

Competition between Liquid-liquid De-mixing, Crystallization, and Glass Transition in Solutions of PLA of Different Stereochemistry and DEET

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Abstract Liquid-liquid (L-L) de-mixing and vitrification of solutions of either crystallizable poly(L-lactic acid) (PLLA) or non-crystallizable poly(D/L-lactic acid) (PDLLA) with 50 m% *N,N*-diethyl-3-methylbenzamide (DEET) were analyzed by calorimetry and cloud-point measurements, which allows drawing conclusions about the effect of polymer stereochemistry on the phase behavior. Regardless of the PLA stereochemistry, vitrification of the solutions on fast cooling, hindering crystallization of PLLA, occurred below -20°C and suppressed prior L-L de-mixing. The experimental results prove that crystallization in samples containing crystallizable PLLA, observed at around 55°C on slow cooling, is not preceded by L-L de-mixing.

Keywords Crystallization; PLA; DEET; Liquid-liquid phase separation; Thermally-induced phase separation (TIPS)

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INTRODUCTION

Recently, the phase behavior of the polymer/solvent system of poly(lactic acid) (PLA)/*N,N*-diethyl-3-methyl-benzamide (DEET) has been investigated.^[1,2] The main purpose of the performed research was to evaluate the possibility of formation of PLA scaffolds via a thermally-induced phase separation (TIPS) of solutions.^[3–5] The specific solvent DEET has been selected since it may simultaneously serve as a drug with a functionality as a mosquito-repellent,^[6,7] being slowly released from the polymer scaffold to the environment by evaporation. In a wider sense, our research focuses on the link between the preparation conditions of scaffolds/crystallization, the scaffold structure, and the DEET evaporation characteristics, with the latter being adjustable for specific applications. Naturally, such link depends on the PLA structure (molar mass, D-isomer content) as well as the concentration of PLA and DEET, requiring in-depth knowledge about the phase diagram. In earlier work, it was found that PLA/DEET solutions show an upper critical solution temperature (UCST), with a cooling-initiated phase-separation-mechanism depending on the molecular architecture/stereochemistry of PLA macromolecules.

Solutions prepared using crystallizable poly(L-lactic acid) (PLLA) phase-separate during slow cooling via crystallization

of the polymer above ambient temperature. In contrast, solutions which contain non-crystallizable racemic poly(D/L-lactic acid) (PDLLA) phase-separate via liquid-liquid (L-L) de-mixing slightly below ambient temperature, with the critical temperature and concentration controlled by the polymer molar mass,^[2] as expected from earlier fundamental analyses of the thermodynamics of polymer/solvent systems.^[8–11]

Crystallization-induced solid-liquid (S-L) TIPS of samples containing crystallizable PLLA is incomplete and leads to a two-phase system composed of segregated PLLA α -crystals and a liquid solution containing both DEET solvent molecules and PLLA macromolecules at a concentration which is controlled by the fraction of PLLA crystals formed. We assumed that the remaining liquid phase separates at lower temperature into two liquid phases of different polymer concentrations according to the observations gained on analysis of a system containing non-crystallizable PDLLA. However, this assumption implied that L-L phase separation of the PLA/DEET system is independent of the PLA macromolecular stereo-isomerism, that is, the fraction of L- and D-units in the PLA chains. Confirmation of this assumption was not obtained since L-L TIPS in samples containing crystals cannot straightforwardly be analyzed by turbidity measurements or by detecting enthalpies of de-mixing. Therefore, with the present work it is attempted to shed further light on the phase behavior of the polymer/solvent system PLA/DEET, focusing on the effect of the stereo-regularity of PLA macromolecules on L-L phase separation. In particular, it is the goal to provide in-

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formation whether the crystallization of PLLA from solution is preceded by L-L de-mixing, which would in the first step lead to the formation of a polymer-enriched phase, reducing the energy barrier for crystallization related to the probability of selecting the required number of crystalline sequences in a solution,^[12] or not.

EXPERIMENTAL

Materials

Crystallizable extrusion-grade PLLA was obtained from Sulzer Chemtec Ltd. (Switzerland) in the form of pellets. The D-isomer concentration was 4% (PLLA-96), and the mass-average molar mass and polydispersity were 117 kDa and 2.4, respectively.^[13,14] Non-crystallizable PDLLA grade R205S with a D-isomer content of 50% (PDLLA-50) and an inherent viscosity between 0.55 and 0.75 dL/g was provided by Evonik (Germany).^[15] The mass-average molar mass and polydispersity were 177 kDa and 2.2, respectively.^[2] *N,N*-diethyl-3-methylbenzamide (DEET) with a purity of 97% (Catalog/Product Number D100951) was purchased from Sigma-Aldrich (Germany).^[16]

Preparation of Solutions

PLLA-96 pellets were sliced using a microtome to obtain thin sections with a thickness of 100 μm , for the purpose of easy dissolution in DEET. PLLA-96 sections and DEET were placed at a concentration of 50/50 (W/W) inside 4 mL-glass-vials which were closed with a lid. Mixing was performed at 160 $^{\circ}\text{C}$ using a Thermo Scientific Reacti-Therm block heater/stirrer, with complete dissolution of the polymer achieved after few minutes. For the preparation of 50/50 (W/W) solutions of PDLLA-50 in DEET, the as-received polymer flakes were dissolved at 60 $^{\circ}\text{C}$.

Instrumentation

Calorimetric measurements were done using a Mettler-Toledo differential scanning calorimeter DSC 1 (Switzerland) connected to a Huber intracooler TC100. The sample environment was purged with nitrogen gas at a flow rate of 60 mL/min. Solutions were placed into closed 40 μL aluminum pans for obtaining DSC thermograms. In the case of visual inspection of the sample appearance as a function of temperature, the pans were not closed. Employment of a transparent furnace lid allowed monitoring the turbidity/clearness of samples during controlled exposure to a specific thermal history using a Navitar objective lens and a digital camera.

RESULTS AND DISCUSSION

For illustration of the aim of our study, and to explain the experimental strategy of obtaining the desired knowledge whether the phase behavior of the PLA/DEET system depends on the stereo-regularity of the polymer, Fig. 1 shows the phase diagram of the polymer/solvent system PLA/DEET.^[1,2] The blue data points represent L-L phase-separation temperatures obtained in samples containing non-crystallizable PDLLA with a molar mass of 177 kDa. At temperatures above the data points, PLA and DEET form a liquid solution while at lower temperatures the two liquid solutions coexist with their composition depending on the temperature, to be estimated by the intersection of tie lines with the phase-coexistence line (blue). The gray and red triangles represent crystallization temperatures of

systems containing crystallizable PLLA with 0 and 4% D-units (PLLA-100 and PLLA-96), respectively, obtained on cooling the solutions at a rate of 5 K/min. Note that neat PLLA-96 with 4% D-units, that is, PLLA-96 in the absence of the solvent, does not crystallize on cooling at 5 K/min.^[14] The decrease of the crystallization temperature with increasing DEET-concentration parallels the glass transition temperature of the solutions and the decrease in the equilibrium melting temperature, shown for the two crystallizable PLLAs with different D-unit contents in the upper part of the plot by the dashed lines. The calculation of the equilibrium-melting-point depression was performed using the Flory equation,^[9] assuming a Flory-Huggins interaction parameter χ of 0.33,^[2] and equilibrium melting points of 214 and 191 $^{\circ}\text{C}$ for PLLA containing 0 and 4% D-units, respectively.^[17] Regarding the glass transition temperature of the solutions, a linear mixing rule is assumed for simplicity, being considered as an upper-limit estimate only.

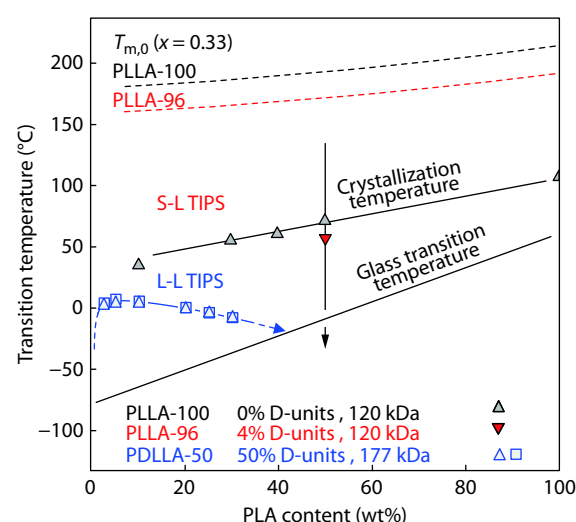


Fig. 1 Phase diagram of the polymer/solvent system PLA/DEET. Blue data points represent L-L phase-separation temperatures obtained in samples containing non-crystallizable PDLLA with 50% D-units, and gray and red triangles represent crystallization temperatures in solutions containing crystallizable PLLA with 0 and 4% D-units, respectively. The dashed lines in the upper part are estimations of equilibrium melting temperatures of PLLA crystals. The dependence of the glass transition temperature on the composition of the solutions is estimated assuming a linear mixing rule. (Data are in part adapted with permission from Refs. [1,2]; Copyright (2017) and (2018) Elsevier.)

The vertical arrow at 50 wt% polymer concentration indicates specific cooling- and heating-experiments performed in the present work for analysis of the effect of D-units in PLA chains on the L-L phase separation of solutions. The particular composition of samples was selected since we failed to analyze L-L phase separation on cooling solutions containing crystallizable PLLA at concentrations lower than 50 wt%. The most straightforward approach to obtain the required information of L-L demixing temperatures in samples containing crystallizable PLLA is the suppression of crystallization by cooling faster than a critical rate, and then to observe sub-ambient L-L demixing by cloud-point measurements or standard differential scanning calorimetry (DSC). However, likely

due to both the increased crystallization rate of PLLA in the presence of the solvent^[18] and the much reduced glass transition temperature, suppression of crystallization, that is, S-L demixing, of PLLA-100 in solution with 50 wt% DEET was not possible even when cooling at rates reaching 30 K/min. The presence of even minute amounts of D-units leads to a distinct deterioration of the crystallization process, caused by required segregation of these units at the crystal growth front.^[19,20] As such, PLLA-96 containing 4% D-units finally was successfully employed to suppress S-L demixing at elevated temperature. Unfortunately, L-L phase separation cannot be detected in samples containing more than about 40 wt% PLA, since the system vitrifies before the demixing temperature (blue line in Fig. 1) is reached on cooling. However, even in this case valuable information about the effect of PLA chain architecture on the thermodynamics of PLA/DEET solution can be observed, as shown below.

Fig. 2 shows rate-normalized DSC heating and cooling scans obtained on 50/50 (W/W) samples of the polymer/solvent system of PLA/DEET. The upper curve (red) represents heating of a sample containing non-crystallizable PDLLA-50. It shows a distinct and broad heat-capacity step due to the glass transition, starting at around -65°C , that is, at a temperature only slightly higher than the glass transition temperature of neat DEET of around -75°C , stretching to around -20°C . Additional thermal events were not observed, confirming that L-L de-mixing of 50/50 (W/W) PDLLA-50/DEET solutions was suppressed during prior cooling since the sys-

tem vitrified before reaching the thermodynamically controlled L-L de-mixing temperature.

The three sets of curves in the lower part of Fig. 2 were collected using samples containing 50 wt% crystallizable PLLA-96, with blue and gray coloring of curves referring to cooling and heating experiments, respectively. If cooling is performed at 5 K/min, then crystallization of the polymer occurs at a temperature slightly higher than at 50°C . The enthalpy of crystallization is around 17 J/g, which translates to 34 J/g when normalizing this value to the polymer content in the sample. As such, about 1/3 of the total polymer fraction has been converted into an ordered state.^[21] We assume that homogeneity in the remaining liquid solution is lost, since crystallization leads to local concentration gradients in direction perpendicular to the crystal growth faces. In accord with this assumption, a distinct glass transition is then not observed on further cooling of the partially crystallized sample, and only the presence of a rather pure DEET phase is indicated with the heat-capacity step at around -75°C on subsequent heating. Note that for instrumental reasons cooling at 5 K/min was possible only down to -70°C ; therefore, the blue curve ends at this temperature. Besides the distinct small heat-capacity step at around -75°C , related to de-vitrification of a small fraction of pure DEET, on heating is then only observed endothermic melting of the PLLA-96 crystals formed on cooling; the small downward peak at around 30°C may be related to minor cold-crystallization; however, it is unimportant in the context of the present study.

Cooling PLLA-96 in solution with 50 wt% DEET at 30 K/min, in contrast, fully suppresses crystallization as the corresponding DSC scan does not show any indication of a crystallization peak. Since linear cooling at this rate was only possible to about 20°C , cooling to lower temperatures was then continued at 5 K/min; the gap in-between the two cooling segments is due to the initial deflection of the heat-flow-rate signal when changing the scanning rate. Most important, however, is the observation of vitrification of the non-crystallized solution, similar to what has been seen for the sample containing non-crystallizable PDLLA-50 (red curve). The distinct downturn of the DSC curve at around -20°C is due to the onset of vitrification of the solution, ending at around -65°C . The performed experiment proves that L-L demixing of solutions containing crystallizable PLLA-96 with low amount of only 4% D-units is not preceded by crystallization at higher temperature but would occur at a temperature lower than the glass transition temperature if the system would not vitrify. There is no indication that PDLLA-50 and PLLA-96, both in solution with DEET, exhibit different L-L demixing behaviors on cooling. Analysis of subsequent heating of the glassy solution reveals its de-vitrification in the same temperature range from -65°C to -20°C , cold-crystallization beginning at around 30°C , followed by melting of crystals formed during heating.

The top two heating curves in the part of Fig. 2, associated with samples containing crystallizable PLLA-96, allow a direct comparison of different de-vitrification of solid solutions in the presence and absence of crystals. The dashed and solid lines represent heating of samples cooled at 5 K/min, containing crystals, and 30 K/min, being free of crystals, respectively. As expected, the sample which does not contain crystals de-

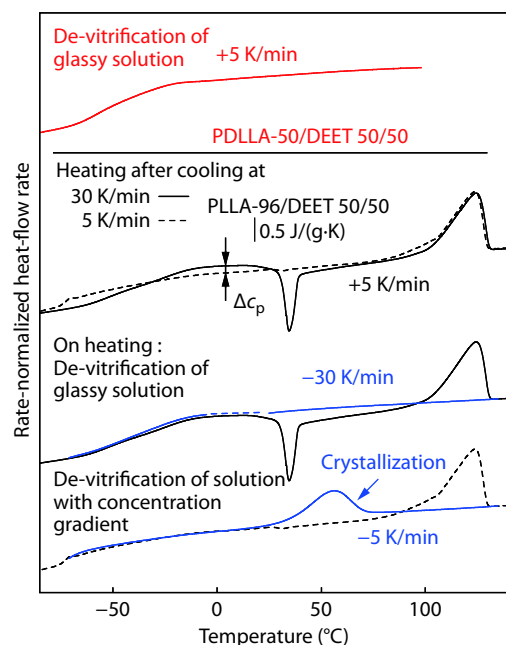


Fig. 2 Rate-normalized DSC heating and cooling scans obtained on 50/50 (W/W) samples of the polymer/solvent system of PLA/DEET. The upper curve represents heating of a sample containing non-crystallizable PDLLA-50 (red), while the three sets of curves below were collected using samples containing crystallizable PLLA-96. Blue and gray colors refer to cooling and heating experiments, respectively. Throughout, heating was performed using a rate of 5 K/min, while cooling scans were measured using rates of 30 and 5 K/min, as indicated.

vitrifies between -65 and -20 °C and then yields a liquid solution with a higher heat capacity (c_p) than the sample which contains solid crystals.

In order to support the interpretation of DSC data in Fig. 2 regarding the absent L-L demixing on cooling solutions which contain 50 wt% PLLA-96, the optical appearance/turbidity was monitored using an experimental setup which allows detection of sub-ambient cloud points in a controlled environment, described in detail elsewhere.^[2] Solutions, placed in open DSC pans, were subject to specific thermal histories while taking photographs either through a transparent furnace cover or by opening the furnace lid. In Fig. 3 are shown optical macrographs taken during cooling solutions of PLLA-96/DEET 50/50 (W/W) (top row), PDLLA-50/DEET 50/50 (W/W) (center row), and PDLLA-50/DEET 10/90 (W/W) (bottom row). The images need to be read row-wise from left to right, in order to follow the optical appearance of the samples during cooling. The sample containing crystallizable PLLA with only 4% D-units (PLLA-96) (top row) was cooled at 30 K/min in

order to suppress crystallization (see also blue DSC curve in Fig. 2, labeled -30 K/min). The images reveal homogeneity at all temperatures since the base of the aluminum pan is clearly visible, proving absence of any turbidity. According to the DSC data in Fig. 2, the initially liquid solution turns glassy between -20 and -65 °C without any sign of de-mixing since the picture taken at -70 °C remains clear. When using non-crystallizable PDLLA containing 50% D-units (PDLLA-50) instead of PLLA-96 in mixtures with 50 wt% DEET, imaging during cooling reveals similarly clear appearance of the sample at all temperatures (center row). For comparison, and in order to illustrate L-L de-mixing during cooling, with the bottom-row images is followed the cooling process of a mixture containing only 10 wt% PDLLA-50. According to the phase diagram shown in Fig. 1, phase separation occurs at around 0 °C. At lower temperatures, the sample is heterogeneous, containing two phases of different DEET and polymer contents. The images taken at -20 and -70 °C confirm the expectation as cloudiness is observed.

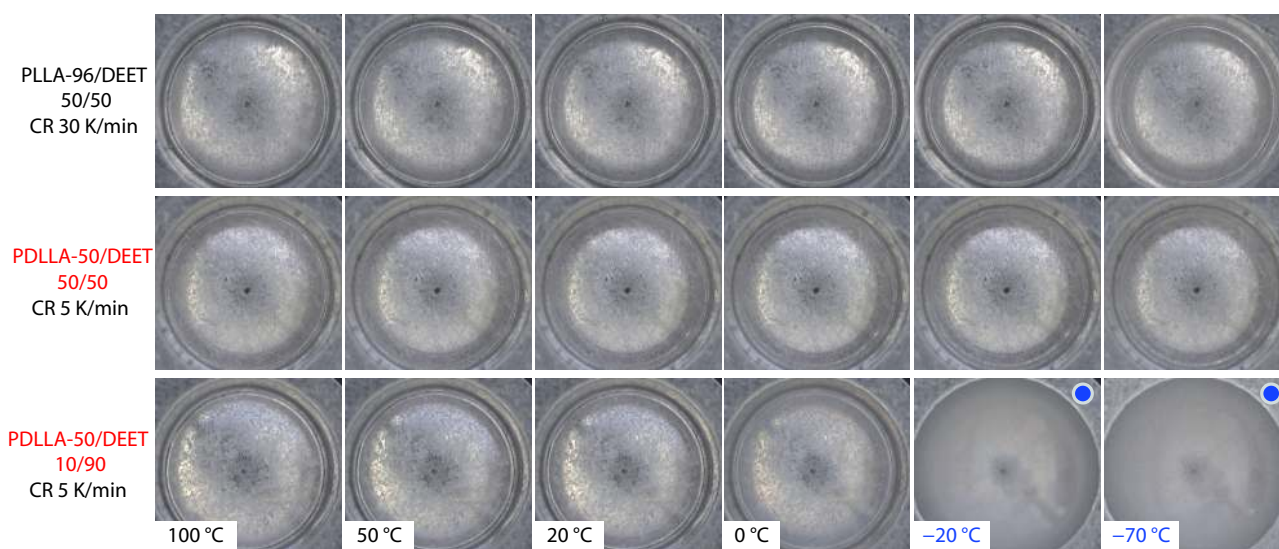


Fig. 3 Optical macrographs taken during cooling solutions of PLLA-96/DEET 50/50 (W/W) (top row), PDLLA-50/DEET 50/50 (W/W) (center row), and PDLLA-50/DEET 10/90 (W/W) (bottom row). Images need to be read from left to right, in order to follow the appearance of the samples during cooling. Images labeled with a blue circle indicate structural heterogeneity by cloudiness.

CONCLUSIONS

It is the aim of the present study to explore whether L-L demixing in the polymer/solvent system of PLA/DEET depends on the stereochemistry of the polymer, that is, on the content of L- and D-units in the PLA macromolecule. PLLA and PDLLA containing 4% and 50% of D-units, respectively, were employed to prepare solutions with 50 wt% DEET. DSC and cloud-point analyses showed that regardless of the D-unit content, L-L demixing on cooling the liquid solutions is suppressed by vitrification of the systems at their identical glass transition temperatures. Main conclusion is the proof of absent L-L de-mixing at temperatures higher than that of crystallization-induced S-L demixing in samples containing crystallizable PLLA.

The results of the present work may enter modelling approaches for prediction of structure formation in polymer/solvent systems, as attempted earlier,^[22,23] and contribute to

further understanding of the complex phase behavior of the polymer/solvent system PLA/DEET.

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