

Solubility and Phase Separation of Poly(L,D-Lactide) Copolymers

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ABSTRACT: In this study, the solubility and precipitation properties of medical-grade stereocopolymers were investigated. The solubility of the polymers was tested with eight different organic solvents and four nonsolvents. The solubility of poly(L,D-lactide) stereocopolymers was highly dependent on the L/D ratio of the copolymer. The phase-separation ability was tested by cloud-point titration with a solvent and a nonsolvent. The solvent was in all cases dichloromethane, and the nonsolvents were *n*-hexane, methanol, ethanol, and isopropyl alcohol. The results showed that *n*-hexane was the most efficient nonsolvent.

Methanol and ethanol showed quite similar precipitation properties. Isopropyl alcohol was the least efficient nonsolvent of those studied. Also, the L/D ratio of the copolymer had an effect on the precipitation properties. The precipitation happened most easily when the L content was high. The molecular weight of the copolymer had only a slight effect on the phase separation. © 2008 Wiley Periodicals, Inc. *J Appl Polym Sci* 110: 2399–2404, 2008

Key words: biopolymers; phase separation; solution properties

INTRODUCTION

Poly lactides are produced by the ring-opening polymerization of lactide into high-molar-mass polymers. Lactide is the cyclic dimer of lactic acid and exists in three stereoisomeric forms: D,D cyclic dimer (D-lactide), L,L cyclic dimer (D-lactide), and D,L cyclic dimer (mesolactide). The racemic lactide consists of an equimolar mixture of L,L and D,D cyclic dimers. D-Lactide and L-lactide are partially crystalline polymers, whereas DL-lactide is an amorphous polymer.¹

Poly lactides are widely used in medical applications because of their bioresorbable and biocompatible properties. The degradation of enantiomerically pure poly lactide is very slow, depending on the purity of the polymers, the molar mass and its distribution, the crystallinity, and the orientation. The complete degradation time could be many years.² In many medical applications, such a long degradation time is not necessary; a shorter degradation time is enough for tissue repair. The degradation rate of poly lactides can be controlled through the copolymerization of L-lactide with a different ratio to D-lactide or DL-lactide.³ When a more rapid degradation

rate is needed, it is possible to use poly-L,D-copolymers to fulfill the requirements.

The dissolution of a polymer is an interaction between the polymer and the solvent. It is due to three different types of interactions. The most common is the dispersion interaction, which arises from atomic forces. The second type is the interaction between two permanent dipoles, and the third is hydrogen bonding; both are molecular interactions. It is possible to measure cohesive energies for these three interactions. Furthermore, Hansen solubility parameters can be calculated from the energies.⁴ Solubility parameters consist of dispersion (δ_d), polar (δ_p), and hydrogen (δ_h) components. The total solubility parameter (δ) can be determined from the three components as follows:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

Hansen solubility parameters can be used for predicting the solubility of the polymers. The polymers will dissolve in solvents whose solubility parameters are close to their own. Also, the molar volume is used as a fourth parameter to describe the solubility. If two solvents have identical solubility parameters, the solvent with the lower molecular volume is better because of its thermodynamic properties.⁴

Solubility parameters of solvents are well known. The solubility parameters of lactic acid based polymers have been investigated mostly for enantiomerically pure poly lactides and mesolactides.^{5–7}

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TABLE I
Solubility Parameters for Various Lactic Acid Based Polymers^{5,6}

	Polymer	Hansen solubility parameter (MPa ^{1/2})			
		δ_d	δ_p	δ_h	δ
1	Poly(D,L-lactide) ^a	15.8	8.7	11.1	21.1
2	Poly(D,L-lactide) ^b	15.7	3.5	11.1	19.8
3	Poly(L-lactide) ^c	17.6	5.3	5.8	19.3
4	Poly(L-lactide) ^d	16.9	9.0	4.1	19.5
5	Poly(L-lactide) ^e	18.5	9.7	6.0	21.7

^a Determined by the contribution method.⁵

^b Determined by turbidity titration.⁵

^c Determined by the intrinsic three-dimensional viscosity method.⁶

^d Determined by the classical three-dimensional geometric method.⁶

^e Determined by the optimization method.⁶

Some examples are shown in Table I. The method employed to determine solubility parameters has an influence on the given results. δ is around 20 MPa^{1/2} in every case, but the most considerable difference between the polymers lies in δ_h .

The solubility of lactic acid based polymers depends on the molar mass, degree of crystallinity, and monomer ratios. Enantiomerically pure poly(L-lactide) is an isotactic polymer and partly crystalline. The increase in the D-lactide content in the copolymer increases disorder in the polymer chains and reduces the crystallinity. Amorphous polymers have fewer hydrogen bonds between polymer chains. Hence, racemic lactide and mesolactide are more soluble than enantiomerically pure poly lactides,⁸ and this can also be determined from the Hansen solubility parameters shown in Table I.

The solvents that dissolve the polymer well are called good solvents, and those solvents that do not dissolve the polymer are called nonsolvents.⁹ The good solvents for enantiomerically pure polylactide are chlorinated or fluorinated organic solvents, such as chloroform. Mesolactide and racemic lactide are soluble also in other organic solvents such as acetone and propylene carbonate.⁵ Suitable nonsolvents

are alcohols such as methanol and ethanol or unsubstituted hydrocarbons, such as hexane and heptane.⁸

Adding a nonsolvent to the polymer solution causes the precipitation of the polymer if the nonsolvent mixes with the good solvent.⁹ Information about the solubility and precipitation properties of polymers is useful for wet spinning. It is a fiber formation method in which the polymer is dissolved in a good solvent, the polymer solution is pumped through the spinneret to the coagulation bath or spin bath, and then the fiber is formed by precipitation. The spin bath includes the polymer nonsolvent and possible additives.^{10,11}

The fiber formation transaction of wet-spun fibers is similar to immersion precipitation, in which phase separation happens through diffusion and convection. In this phase separation, at least three components—the polymer, solvent, and nonsolvent—are involved, as well as possible additives.¹¹

Several researchers have reported the wet spinning of enantiomerically pure poly(L-lactide).^{12–15} However, little attention has been focused on poly(L,D-lactide) [P(L,D)LA] stereocopolymers. Before the wet spinning of P(L,D)LA stereocopolymers can be studied, the solubility and phase-separation ability of the polymers should be examined. Many studies of the precipitation properties of lactic acid based polymers have paid attention to membrane^{16–18} and microparticle or nanoparticle production^{19,20} but have not paid attention to wet-spun fiber formation.

In this work, the solubility of P(L,D)LA copolymers was tested by solubility tests, and the precipitation properties were evaluated with cloud-point titration. This study focuses on using the solubility and precipitation information for wet-spinning fiber production.

EXPERIMENTAL

Materials

Medical-grade polylactides having various L/D and L/DL ratios were used for solubility experiments and cloud-point titration, as shown in Table II. The inherent viscosities (IVs) were reported by the

TABLE II
Tested Copolymers and Their IVs and Molecular Weights

	Polymer	IV (dL/g)	M_w	Manufacturer
1	P(L,D)LA, L/D ratio = 96/4	2.2	100,400	Purac Biochem bv (Gorinchem, The Netherlands)
2	P(L,D)LA, L/D ratio = 96/4	4.8	271,000	Purac Biochem bv
3	P(L,DL)LA, L/DL ratio = 70/30	3.1	178,000	Purac Biochem bv
4	P(L,D)LA, L/D ratio = 50/50	1.6	235,500	Boehringer Ingelheim GmbH & Co. (Ingelheim am Rhein, Germany)

TABLE III
Tested Solvents and Nonsolvents and Their Hansen Solubility Parameters and Molar Volumes⁴

Solvent	Hansen solubility parameter (MPa ^{1/2})				Molar volume (cm ³ /mol)
	δ_d	δ_p	δ_h	δ	
Dichloromethane	18.2	6.3	6.1	20.3	65.3
1,4-Dioxane	19.0	1.8	7.4	20.5	85.7
Propylene carbonate	20.0	18.0	4.1	27.3	85.0
Acetone	15.5	10.4	7.0	20.0	74.0
Methylacetate	15.5	7.2	7.6	18.7	79.7
Tetrahydrofuran	16.8	5.7	8.0	19.4	81.7
Pyridine	19.0	8.8	5.9	21.8	80.9
Formic acid (98%)	14.3	11.9	16.6	24.9	37.8
Nonsolvent					
Isopropyl alcohol	15.8	6.1	16.4	23.6	76.8
Ethanol	15.8	8.8	19.4	26.5	58.5
Methanol	15.1	12.3	22.3	29.6	40.7
<i>n</i> -Hexane	14.9	0.0	0.0	14.9	131.6

polymer suppliers. The weight-average molecular weight (M_w) values of the studied copolymers were determined by gel permeation chromatography.²¹

Solubility experiments

The solubility of P(L,D)LA stereocopolymers was analyzed with eight analytical-grade solvents and four nonsolvents. The tested liquids and their solubility parameters and molar volumes are shown in Table III. The solvents and nonsolvents were selected with respect to their suitability for the wet-spinning process.

The solubility was tested in test tubes and determined by visual observation.⁵ Each polymer sample was weighed (0.2 g) in a test tube, and 2.0 mL of the solvent was measured into the test tube. The test tubes were closed instantly with polytetrafluoroethylene-coated stoppers to prevent the evaporation of the solvent. The test tubes were shaken after 1 h. The solubility was defined visually after 24 h. The interactions between the polymer and the solvent were classified into six groups. The scale ranged from 1 to 6: (1) a clear solution; (2) gel-like, thread-shaped structures; (3) a gelatinous solid; (4) very swollen; (5) slightly swollen; and (6) insoluble.

Cloud-point titration

The cloud points of solvent-polymer-nonsolvent mixtures were evaluated with titration.^{5,19,20} This method is suitable for evaluating the affinity of P(L,D)LA stereocopolymers to different nonsolvents. Three different amounts (0.3, 0.8, and 1.3 g) of the polymer materials were used. The polymer was dissolved in 10.0 mL of analytical-grade dichlorome-

thane in a conical flask with a glass stopper. The dissolution was performed at room temperature. Four different analytical-grade nonsolvents, as shown in Table III, were used. The titration of the nonsolvent was stopped at the first visually observed sign of precipitation.

The volumes of nonsolvents in the cloud point were converted to mass units. The nonsolvent percentage in the polymer solution at the cloud point (CL_{ns}) was determined as an index.^{19,20}

RESULTS AND DISCUSSION

Solubility behavior

The results of the solubility experiments are shown in Table IV. Dichloromethane dissolved all the tested polymers. P(L,D)LA 50/50 was soluble in every tested solvent. As expected, none of the nonsolvents dissolved any of the polymers.

The results can be deduced from Hansen solubility parameters. The solubility parameters of the tested copolymers were not known. Presumably, they were between the values of poly(L-lactide) and poly(D,L-lactide), which are given in Table I. The solubility parameters of dichloromethane (Table III) are similar to those of the polymers (Table I), and it also has a low molar volume. Both facts promote interactions between the solvents and polymers. On the other hand, the parameters of propylene carbonate are dissimilar, and it has a high molar volume. The analyzed polymers were least soluble in propylene carbonate among the tested solvents. According to these results, it is possible to estimate the

TABLE IV
Results of the Solubility Experiments for the Polymers and Solvents

Solvent	Polymer			
	P(L,D)LA 96/4, IV = 2.2 dL/g	P(L,D)LA 96/4, IV = 4.8 dL/g	P(L,DL)LA 70/30	P(L,D)LA 50/50
Dichloromethane	1	1	1	1
1,4-Dioxane	3	4	3	1
Propylene carbonate	6	5	4	1
Acetone	5	5	3	1
Methyl acetate	5	5	3	1
Tetrahydrofuran	4	5	3	1
Pyridine	3	5	3	1
Formic acid (98%)	5	5	2	1
Nonsolvent				
<i>n</i> -Hexane	6	6	6	6
Methanol	6	6	6	5
Ethanol	6	6	6	5
Isopropyl alcohol	6	6	6	6

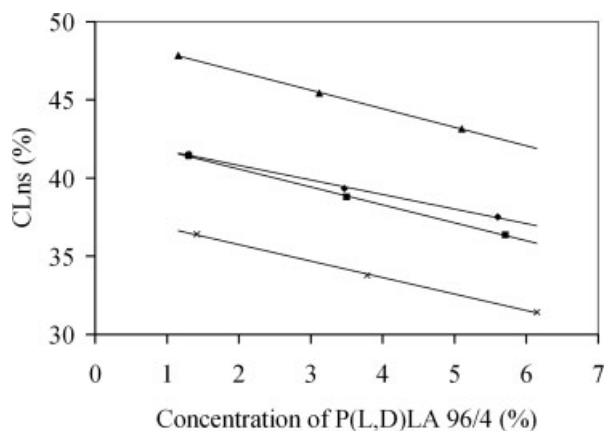


Figure 1 Dependence of CL_{ns} on the concentration of P(L,D)LA 96/4 (IV = 2.2 dL/g) in various nonsolvents: (◆) methanol, (■) ethanol, (▲) isopropyl alcohol, and (×) *n*-hexane.

solubility of polymers by means of Hansen solubility parameters.

The solubility of the analyzed copolymers was clearly dependent on the L/D ratio of the polymer. The P(L,D)LA 96/4 copolymer was soluble only in dichloromethane among the tested solvents. On the other hand, the P(L,D)LA 50/50 copolymer was soluble in all eight solvents. The solubility of the poly(L,DL-lactide) 70/30 copolymer was between those of the two aforementioned copolymers. The increase in the D segment in the polymer structure enhanced the amorphous region of the copolymer, and normally the solvents penetrated the amorphous regions first. The given solubility results agree with previous finding.^{5,8}

The analyzed P(L,D)LA 96/4 copolymer had two different IVs (2.2 and 4.8 dL/g) and M_w 's. These samples showed only small differences in solubility. The P(L,D)LA 96/4 copolymer (IV = 2.2 dL/g) was slightly more soluble than the copolymer with a higher IV (IV = 4.8 dL/g). The lower molecular weight of P(L,D)LA 96/4 (IV = 2.2 dL/g) promoted the solubility, and solvent molecules could penetrate the copolymer more easily.

Cloud-point titration

Dichloromethane was the solvent used in the cloud-point titration experiments because all the copolymers were soluble in it. All the analyzed nonsolvents are miscible with dichloromethane. Dichloromethane and *n*-hexane are hydrophobic, whereas the analyzed alcohols are water-soluble.

The dependence of CL_{ns} on the polymer concentration is presented in Figures 1–3. The results were uniform for all the tested polymers.

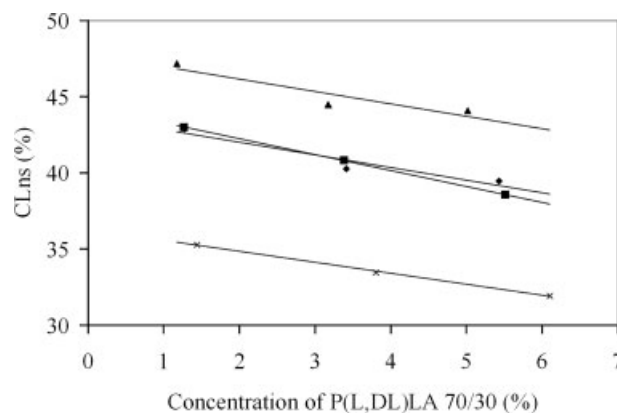


Figure 2 Dependence of CL_{ns} on the concentration of P(L,DL)LA 70/30 (IV = 3.1 dL/g) in various nonsolvents: (◆) methanol, (■) ethanol, (▲) isopropyl alcohol, and (×) *n*-hexane.

As the polymer solution concentration increased, the nonsolvent concentration decreased at the precipitation point. In wet spinning, this means that fiber formation occurs more quickly at higher polymer concentrations. However, the selection of the polymer concentration is restricted because the practical polymer solution viscosity gives the upper and lower limits for the polymer concentration. Also, the targeted fiber diameter defines the limits.

n-Hexane was the most precipitative nonsolvent for each tested P(L,D)LA copolymer. The cloud points of ethanol and methanol are close to each other. Isopropyl alcohol was the least efficient nonsolvent of the tested chemicals. When applying the precipitation results to the wet-spinning process, we found that the phase separation and fiber formation of P(L,D)LA copolymers occurred most rapidly in the spin bath containing *n*-hexane.

The size and shape of nonsolvent molecules are important factors in phase separation. Smaller and

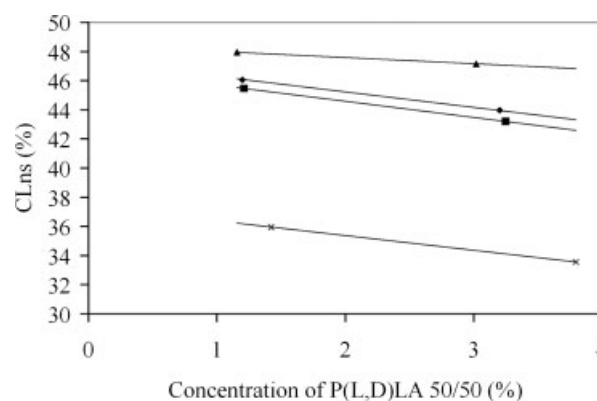


Figure 3 Dependence of CL_{ns} on the concentration of P(L,D)LA 50/50 (IV = 1.6 dL/g) in various nonsolvents: (◆) methanol, (■) ethanol, (▲) isopropyl alcohol, and (×) *n*-hexane.

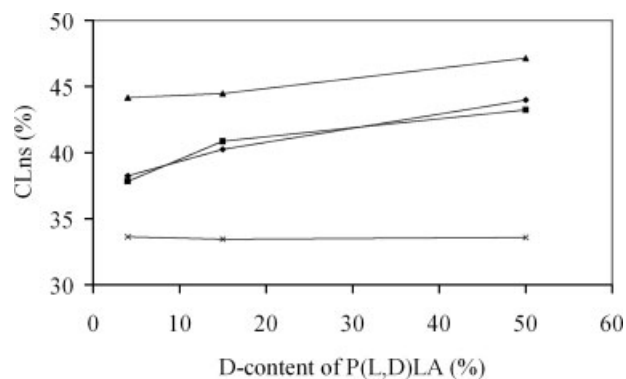


Figure 4 Dependence of the cloud point on the D content of the copolymer (0.8 g of polymer in 10 mL of dichloromethane) in various nonsolvents: (◆) methanol, (■) ethanol, (▲) isopropyl alcohol, and (×) *n*-hexane.

more linear molecules, such as *n*-hexane, diffuse more rapidly than larger and bulkier molecules, such as alcohols. Alcohols form bigger aggregates, and their diffusion is more difficult than the diffusion of linear molecules.

The cloud-point titration results show that the phase-separation ability can also be deduced from the solubility parameters shown in Tables I and III. *n*-Hexane has the highest molar volume of the analyzed nonsolvents, and its solubility parameters differ from the parameters of polylactides given in other research presented in Table I.^{5,6}

The composition of the coagulation bath has an influence on the shape and properties of the formed fibers.^{11,22} The skin-core structure is very common in wet-spun fibers. This is caused by very rapid fiber surface coagulation. The formed skin slows the coagulation speed inside the fiber. This causes morphological differences between the skin and the core. The more efficient the coagulation bath is, the higher the tendency is for skin-core structure formation. According to our experiments, the skin-core structure is more likely formed by the use of *n*-hexane and less likely formed by the use of isopropyl alcohol.

The coagulation conditions and skin-core structure formation affect the fiber cross section. If the volume of the nonsolvent diffusing inside is greater than the volume of the polymer solvent diffusing outside, the formed fiber has a round shape. If the volume of the polymer solvent diffusing inside is greater than the volume of the nonsolvent diffusing outside, the cross section of the fiber collapses. For example, viscose rayon fibers have round, irregular, Y-shaped, E-shaped, U-shaped, T-shaped, and flat cross sections, depending on the coagulation and polymer properties.²²

Also, the spinning temperature affects the fiber cross section. An increase in the spinning tempera-

ture increases the tendency for round-shape formation.¹¹ In the case of dichloromethane, the increase in the spinning temperature is limited by the low boiling point of dichloromethane (40°C).

Normally, wet-spun fibers are porous because of the phase separation of the solvent and nonsolvent. The pore structure is affected by the coagulation conditions. The morphological properties also have an effect on the mechanical properties. If the fiber is highly porous, its mechanical strength is lower than that of low-porosity fibers. If a minimal number of pores and capillaries inside the fiber are preferred, the efficiency of the coagulation bath should be reduced.¹¹ However, a porous structure is favorable when a large specific surface area is needed. For example, scaffolds used in tissue engineering benefit from a large specific surface area because of the better cell-growth possibilities. According to the titration results, a highly porous fiber structure precipitates from a coagulation bath containing *n*-hexane.

The D content of P(L,D)LA has an effect on the phase separation, as shown in Figure 4. An increase in the D content in the copolymer reduced the phase-separation ability of nonsolvent alcohols.

The phase separation of P(L,D)LA 96/4 occurred most rapidly because the analyzed nonsolvents were further away from the solubility gap of the polymer. *n*-Hexane did not have the dependence like the analyzed alcohols, and its solubility parameters also differed from the values of the alcohols.

Figure 5 shows the cloud points for P(L,D)LA 96/4 samples with different molecular weights (0.3 g of the polymer in 10 mL of the solvent). The results are based on only two samples of different molecular weights. The cloud point slightly decreased when the molecular weight of the polymer increased.

Murakami et al.¹⁹ showed that the dependence is clearest when the molecular weight is between 5000

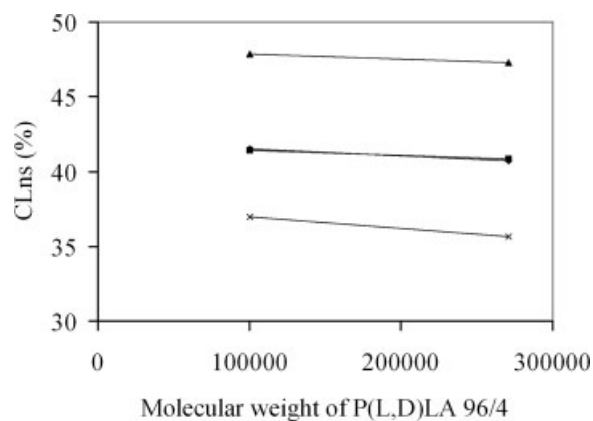


Figure 5 Dependence of the cloud point on the molecular weight of P(L,D)LA 96/4 in various nonsolvents: (◆) methanol, (■) ethanol, (▲) isopropyl alcohol, and (×) *n*-hexane.

and 20,000. The molecular weights used in our study were much higher. According to the results, the phase separation of high-molecular-weight polymers is achieved more easily. However, the molecular weight has an effect on the IV of a polymer, and it determines the limits for practical polymer concentrations in wet spinning.

CONCLUSIONS

The solubility and phase-separation ability of P(L,D)LA copolymers with different D to L ratios were tested. The solubility properties were tested with eight different solvents, and the phase-separation ability was tested with dichloromethane and four different nonsolvents.

The solubility experiments indicated that the copolymers with close to a 50/50 L/D structure showed improved solubility. The Hansen solubility parameters were helpful in predicting the solubility.

The cloud-point titration of polylactide polymer solutions with nonsolvents is an easy method of defining the precipitation properties of solvent-polymer-nonsolvent systems. The phase separation of the P(L,D)LA stereocopolymer is generated most easily from an *n*-hexane solution. Methanol and ethanol have quite similar precipitation properties. Isopropyl alcohol is the least efficient nonsolvent of the tested chemicals. The use of *n*-hexane in the coagulation bath for wet spinning is problematic because it is highly flammable and volatile. Therefore, methanol and ethanol are the most suitable tested nonsolvents for the coagulation bath for practical purposes.

Also, the polymer has an effect on the phase-separation ability. An increase in the polymer concentration reduces the precipitation point, so precipitation occurs more easily with concentrated polymer solutions. A high L content in the copolymer is favorable for phase separation because its solubility parameters are far from those of the nonsolvents. In addition,

precipitation occurs more easily if the molecular weight of the copolymer is high.

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