A Morphological Study of Membranes Obtained from the Systems Polylactide-Dioxane-Methanol, Polylactide-Dioxane-Water, and Polylactide-*N*-Methyl Pyrrolidone-Water

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SYNOPSIS

The influence of liquid–liquid demixing, solid–liquid demixing, and vitrification on the membrane morphologies obtained from several polylactide-solvent–nonsolvent systems has been investigated. The polymers investigated were the semicrystalline poly-L-lactide (PLLA) and the amorphous poly-DL-lactide (PDLLA). The solvent–nonsolvent systems used were dioxane-water, *N*-methyl pyrrolidone-water and dioxane-methanol. For each of these systems it was attempted to relate the membrane morphology to the ternary phase diagram at 25°C. It was demonstrated that for the amorphous poly-DL-lactide the intersection of a glass transition and a liquid–liquid miscibility gap in the phase diagram was a prerequisite for the formation of stable membrane structures. For the semicrystalline PLLA a wide variety of morphologies could be obtained ranging from cellular to spherulitical structures. For membrane-forming combinations that show delayed demixing, trends expected on the basis of phase diagrams were in reasonable agreement with the observed membrane morphologies. Only for the rapidly precipitating system PLLA-*N*-methyl pyrrolidone-water were structures due to liquid–liquid demixing obtained when structures due to solid–liquid demixing were expected. Probably, rapid precipitation conditions promote solid–liquid demixing over liquid–liquid demixing, because the activation energy necessary for liquid–liquid demixing is lower than that for crystallization.
Keywords: polylactide • membrane formation • morphology • crystallization • liquid–liquid demixing

INTRODUCTION

Porous membranes are frequently applied in separation technology. Most of the membranes that are in use are prepared via the immersion precipitation process. For each of the applications, tailoring of the membrane morphology is necessary. Therefore much research is performed to elucidate the mechanisms that are responsible for the membrane morphology.[1]

The relation between phase diagrams, kinetics of demixing, and the membrane morphology for polylactide-chloroform-methanol systems has been discussed earlier.[2–5] Several polylactide stereoisomers were used for the experiments. In order of decreasing stereoregularity and crystallizability the following polymers were used: poly-L-lactide (PLLA), poly-L95/D5-lactide (PLA95), poly-L80/D20-lactide (PLA80)), and poly-L50/D50-lactide (PDLLA). A good correlation between phase diagram and membrane morphology was found. In refs. 6 and 7 the preparation of suitable hollow fiber membranes for drug delivery applications was described in detail.

The objective of this contribution is to investigate whether the principles established for the ternary

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systems with chloroform-methanol can be extended to other polylactide-solvent–nonsolvent systems. The attention is focused primarily on the correlation between phase diagram and membrane morphology. The following polymer-solvent–nonsolvent systems have been investigated:

- PLLA-dioxane-methanol
- PLLA-dioxane-water
- PLLA-*N*-methyl pyrrolidone-water
- PDLLA-dioxane-methanol
- PDLLA-dioxane-water
- PDLLA-*N*-methyl pyrrolidone-water

The indicated solvent–nonsolvent combinations have been previously used for the preparation of porous fibers.[6,7] For these combinations, the positions of the phase boundaries in the isothermal phase diagram (25°C) were identified in the preceding work of this series.[4] For each of these systems, membranes as a function of polymer concentration in the casting solution were prepared. The morphology and the crystallinity of the membranes have been evaluated using scanning electron microscopy (SEM), wide-angle x-ray scattering (WAXS), and differential scanning calorimetry (DSC), respectively.

The preparation of membranes that are useful for application is not part of the subject chosen for this study. A detailed treatment, however, of the procedures and the systems needed to provide useful membranes can be found in ref. 6 to this article. For instance, procedures to successfully prepare highly porous fiber membranes, free of macrovoids, for drug delivery are described in full detail in that article.

EXPERIMENTAL

Materials

Poly-L-lactide and poly-DL-lactide fractions with varying molecular weights were obtained from Purac biochem BV (Gorinchem, The Netherlands). The intrinsic viscosities of the fractions varied between 0.7 and 5.1 dL/g (chloroform, 25°C). Dioxane and *N*-methyl pyrrolidone (NMP) were of analytical quality (Merck–Schuchardt, Darmstadt, Germany). Water was demineralized.

Methods

Solutions were prepared by adding the components together and stirring for two days at room temperature. Casting solutions which were not stable in time were kept at elevated temperatures (ca. 60°C). Shortly before use the solutions were rapidly cooled to room temperature. Solutions treated in this way were 25% PLLA in dioxane and all solutions of PLLA in NMP. These solutions remained homogeneous for at least half an hour.

Membranes were prepared by casting the polymer solution on a glass plate with a doctor's blade and immersing the solution in nonsolvent. The temperature of the nonsolvent bath was kept at 22 ± 2°C. The initial casting thickness was 400 μm. The time between casting and immersion amounted to circa 10 s. The membranes were kept in nonsolvent for a period of three days and dried afterwards (1 day air drying, 1 day in vacuo). Thereafter the membranes were characterized with SEM and DSC. For analysis with SEM, parts were cut from the membranes (before drying), fractured in liquid nitrogen and dried in vacuo. Cross sections, top surfaces, and bottom surfaces were transferred to a Balzers Union sputter unit, provided with a gold layer and examined using a JEOL 35CF Scanning Electron Microscope. For DSC analysis samples of 5 mg were cut from the membranes and heated with a scan rate of 10°C/min from 30 to 220°C in sealed aluminum sample pans. X-ray diffractograms of the membranes were recorded using a Guinier–Simon camera with monochromatic CuK_α radiation.

RESULTS

Membranes Prepared From the System PLA-Dioxane-Methanol

Solutions of PDLLA in dioxane became turbid in about 1 min after immersion in nonsolvent. However after prolonged incubation of membranes in methanol the turbidity gradually disappeared. After 1 day or longer of equilibration in methanol the membranes contained almost no pores (see Fig. 1, equilibration time 3 days).

Precipitation times in methanol of solutions of PLLA in dioxane were in the order of few seconds. However the nascent membrane gained mechanical strength very slowly. The dried membranes remained rather weak. The membranes prepared from a casting solution with a polymer concentration of 5% v/v had a very open leafy morphology (see Fig. 2). No differences were observed between the morphology of the top layer, the bottom layer, and the cross section. The morphology did not depend on

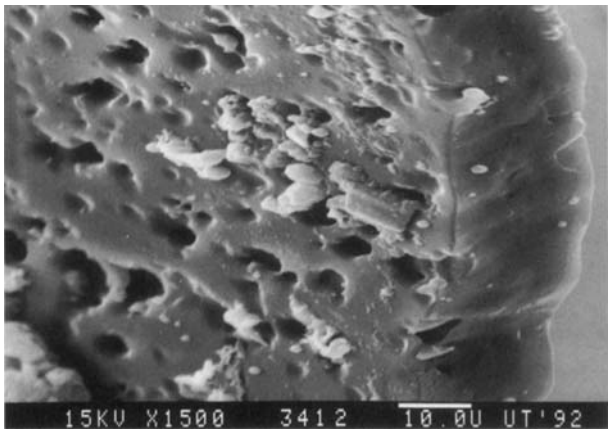


Figure 1. Edge view of membrane morphology of a 5% v/v solution of PDLLA in dioxane immersed in methanol ($[\eta]$ = 5.1 dL/g). Morphology after 3 days of equilibration in the methanol.

the molecular weight of the polymer. For PLLA fractions with intrinsic viscosities of 2.0 dL/g and 4.7 dL/g membranes with similar morphologies were obtained. When the polymer concentration of the casting solution was increased to 8% v/v very porous spherulites appeared in the top surface of the cross section (see Fig. 3A). The sublayer still had a leafy morphology. The membrane prepared from the 17% v/v solution ($[\eta]$ = 1.9 dL/g) consisted mainly of hairy spherulites of 5–10 μm diameter (see Fig. 3B). The bundles of lamellae radiating from the center can be easily distinguished.

Membranes Prepared From the System PLA-Dioxane-Water

Stable porous membranes were obtained from the system PDLLA-dioxane-water. Precipitation times amounted to 30–40 s independent of polymer concentration and molecular weight. The membranes prepared with PDLLA all had cellular morphologies. For casting solutions with low polymer concentrations the cross section can be divided in two sections (Fig. 4A). The upper part close to the top layer contains very large pores and the part close to the bottom layer contains very small pores. The surface layer is irregular and always contains pores. The membranes prepared from a 13% v/v polymer solution consist only of very large pores (Fig. 4B).

The cross sections of the membranes obtained with PLLA at low polymer concentrations in the casting solution contain the same structural characteristics as those obtained with PDLLA (Fig. 5A). Small pores exist at the bottom layer and larger pores close to the interface. In contrast to the membranes prepared from PDLLA containing solutions the membrane surfaces do not contain any pores. Cracks can be observed at high magnifications (magn. 5000–10,000×). The delay times for low concentrated solutions of PLLA were comparable to those of PDLLA. The membranes prepared from solutions with a polymer concentrations of 8 and 13% v/v have an entirely different morphology (see Fig. 5B). The membranes appear to be composed of leafy or rodlike structures. The characteristic size of the structures is approximately $0.1 \times 1 \times 0.5$ μm. In the lower part of the membrane the structure of the membrane is more open and also a small amount of large pores are present. The sublayer close to the top surface of the membranes contains more densely packed structures than the sublayer more remote from the top surface and does not contain any large pores. The top surface contains very small circular pores. The membranes prepared with the casting solutions with PLLA concentrations of 17% v/v and 22% v/v contain large macrovoids. The walls of the voids consist of spherulites (Fig. 5C). The spherulites are difficult to distinguish from each other and contain some large pores (Fig. 5D, pore diameter 5 μm).

The spherulites in the membrane prepared from the casting solution with a polymer concentration of 17% v/v were less easy to identify than the membrane prepared with a polymer concentration of 22% v/v. The concentrated solutions (17–22% v/v) precipitated almost instantaneously after immersion.

Membranes Prepared From the System PLA-NMP-Water

Membranes prepared from the system PDLLA-NMP-water contain very large macrovoids and a very thin dense top layer (Fig. 6A). The walls of the macrovoids of PDLLA consist of a fine bicontinuous network structure (Fig. 6B). The characteristic size of the voids of the network is approximately 0.1–1 μm. The morphology of the membranes was hardly influenced by the polymer concentration of the casting solution (5–10% v/v).

The differences in morphology between membranes of PLLA and PDLLA are relatively small. The membranes obtained with PLLA also contain macrovoids with a very open pore structure (comparable to Fig. 6A). A detail of the structure is shown in Figure 6C. However in lower parts of the cross section some tendency for the formation of leafy structures can be observed (Fig. 6D). The top surface of PLLA membranes also consists of leafy struc-

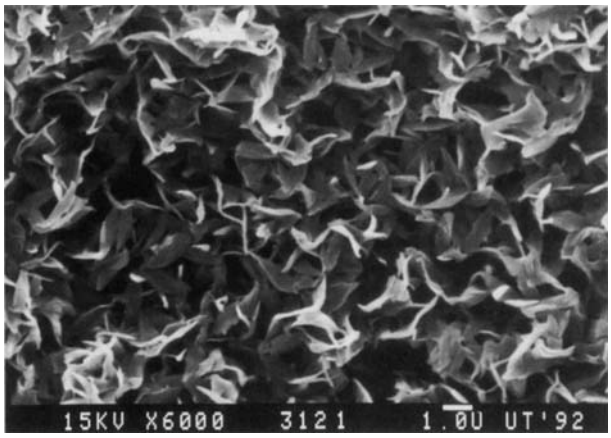


Figure 2. Cross section of membranes prepared from the system PLLA-dioxane-methanol. Polymer concentration of the casting solution was 5% v/v ([η] = 2.0 dL/g).

tures. Because of the large macrovoids the membranes have a low mechanical strength.

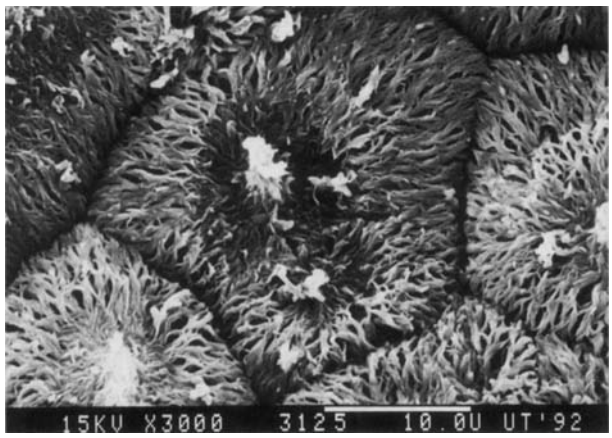
Melting Points and Heats of Fusion of PLLA Membranes

The DSC results show that all PLLA membranes are highly crystalline (Table I). When a value of 140 J/g is taken for the heat of fusion of 100% crystalline polymer, the crystallinities of the membrane vary between 25 and 40%.[8] The crystallinity appears to decrease slightly with increasing molecular weight. The membranes obtained with the system dioxane/methanol have a somewhat higher crystallinity than found for other solvent–nonsolvent systems. In general the melting temperatures increase slightly with increasing molecular weight. The x-ray diffractograms revealed that in all membranes PLLA crystallized in the common α-crystal modification (10/3 helix).[9]

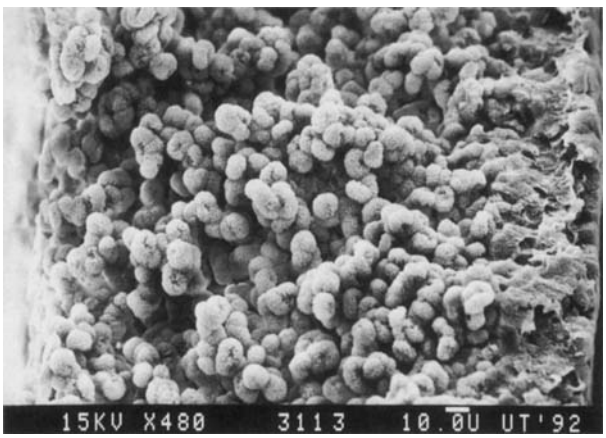
DISCUSSION

Many parameters are known to exert an influence on the membrane morphology.[1] Factors which have a large influence on the membrane morphology are the composition of the casting solution and the composition of the coagulation bath. A second class of variables consists of the thermodynamical and frictional interactions between the components in solution.[10–13]

The structure formation in solution is induced by phase transitions.[1] The cellular structures commonly found in the cross sections of membranes are due to liquid–liquid demixing by nucleation and growth of polymer poor droplets. Not much attention has been paid to phase transitions other than liquid–liquid demixing. However also crystallization processes and vitrification processes are important transitions for the membrane morphology. It is thought that both the glass transition and crystallization processes play an important role in the stabilization of the membrane morphology.[1,14–17] However crystallization processes during immersion precipitation can also induce the formation of porous membranes without the occurrence of liquid–liquid demixing.[2,18–22] The relative locations of these transitions with respect to the liquid–liquid miscibility gap and the kinetics of these transitions will determine the importance of each transition for the membrane morphology during membrane forma-

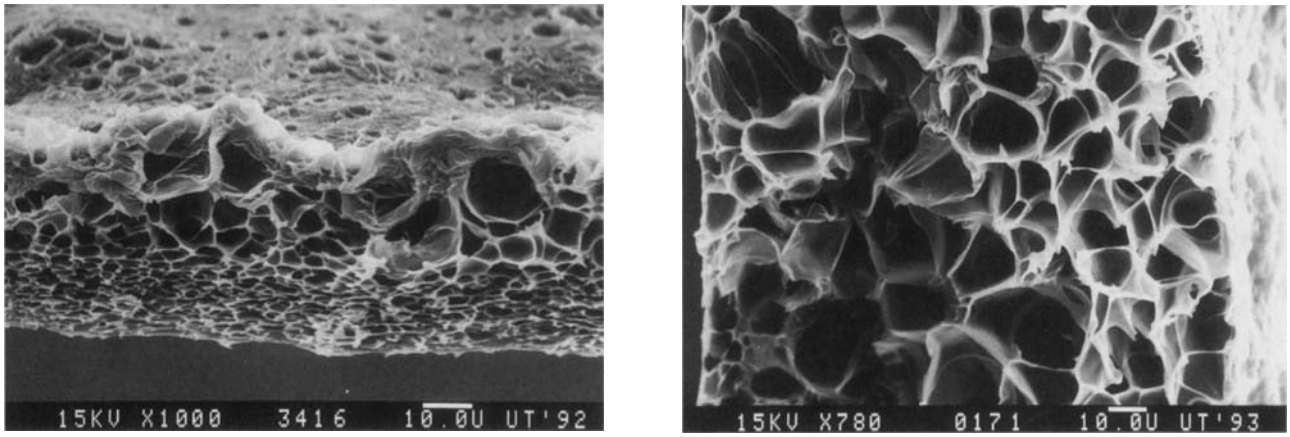


(a)



(b)

Figure 3. Membranes prepared from the system PLLA-dioxane-methanol. (a) Top surface of a membrane, polymer concentration casting solution: 8% v/v, [η] = 3.1 dL/g. (b) Part of the cross section of a membrane, polymer concentration casting solution: 17% v/v, [η] = 1.9 dL/g.



(a) (b)

Figure 4. Membranes prepared from the system PDLLA-dioxane-water (top surfaces (a) upper side and (b) right hand side). (a) Membrane prepared with a PDLLA fraction with an intrinsic viscosity of 5.1 dL/g. The polymer concentration of the casting solution was 5% v/v. (b) Membrane prepared with a PDLLA fraction with an intrinsic viscosity of 2.6 dL/g. The polymer concentration of the casting solution was 13% v/v.

tion.[1] The complexity of the immersion precipitation process is illustrated by the largely differing membrane morphologies that were obtained using the different polylactide-solvent–nonsolvent combinations.

Systems With Dioxane/Methanol

The systems with dioxane-methanol resemble in many respects the systems with chloroform-methanol.[2] As was also the case for the corresponding system with chloroform no stable membranes could be obtained from solutions of PDLLA in dioxane. Due to the low nonsolvent power of methanol the swelling of the polymers in the nonsolvent was too high to allow stabilization of the liquid–liquid demixed morphology by vitrification (Fig. 7A). For membranes prepared from low PLLA concentrations using the system PLLA-chloroform-methanol the structure generated by liquid–liquid demixing was stabilized by crystallization processes. However no indications for liquid–liquid demixing are visible in the morphologies of the membranes obtained with PLLA-dioxane-methanol. At low polymer concentrations leafy structures were obtained and at high polymer concentrations spherulites. Both leafy structures and spherulitical structures have been earlier obtained by thermally induced phase separation of PLLA containing solutions and obviously are the result of crystallization processes.[22-24] The gradual transition from leafy structures to spherulitical structures with increasing polymer concentrations is a commonly observed phenomenon and can be attributed to the fact that the nucleation and growth rates of the crystals increase at increasing polymer concentrations.[25] The more prominent role of solid–liquid demixing processes for the system PLLA-dioxane-methanol than for PLLA-chloroform-methanol can be related to differences in location of the phase boundaries in the phase diagram at 25°C. Earlier it has been demonstrated that during cooling of solutions of PLLA in dioxane/methanol mixtures phase separation was induced by solid–liquid demixing processes.[4] For the system PLLA-chloroform-methanol liquid–liquid demixing occurred during the cooling of solutions with low PLLA concentrations and solid–liquid demixing processes during cooling of concentrated polymer solutions. The distance in location of the liquid–liquid miscibility gap and solubility curve in the phase diagram was much larger in the case of the system PLLA-dioxane-methanol than for the corresponding system with chloroform-methanol (see Fig. 7B). This effect results from the lower solvent power of dioxane for PLLA compared to chloroform.

Systems with Dioxane/Water

Water is a very powerful nonsolvent for polylactides. This is reflected in the fact that stable porous membranes can be obtained from the system PDLLA-dioxane-water. This again demonstrates clearly that an intersection of the vitrification boundary with the liquid–liquid miscibility gap is a prerequisite for

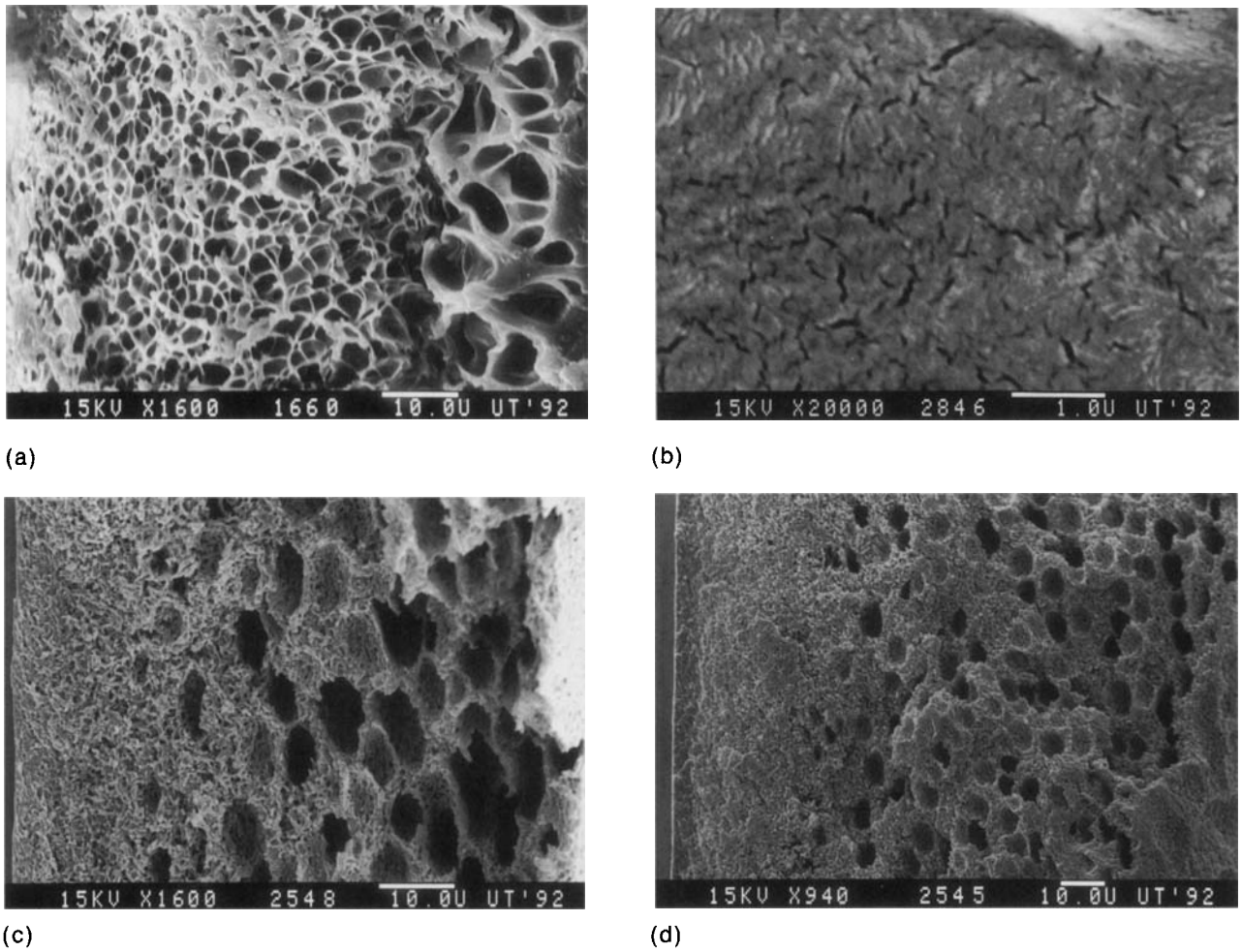


Figure 5. Membranes prepared from the system PLLA-dioxane-water (a) Cross section of a membrane prepared with casting solutions containing 5% v/v polymer ([η] = 4.7 dL/g). Top surface right hand side. (b) Cross section of a membrane prepared with a casting solution with a polymer concentration of 8% v/v ([η] = 1.9 dL/g). (c) Cross section of a membrane prepared with a casting solution with a polymer concentration of 22% v/v ([η] = 0.7 dL/g). Top surface left hand side. (d) Magnification of C.

the formation of stable structures in solution for the amorphous PDLLA. It is surprising that for concentrated PDLLA solutions the dimensions of the pores are larger than for the less concentrated solutions. Usually the reverse trend is found.[26–28] Most likely this can be attributed to the fact that the gel transition for the systems used in refs. 26–28 is located at much lower polymer concentrations than for the PDLLA-dioxane-water system. From a thermodynamical point of view, a smaller number of polymer poor nuclei is expected at high polymer concentrations because of the larger activation energy necessary for nucleation. Because the glass transition for the systems with PDLLA is located at high polymer concentrations these nuclei still can grow to large dimensions. If the gel transition is located at much lower polymer concentrations the pores will remain small. This effect is also reflected in the asymmetric pore size distribution of membranes obtained at low PDLLA concentrations. The pores are larger close to the interface than in the lower part of the cross section due to the higher polymer concentrations close to the interface at the onset of demixing. The irregular surface of the membranes obtained with the highest intrinsic viscosity can be attributed to the high viscosity of the concentrated interfacial layer. This layer forms a barrier for the growth of the nuclei. For low intrinsic viscosities the nuclei grow more easily through the top layer because of the lower vis-

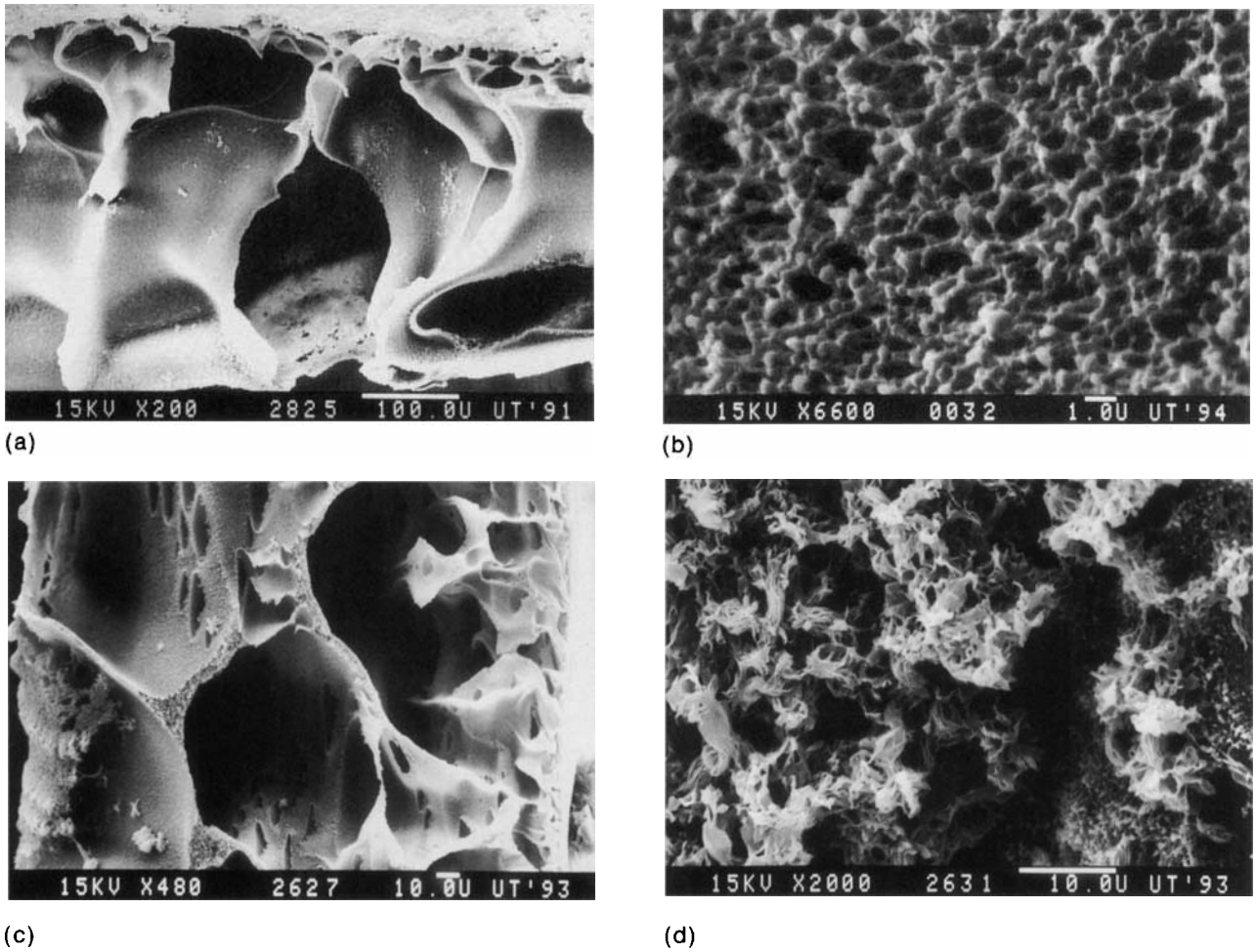


Figure 6. Membranes prepared from the system PLA-NMP-water. (a) Cross section of a membrane prepared with a casting solution of 5% v/v PDLLA ([η] = 5.1 dL/g) top surface up. (b) Detail of the wall of a macrovoid of a membrane prepared with a casting solution of 5% v/v PDLLA ([η] = 5.1 dL/g). (c) Detail of cross section close to macrovoid of a membrane prepared with a solution of 5% v/v PLLA in NMP ([η] = 1.9 dL/g), top surface right hand side). (d) Detail of the membrane cross section in the lower part of the cross section.

Table I. Melting Points and Heats of Fusion of PLLA Membranes

[η] (dl/g)	Solvent/Nonsolvent[a]	Melting Temp. (°C)	Heat of Fusion (J/g)[b]
0.7	D/W	175	50
2	D/W	180	43
3	D/W	190	42
4.7	D/W	186	35
2	D/M	180	58
4.7	D/M	185	53
2	N/W	180	45 (10)
4.7	N/W	183	45 (5)

[a] D: dioxane, M: methanol, N: NMP, W: water.
[b] Numbers between brackets indicate the heat of recrystallization during heating.

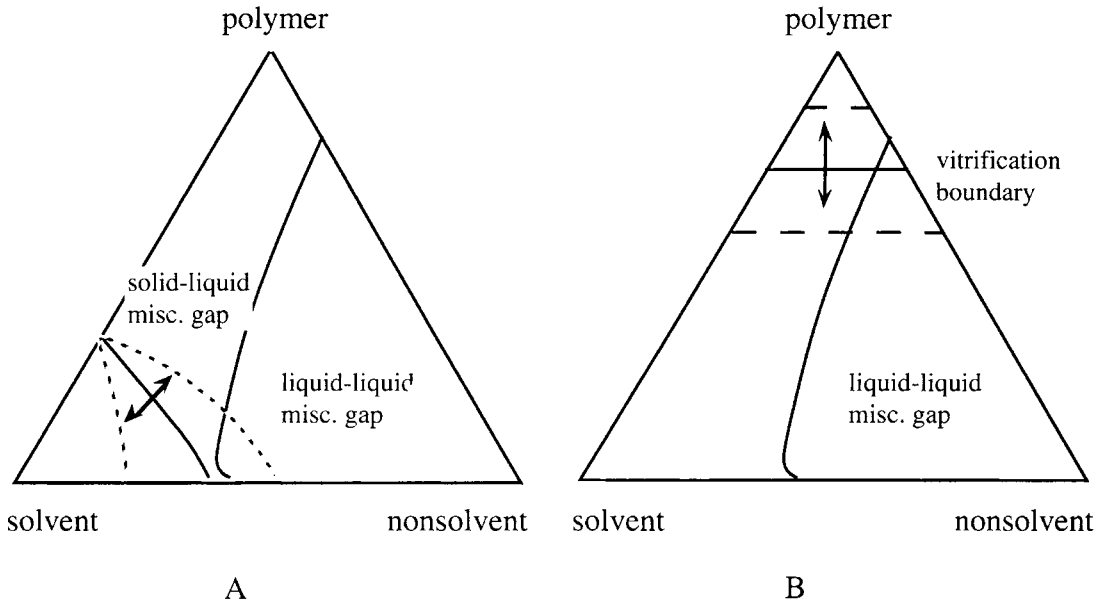


Figure 7. Schematic isothermal phase diagrams for combinations of polymer, solvent and nonsolvent. (A) Combination of a solid–liquid miscibility gap and a liquid–liquid miscibility gap. The relative position of the solid–liquid miscibility gap with respect to the liquid–liquid miscibility gap determines the importance of solid–liquid demixing for the structure formation. Changes in the location of the solid–liquid miscibility gap are indicated with dotted lines and an arrow. (B) Combination of a vitrification boundary and a liquid–liquid miscibility gap. The relative position of the vitrification boundary with respect to the liquid–liquid miscibility gap determines the importance of the glass transition for the structure formation. Changes in the location of the vitrification boundary are indicated with dotted lines and an arrow.

cosity and the surface becomes smoother and more porous.

For casting solutions with a low PLLA concentration the membrane morphologies strongly resemble those obtained with PDLLA. For both PLLA and PDLLA the conventional cellular morphologies have been found. Despite the fact that the PLLA membranes are highly crystalline no structural evidence for crystallization is found. This indicates that the liquid–liquid demixed structure is not stabilized by crystallization but by vitrification. Crystallization must have taken place in the polymer-rich phase just below the vitrification boundary. Compared to the system PLLA-dioxane-methanol the precipitation mechanism has shifted from solid–liquid demixing to liquid–liquid demixing. This is reflected again in the experimentally determined phase diagram. The solubility curve for the system with PLLA-dioxane-water is located at only slightly lower water concentrations than the liquid–liquid miscibility gap.[4] For the system PLLA-dioxane-methanol the distance between the solubility curve and the liquid–liquid miscibility gap in the ternary phase diagram is much larger. A large supersaturation is necessary for crystallization processes to proceed at a sufficiently high rate. For the system PLLA-dioxane-water the solution enters the liquid–liquid miscibility gap before crystallization can occur, while for the system PLLA-dioxane-methanol the distance between the solubility curve and the liquid–liquid miscibility gap is too large too reach the liquid–liquid miscibility gap (compare Fig. 7B).

The distance between solubility curve and liquid–liquid miscibility gap increases with increasing polymer concentrations. At slightly higher polymer concentrations of the casting solution membranes with leafy morphologies have been obtained for PLLA (8–13% v/v). At very high polymer concentrations (17–22% v/v) of the casting solution the leafy structures gradually change to a spherulitic morphology with large macrovoids. The spherulites strongly differ in shape and morphology from the spherulites obtained for the systems with chloroform/methanol and dioxane/methanol. The reason for these differences cannot be explained at the moment. Also the rea-

son for the presence of macrovoids is unclear. The conventional explanations for macrovoid formation do not seem to offer an explanation in this case.[29,30]

Systems With NMP-Water

Also for combinations of PDLLA-NMP-water stable membranes can be obtained. This is in line with the view that only the nonsolvent power determines whether the structure in solution can be stabilized by vitrification. The membranes contain large macrovoids and a bicontinuous morphology. Bicontinuous morphologies are generally associated with spinodal decomposition.[31] However on the basis of diffusion models it has been argued that spinodal decomposition cannot occur during immersion precipitation because the driving force for diffusion is zero at the spinodal.[32] It has been stated that the change of demixing mechanism from spinodal decomposition and binodal decomposition is gradual rather than instantaneous.[31] Possibly bicontinuous structures can be obtained by a deep quench in the metastable liquid–liquid miscibility gap. Compared to dioxane, NMP is a poorer solvent for PLLA. Theoretically it is expected that for poor solvents the structure formation will shift to solid–liquid demixing. At room temperature PLLA precipitates from NMP already at polymer concentrations below 1% v/v.[4] Still the membranes do not have a crystalline morphology. Only in the lower part of the cross section leafy structures were observed. The fact that no large differences are observed between the morphologies of the PLLA and PDLLA membranes indicates that the glass transition is the real stabilizing transition. Most likely the differences between the membrane structures are due to differences in kinetics of solvent–nonsolvent exchange. In contrast with the solvent/nonsolvent combinations dioxane/water, dioxane/methanol and chloroform/methanol, NMP-water is a solvent/nonsolvent combination with a high mutual affinity.[33,34] The polymer solutions phase separate almost immediately after immersion in the nonsolvent bath. Probably the solvent-nonsolvent exchange rate is too high to allow phase separation by crystallization. For the system PLLA-NMP-water an exotherm due to recrystallization is found during heating of the membrane in the DSC. This confirms that crystallization has not proceeded until completion.

CONCLUSIONS

It has been shown that the intersection of the glass transition with the liquid–liquid miscibility gap is a prerequisite for the formation of stable porous PDLLA membranes. For PLLA the structure formation is very complex because of the competition between liquid–liquid demixing and solid–liquid demixing. The importance of solid–liquid demixing appears to be related to the distance of the solubility curve and the liquid–liquid miscibility gap in the ternary phase diagram and the rate of solvent/nonsolvent exchange. Slow exchange rates and large differences in location between the solubility curve and the liquid–liquid miscibility gap promote solid–liquid demixing over liquid–liquid demixing. However, because of the poor knowledge of the solvent–nonsolvent exchange processes after immersion, a complete understanding of all morphological details is not obtained. In a future communication the exchange processes occurring during immersion precipitation will be investigated in more detail.[35]

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