

# Competition between liquid-liquid demixing, 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, allowing drawing conclusions about the effect of the 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)

## INTRODUCTION

Recently the phase behavior of the polymer/solvent system poly (lactic acid) (PLA) / *N,N*-diethyl-3-methylbenzamide (DEET) has been investigated.<sup>[1,2]</sup> The main purpose of the performed research was the evaluation of the possibility of formation of PLA scaffolds via a thermally-induced phase separation (TIPS) of solutions.<sup>[3-5]</sup> The specific solvent DEET has been selected since it may simultaneously serve as a drug with a functionality as a mosquito-repellent,<sup>[6,7]</sup> being slowly released from the polymer scaffold to the environment by evaporation. In a wider sense, our research focuses on the link between the conditions of preparation 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 the 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 contained 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,<sup>[2]</sup> as expected from earlier fundamental analyses of the thermodynamics of polymer/solvent systems.<sup>[8-11]</sup>

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  $\alpha$ -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 concentration according to 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 on the stereoisomerism of the PLA macromolecules, that is, on 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 stereoregularity of PLA macromolecules on L-L phase separation. In particular it is the goal to provide information whether crystallization of PLLA from solution is preceded by L-L de-mixing, which would in a 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,<sup>[12]</sup> 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 117 kDa and 2.4, respectively.<sup>[13,14]</sup> 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).<sup>[15]</sup> The mass-average molar mass and polydispersity were 177 kDa and 2.2, respectively.<sup>[2]</sup> *N,N*-diethyl-3-methylbenzamide (DEET) with a purity of 97 % (Catalog/Product Number D100951) was purchased from Sigma-Aldrich (Germany).<sup>[16]</sup>

### Preparation of solutions

PLLA-96 pellets were sliced using a microtome to obtain thin sections with a thickness of 100  $\mu\text{m}$ , for the purpose of easy dissolution in DEET. PLLA-96 sections and DEET were placed at a concentration of 50/50 m% 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. In case of preparation of 50/50 m% solutions of PDLLA-50 in DEET, the as-received polymer flakes were dissolved at 60  $^{\circ}\text{C}$ .

### Instrumentation

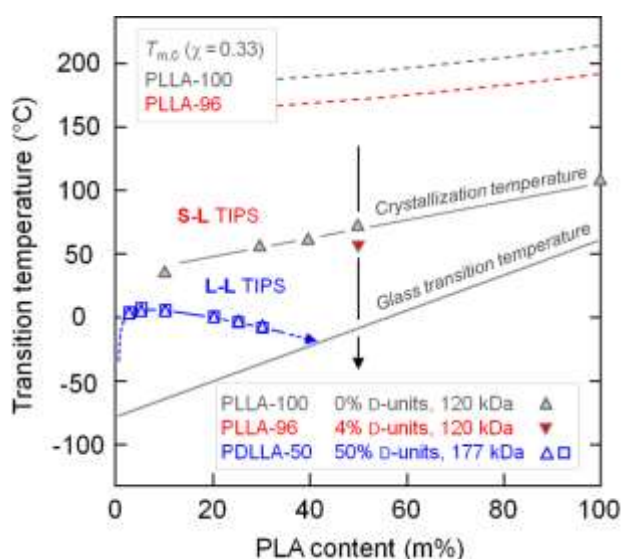
Calorimetric measurements were done using a Mettler-Toledo differential scanning calorimeter DSC 1 (Switzerland) connected to a Huber intracooler TC100. The sample environment was purged with nitrogen gas at a flow rate of 60 mL/min. Solutions were placed into closed 40  $\mu\text{L}$  aluminum pans for obtaining DSC thermograms. In 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/clarity 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, Figure 1 shows the phase diagram of the polymer/solvent system PLA/DEET.<sup>[1,2]</sup> 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 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, neat PLLA-96 with 4 % D-units, that is, PLLA-96 in absence of the solvent, does not crystallize on cooling at 5 K/min.<sup>[14]</sup> 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 PLLA's of different D-unit content in the upper part of the plot with the dashed lines. The calculation of the equilibrium-melting-point depression was performed using the Flory equation,<sup>[9]</sup> assuming a Flory-Huggins interaction parameter  $\chi$  of 0.33,<sup>[2]</sup> and equilibrium melting points of 214 and 191  $^{\circ}\text{C}$  for PLLA containing 0 and 4 % D-units, respectively.<sup>[17]</sup> Regarding the glass transition temperature of solutions, for simplicity a linear mixing rule is assumed, being considered as an upper-limit estimate only.

The vertical arrow at 50 m% polymer concentration indicates specific cooling- and heating-experiments performed in the present work for analysis of the effect of presence of D-units in the PLA chains on L-L phase separation of solutions. The particular composition of samples was selected since we failed analyzing L-L phase separation on cooling solutions containing crystallizable PLLA at concentrations lower than 50 m%. 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 differential scanning calorimetry (DSC). However, likely due to both the increased crystallization rate of PLLA in presence of the solvent,<sup>[18]</sup> and the much reduced glass transition temperature, suppression of crystallization, that is, S-L demixing, of PLLA-100 in solution with 50 m% 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.<sup>[19,20]</sup> 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 m% PLA, since the system vitrifies before the demixing temperature (blue line in Figure 1) is reached on cooling. However, even in this case valuable information about the effect of the PLA chain architecture on the thermodynamics of PLA/DEET solution can be observed, as shown below.

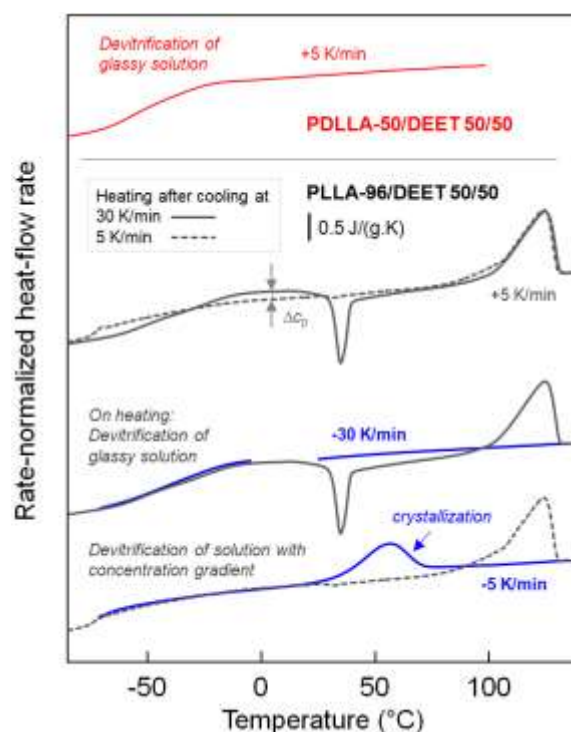


**Fig 1** Phase diagram of the polymer/solvent system PLA/DEET. Blue data points represent L-L phase-separation temperatures obtained in samples containing non-crystallizable PDLLA with 50 % D-units, and gray and red triangles represent crystallization temperatures in solutions containing crystallizable 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 from [1,2], with permission from Elsevier.

Figure 2 shows rate-normalized DSC heating and cooling scans obtained on 50/50 m% samples of the polymer/solvent system 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 demixing of 50/50 m% PDLLA-50/DEET solutions was suppressed during prior cooling since the system vitrified before reaching the thermodynamically controlled L-L demixing temperature.

The three sets of curves in the lower part of Figure 2 were collected using samples containing 50 m% 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 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 converted into an ordered state.<sup>[21]</sup> 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, is unimportant in the context of the present study.



**Fig 2** Rate-normalized DSC heating and cooling scans obtained on 50/50-m% samples of the polymer/solvent system 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.

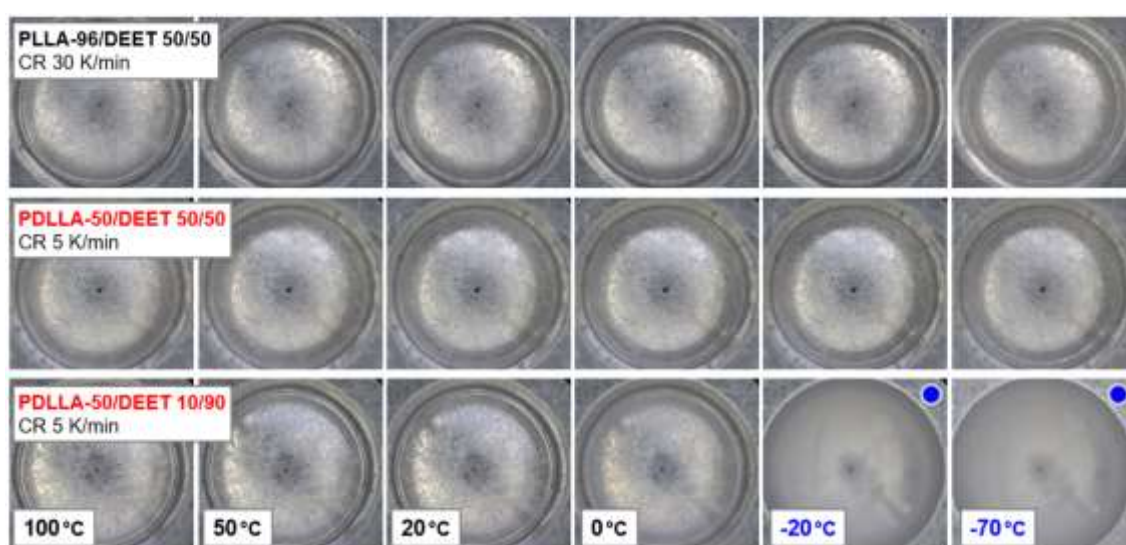
Cooling PLLA-96 in solution with 50 m% DEET at 30 K/min, in contrast, fully suppresses crystallization as the corresponding DSC scan does not show any indication of a crystallization peak. Since linear cooling at this rate was possible to about only 20 °C, cooling to lower temperatures was then continued at 5 K/min; the gap in-between the two cooling segments is owed 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 as has been seen for the sample containing non-crystallizable PDLLA-50 (red curve). The distinct downturn of the DSC curve at around  $-20\text{ }^{\circ}\text{C}$  is due to onset of vitrification of the solution, ending at around  $-65\text{ }^{\circ}\text{C}$ . 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 devitrification in the same temperature range from  $-65$  to  $-20\text{ }^{\circ}\text{C}$ , cold-crystallization beginning at around  $30\text{ }^{\circ}\text{C}$ , followed by melting of crystals formed during heating.

The top two heating curves in the part of Figure 2, associated to samples containing crystallizable PLLA-96, allow a direct comparison of different de-vitrification of solid solutions in presence and absence of crystals. The dashed and solid lines represent heating of samples cooled at  $5\text{ K/min}$ , containing crystals, and  $30\text{ K/min}$ , being free of crystals, respectively. As expected, the sample which does not contain crystals devitrifies between  $-65\text{ }^{\circ}\text{C}$  and  $-20\text{ }^{\circ}\text{C}$  and yields then a liquid solution with a higher heat capacity ( $c_p$ ) than the sample which contains solid crystals.

In order to support the interpretation of the DSC data of Figure 2 regarding absent L-L demixing on cooling solutions which contain 50 m% 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.<sup>[2]</sup> 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 Figure 3 are shown optical macrographs taken during cooling solutions of PLLA-96/DEET 50/50 m% (top row), PDLLA-50/DEET 50/50 m% (center row), and PDLLA-50/DEET 10/90 m% (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  $30\text{ K/min}$  in order to suppress crystallization (see also blue DSC curve in Figure 2, labeled  $-30\text{ K/min}$ ). 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 Figure 2, the initially liquid solution turns glassy between  $-20$  and  $-65\text{ }^{\circ}\text{C}$  without any sign of demixing since the picture taken at  $-70\text{ }^{\circ}\text{C}$  remains clear. When using non-crystallizable PDLLA containing 50 % D-units (PDLLA-50) instead of PLLA-96, in mixtures with 50 m% 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 demixing during cooling, with the bottom-row images is followed the cooling process of a mixture containing only 10 m% PDLLA-50. According to the phase diagram shown in Figure 1, phase separation occurs at around  $0\text{ }^{\circ}\text{C}$ . At lower temperatures, the sample is heterogeneous, containing two phases of different DEET and polymer content. The images taken at  $-20\text{ }^{\circ}\text{C}$  and  $-70\text{ }^{\circ}\text{C}$  confirm the expectation as cloudiness is observed.



**Fig 3** Optical macrographs taken during cooling solutions of PLLA-96/DEET 50/50 m% (top row), PDLLA-50/DEET 50/50 m% (center row), and PDLLA-50/DEET 10/90 m% (bottom row). Images need being 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 was the aim of the present study to explore whether L-L de-mixing in the polymer/solvent system 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 m% of DEET. DSC and cloud-point analyses showed that regardless the D-unit content, L-L de-mixing on cooling the liquid solutions is suppressed by vitrification of the systems at their identical glass transition temperatures. Main conclusion is the proof of absence of L-L de-mixing at temperatures higher than crystallization-induced S-L de-mixing 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,<sup>[22,23]</sup> and contribute to further understanding of the complex phase behavior of the polymer/solvent system PLA/DEET.

## ACKNOWLEDGMENTS

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### Competition between liquid-liquid demixing, crystallization and glass transition in solutions of PLA of different stereochemistry and DEET

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In this study it is shown that solutions of both crystallizable PLLA and non-crystallizable PDLLA with 50 m-% DEET vitrify on fast cooling below  $-20\text{ }^{\circ}\text{C}$ , without prior liquid-liquid demixing. As such it is concluded that crystallization of PLLA, observed at around  $55\text{ }^{\circ}\text{C}$  on slow cooling, is not preceded by liquid-liquid demixing.

