 5 A series of POM images recording the formation processes of the nested spherulites. Red ovals in part c highlight the initial formation of the external large spherulite. The moment when we could observe the small spherulite was marked as 0 min. And before the "0 min", the POM image was completely dark and featureless, indicative of no crystals.

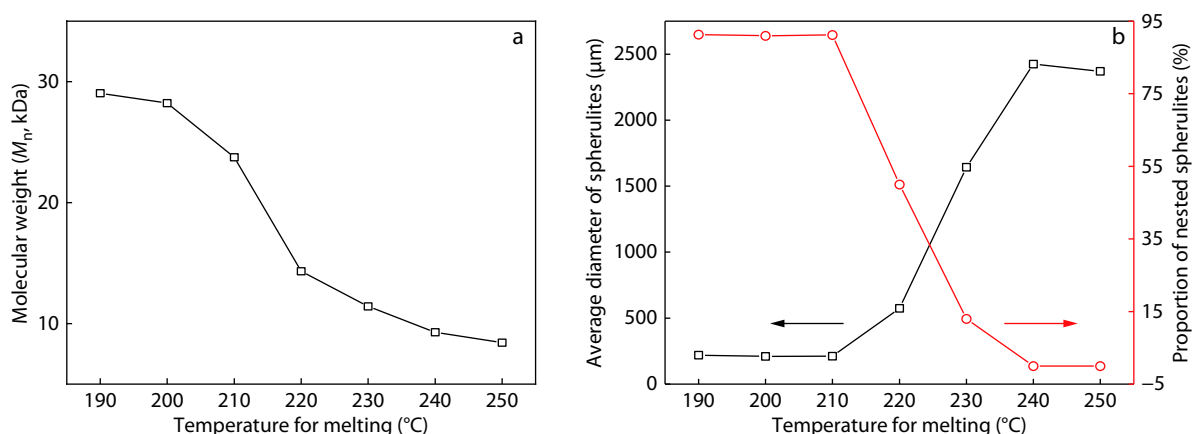


Fig. 6 Influence of temperature used for melting on PLLA spherulites. (a) Number-average molecular weight (M_n) of PLLA heated under different temperatures for half an hour. (b) Correlations between temperatures used for melting and average diameter of large spherulites as well as proportion of nested spherulites.

chains are more mobile and tend to pack densely into the stable α -form crystals as the large spherulites instead of α' -form as the small spherulites.

Degradation Properties Associated with the Texture

There are reports indicating the non-uniform structure and properties within polymer spherulites.^[28,30,68–72] Similarly, the texture of nested spherulites herein should lead to corresponding unique properties. Degradation, a critical issue for PLLA's application in biomedical materials, has been widely concerned.^[25,73–75] It has been found that amorphous regions between the crystalline regions in spherulites or loosely chain-packing regions in lamellae could accelerate degradation.^[71,76,77] In the context of these work, we examined the degradation of the PLLA crystals with the nested spherulites. A

dilute alkaline solution (NaOH, 0.01 mol/L) was used to ensure the slow degradation of PLLA spherulite films. OM images of the films soaked in the alkaline solution after varied time are shown in Fig. 7. After an hour, observable cracks began to appear mainly at the small spherulites where molecules pack more loosely (Fig. 7a), and these cracks continued to develop wider and longer over time (Figs. 7b–7d). In contrast, for the small proportion of spherulites without an internal small spherulite, no crack was observed even after soaking for 10 h (Figs. 7e and 7f). Obviously, the small spherulites have a great impact on the degradation property of PLLA. Due to their looser molecular packing, penetration of solutions into the small spherulites occurs more easily, initiating and accelerating the degradation of PLLA films.

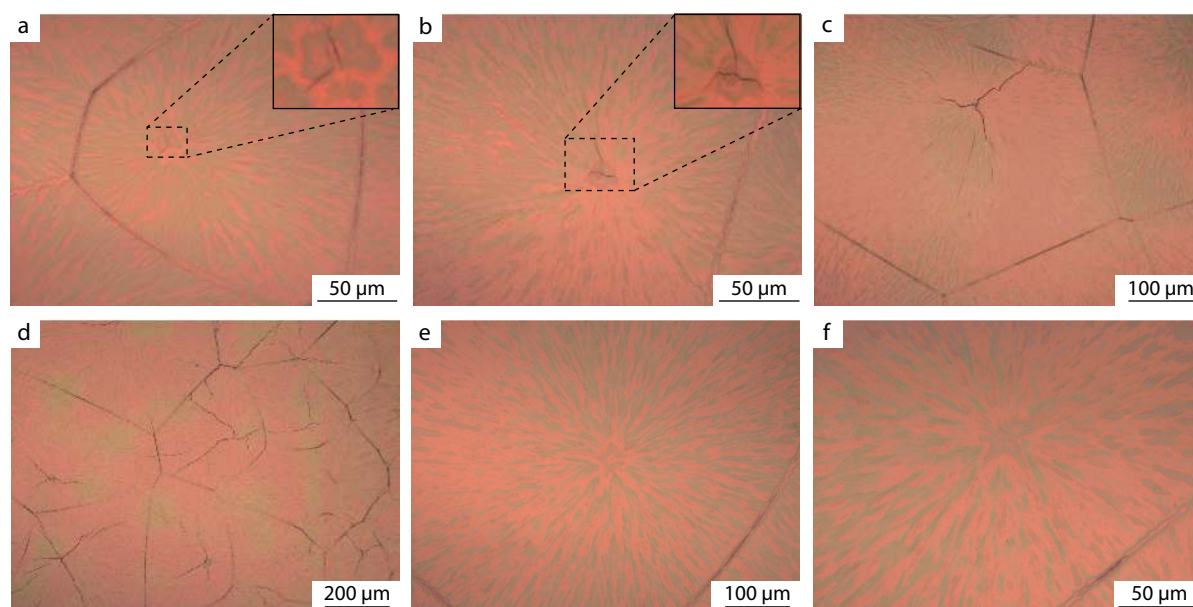


Fig. 7 OM images showing the degradation properties of the PLLA spherulites. (a–d) OM images of the nested spherulites soaked in a dilute alkaline solution for (a) 1 h, (b) 2 h, (c) 4 h, and (d) 10 h, respectively. Cracks can be observed at the small spherulites after 1 h. Insets: images at high magnification highlighting the cracks. (e, f) OM images of the conventional spherulites soaked in a dilute alkaline solution for (e) 4 h and (f) 10 h, respectively. No crack was observed.

CONCLUSIONS

In summary, we have examined the structure and properties of PLLA spherulites in spin-coated films prepared through isothermal crystallization. In particular, we have identified that two types of spherulites emerge in pairs, with different sizes and polymorphs. For each pair, a small spherulite of α' -form with a diameter of about 10 μm is embedded in a large spherulite of α -form with a diameter ranging from 100 μm to 300 μm . As a result, a texture of two spherulites nested together forms, distinct from the conventional polymer spherulites. The emergence of this non-conventional texture is attributed to the polydispersity of molecular weight and the resulting fractional precipitation. Furthermore, this texture leads to accelerated degradation of PLLA films initiated from the small spherulites where polymers pack more loosely. By showing the texture of nested large and small spherulites and its effect on degradation,

this work presents a critical structural feature associated with the technological applications of PLLA. Also, similar texture-properties relationship might be applicable to other polymers, considering that polydispersity of molecular weight is popular for synthetic polymers.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at <https://doi.org/10.1007/s10118-020-2464-0>.

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