Poly(L,L-lactide) Microspheres by Ring-Opening Polymerization

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ABSTRACT: Poly(L,L-lactide) microspheres were synthesized directly during the ring-opening precipitation polymerizations of L,L-lactide. The polymerizations were carried out in heptane−1,4-dioxane (4:1 v/v) mixed solvent in the presence of various poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) copolymers (poly(DA−CL)) used as surface active agents. Copolymers with different molecular weights, different average number of poly(ϵ-caprolactone) grafts per macromolecule, and different molecular weights of these grafts were used. Poly(L,L-lactide) microspheres with number-average diameters ($\bar{D}_n$) from 2.46 to 4.07 μm and with polydispersity parameters ($\bar{D}_v/\bar{D}_n$, where $\bar{D}_v$ denotes the volume-average diameter) from 1.08 to 1.45 were obtained. The dependence of $\bar{D}_n$ and $\bar{D}_v/\bar{D}_n$ on the structure and on the concentration of poly(DA−CL) was investigated. The narrow diameter polydispersity ($\bar{D}_v/\bar{D}_n = 1.08$) was obtained when poly(DA−CL), containing an average of 1.3 poly(ϵ-caprolactone) grafts (with $\bar{M}_n = 4700$ g/mol) per copolymer macromolecule, was used at a concentration of 1.6 g/L, i.e., below the critical concentration of micellization of this surface active agent (ccm = 5.1 g/L). Poly(L,L-lactide) microspheres contained from 1.5 to 6.6 wt % of the unreacted lactide. The optical purity of monomer (95.4%) and of the corresponding polylactide from microspheres (from 91.0% to 94.9%) indicated that polymerization in the investigated heterogeneous system proceeds with retention of configuration on the chiral carbon atom. The DSC studies revealed that the crystallinity of the poly(L,L-lactide) microspheres was strongly dependent on the thermal history of these materials and on the concentration of the surface active agent used for the polymerization. Microspheres partly composed of crystalline and/or amorphous poly(L,L-lactide) were obtained.

Introduction

Ionic and/or pseudoionic polymerizations are frequently used as convenient methods for the synthesis of polymers with controlled molecular weight, narrow molecular weight distribution, and required end groups.[1−5] These polymerizations are often carried out in homogeneous systems. In nonsolvents, products form a shapeless precipitate. On the other hand, it is very well-known that in radical polymerization, the proper choice of initiators and surface-active additives leads to uniform polymeric latex particles.[6] In principle, there are no reasons why a similar approach could not be adapted for the ionic and/or pseudoionic polymerizations. The majority of heterocyclic monomers polymerize according to the ionic and/or pseudoionic ring-opening mechanisms. The dispersion polymerization of this group of monomers should lead to microspheres made of macromolecules containing heteroatoms in the chain.

The conditions allowing us to obtain uniform latexes and microspheres in radical polymerization are well defined.[6−9] On the other hand, the knowledge of ionic and/or pseudoionic dispersion polymerization is very limited. In 1968, Penczek et al. reported for the first time on the cationic ring opening copolymerization of 1,3,5-trioxane and 1,3-dioxolane, leading to microspheres.[10] Then, direct synthesis of polyester particles during the polymerization of heterocyclic monomers was patented in the early 1970s.[11] Subsequent papers on the ionic and/or pseudoionic dispersion polymerization were published only very recently. We described the dispersion ring-opening polymerization of ϵ-caprolactone and D,L-lactide which, in the presence of poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) surface active agent, allowed us to obtain particles with a narrow diameter polydispersity ($\bar{D}_v/\bar{D}_n = 1.038$ and 1.15 for poly(ϵ-caprolactone) and poly(D,L-lactide) particles, respectively).[12] El-Aasser et al. reported on the anionic dispersion polymerization of styrene, carried out in the presence of the polystyrene-*block*-polybutadiene stabilizer, during which spherical particles with $1.02 \le \bar{D}_v/\bar{D}_n \le 1.11$ and $1.04 \le \bar{M}_w/\bar{M}_n \le 1.15$ were obtained.[13] Teyssié et al. observed the formation of nanoparticles in the pseudoanionic polymerization of glycolide initiated with ω-aluminum alkoxide poly(ϵ-caprolactone) macroinitiator.[14] This polymerization was carried out in THF, and the THF soluble poly(ϵ-caprolactone) blocks from macroinitiators provided the steric stabilization.

Interest in the dispersion ring opening polymerization of cyclic esters is intensified by various biomedical applications of the biodegradable polyester latexes and microspheres. Microspheres made of the earlier synthesized homo- and copolyesters have been used in drug-delivery systems: as the biodegradable carriers of steroids and hormones,[15−18] antibiotics,[15] anticancer drugs,[15,16,19] narcotic antagonists,[15,20] and recently also as carriers of vaccines.[21] However, the methods used for the preparation of microspheres from polymers usually provide particles with diameters larger than 5 μm and with broad diameter polydispersity.[16] In many instances, the application of uniform biodegradable particles with diameters lower than 5 μm is essential. Recently, it has been shown that such particles could be obtained in the dispersion ring-opening polymerization of cyclic polyesters.[12,14]

The current status of the studies in the field of dispersion ring-opening polymerizations indicates that this domain is at its infancy. Many fundamental questions have to be answered before the theory of this process could be formulated, establishing the basis for the effectively controlled synthesis of particles. In this paper, we present the results of our recent studies on the dispersion polymerization of the optically active L,L-lactide. Our intention was to determine how the length of the blocks of poly(ϵ-caprolactone) in the poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) surface-active agent and

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the concentration of this compound affect the size and size distribution of poly(L,L-lactide) microspheres. We also wanted to find out whether the molecular weights of the polymers in the microspheres are dependent on the concentration and detailed composition of the surface-active agent. In the area of our interest were also investigations of microspheres by differential scanning calorimetry. We expected that these studies would provide information on the temperatures corresponding to the transitions between the different physical forms (amorphous and crystalline) of polymers constituting the microspheres.

Experimental Section

L,L-Lactide was obtained from L-lactic acid (Aldrich) according to the method described earlier.[22] This method consists of polycondensation followed by depolymerization. The monomer was stored at room temperature in an evacuated glass vessel equipped with a Teflon stopcock. The required amount of L,L-lactide was sublimed immediately before polymerization. The specific optical rotation of sublimed monomer was equal to $[\alpha]^{25}_{D} = -272°$ (*c* 1 g/100 mL, toluene). According to Beilstein (**19**^{4}, 1927), for the 100% pure L,L-lactide, $[\alpha]^{25}_{D}$ $-285°$. We noticed that polycondensation followed by depolymerization leads to some racemization. In the ^{1}H NMR spectra of the monomer, only signals at 1.72 ppm (doublet of CH_3 groups) and at 5.03 ppm (quartet of CH protons) were present. The signal at 1.78 ppm, characteristic for the meso D,L-lactide, was absent, which means that the monomer contained only the admixture of D,D isomer. This is not surprising. Duda observed that, even when starting from the racemic lactic acid, mainly the D,D- and L,L- isomers are produced and the fraction of meso isomer does not exceed 10%.[23]

ϵ-Caprolactone was purified as was described in our earlier paper.[24] Predetermined amounts of monomer were distilled into glass ampules equipped with breakseals and before polymerization were stored at −15 °C. Dodecyl acrylate (Fluka) was distilled on a vacuum line.

Initiators. α,α'-Azoisobutyronitrile (AIBN, Fluka), after crystallization from methanol, was stored in a refrigerator. Diethylaluminum ethoxide and tin(II) 2-ethylhexanoate (Aldrich) were used as received. Directly before polymerization, the required amounts of these initiators were distilled under vacuum into the thin-walled vials.

Solvents. THF, hexane, and 1,4-dioxane, after usual purification by distillation, were dried over sodium wire and then transferred into evacuated vessels containing a sodium−potassium alloy. This vessel was equipped with a Teflon stopcock. The required amounts of solvents were distilled under vacuum to the reaction vessels.

The surface-active agents, poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) copolymers, were produced in a three-step synthesis, according to the procedure described in detail in our earlier paper.[12] In the first step, the hydroxypoly(ϵ-caprolactone) was synthesized by polymerization of ϵ-caprolactone initiated with diethylaluminum ethoxide. Then, poly(ϵ-caprolactone) methacrylate (macromonomer) was obtained by reacting hydroxypoly(ϵ-caprolactone) with methacryloyl chloride. Finally, poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) was produced in the radical copolymerization of poly(ϵ-caprolactone) methacrylate and dodecyl acrylate initiated with AIBN.

Dispersion polymerizations of L,L-lactide initiated with tin(II) 2-ethylhexanoate were carried out in the 1,4-dioxane: heptane mixture (1:4 v/v) in a similar way as described in our previous paper for the dispersion polymerization of racemic monomer.[12] The diameters of the poly(L,L-lactide) microspheres were determined from microphotographs registered on a JEOL 35C scanning electron microscope. Microphotographs were analyzed by using the computer program MultiScan 4.02 (Computer Scanning Systems, Warsaw, Poland). ^{1}H NMR spectra were registered using a Bruker AC 200 spectrometer. Molecular weights and molecular weight distributions were determined by using a Knauer vapor pressure osmometer (tonometer), a Knauer membrane osmometer, and a gel permeation chromatography system combining a LKB 2150 pump, a set of Ultrastyragel 1000, 500, 100, and 100 columns, and Wyatt Optilab 903 interferometric refractometer. The optical rotatory power of the lactide and polylactide was measured with a Perkin Elmer 241 MC polarimeter. The DSC measurements were performed using a Du Pont 2000 thermal analysis system. Usually, two scans were registered for each sample. During the first one, the sample of poly(L,L-lactide) microspheres obtained from the synthesis was heated from 20 to 160 °C at a rate equal to 10 °C/min. Then, the sample was cooled to 20 °C and heated again.

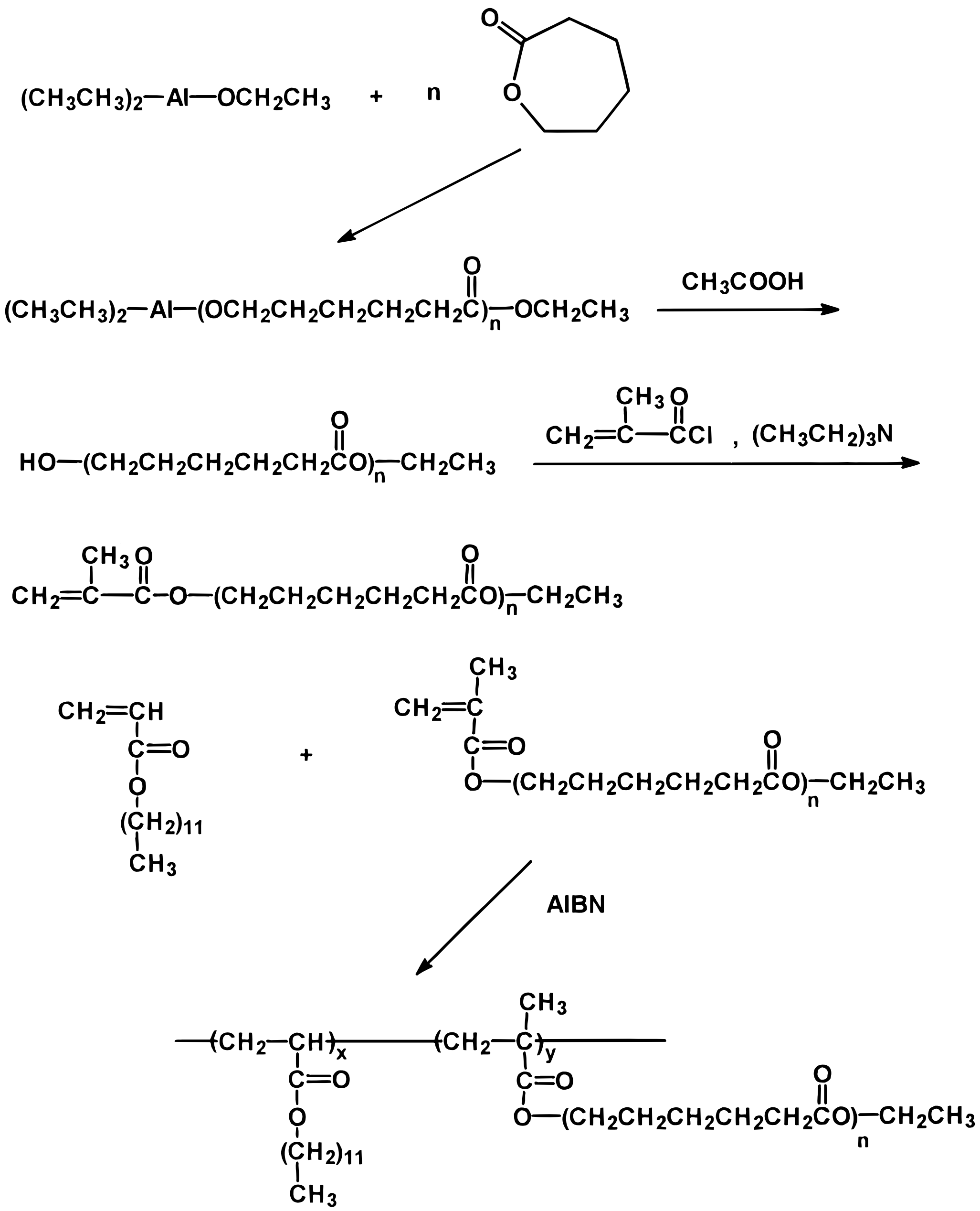
Results

Surface-Active Agents: Poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) Copolymers. Poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) copolymers (poly(DA−CL)) were synthesized in the sequence of reactions illustrated in Scheme 1. A detailed description of the synthetic procedure was described in our earlier paper.[12] Replacement of the hydroxyl end groups of ω-hydroxypoly(ϵ-caprolactone) (ω-hydroxypoly(CL)) with methacryloyl end groups of poly(CL) methacrylate was determined by using ^{1}H NMR spectroscopy. The spectra of ω-hydroxypoly(CL), poly(ϵ-caprolactone) methacrylate, and poly(DA−CL) are given in Figure 1a, 1b, and 1c. From these spectra, it follows that, in the reaction of ω-hydroxypoly(CL) with methacryloyl chloride, the signal of the $CH_2\mathit{CH_2}OH$ end groups (multiplet at 3.65 ppm which results from coupling with protons of the neighboring CH_2 group and with the hydroxyl protons; in the presence of traces of water, due to the fast exchange of hydroxyl protons, this signal is simplified to a triplet, cf. ref 25) was completely replaced with the signals of the $\mathit{CH_2}{=}C(CH_3)$ end group (at 5.55 and 6.08 ppm). This indicates that functionalization of poly(CL) with the methacryloyl end groups was quantitative. ^{1}H NMR spectroscopy was also used for the determination of the composition of poly(DA−CL). By integration of the signals from 3.85 to 4.1, corresponding to the $CH_2\mathit{CH_2}OC(O)$ of the poly(CL) side chains and of the poly(dodecyl acrylate) units, and the signal at 0.87 ppm (t) of the CH_3 groups of poly(dodecyl acrylate), we could determine the weight fraction of poly(CL) (f_{CL}) in the copolymer. The molecular weights of ω-hydroxypoly(CL) and poly(ϵ-caprolactone (poly(CL)) methacrylate were determined by GPC (poly(CL) samples with narrow molecular weight distributions, synthesized earlier in our laboratory, were used for the calibration), by ^{1}H NMR end group analysis, and tonometrically. The molecular weights of poly(DA−CL) were determined osmometrically. The number of poly(CL) grafts per one copolymer macromolecule ($\bar{NG}$) was calculated from the formula

$$\bar{N}\bar{G} = \bar{M}_n(\text{copolymer})f_{CL}/\bar{M}_n(\text{CL}) \qquad (1)$$

The molecular weights and $\bar{M}_w/\bar{M}_n$ of the ω-hydroxypoly(CL)s and poly(CL) methacrylates are given in Table 1. The values of $\bar{M}_n$ determined by the GPC and VPO methods are reasonably close, however, in some instances, they differ from those evaluated from the ^{1}NMR spectra. This reflects the lower accuracy of the molecular weight determinations by the ^{1}H NMR end group analysis. Quantitative comparison of the weak signals of the end groups with the signals of the main-chain atoms is usually not very accurate. Poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) copolymers were synthesized by radical copolymerization of dodecyl acrylate and poly(CL) macromonomers used in the proportion 4:1 (weight), regardless of the molecular weight of the macromono-

Scheme 1



mer. The molecular weights of the poly(DA−CL) copolymers and the number of grafts per one copolymer macromolecule are given in Table 2. The molecular weight of poly(CL) was varied from ca. 1000 to 9000 g/mol ($\bar{M}_n$ values determined tonometrically). The data collected in Table 2 indicate that, regardless of the molecular weights of the poly(CL) macromonomers, the weight fraction of poly(CL) in the poly(DA−CL) copolymers (f_{CL}) varied only within a narrow range, namely, from 0.19 to 0.24. The molecular weights of the synthesized copolymers fluctuated within the range from 21 800 to 32 300 g/mol. On the other hand, we observed a large and systematic change of the average number of poly(CL) grafts per one copolymer macromolecule. The values of $\overline{NG}$ were found to be dependent on the $\bar{M}_n$ of the poly(CL) macromonomer used for copolymerization. For copolymers made of macromonomers with $\bar{M}_n$(osm) equal to 9000 and 970 g/mol, $\overline{NG}$ was equal to 0.6 and 6.9, respectively. Thus, in the case of the surface active agent made of poly(CL) macromonomer with the highest molecular weight, apparently not all the poly(dodecyl acrylate) chains were equipped with even one poly(CL) side chain. It is worth noting that, for copolymers K5 and K8 the values of $\overline{NG}$ are only slightly higher than 1. Apparently, in the case of polymers K5, K8, and K10, the macromolecules with poly(CL) chains are mainly of the T type, with polyacrylate branches of various lengths.

In our earlier studies, we found that the 1,4-dioxane−heptane mixture (1:4 v/v) is suitable for the direct synthesis of the poly(D,L-lactide) microspheres by ring-opening polymerization.[12] We decided to also use this medium for the synthesis of the poly(L,L-lactide) microspheres.

One of the important parameters characterizing any surfactant in the given medium is the critical concentration of micellization (ccm), i.e., the lowest concentration of surfactant at which it begins to form micelles. Formation of micelles could be easily detected turbidimetrically, because these aggregates scatter the visible light much stronger than the single macromolecules do. The turbidity of poly(DA−CL) in the 1,4-dioxane−heptane mixture was monitored at 320 nm. We checked that, at this wavelength, neither poly(dodecyl acrylate)

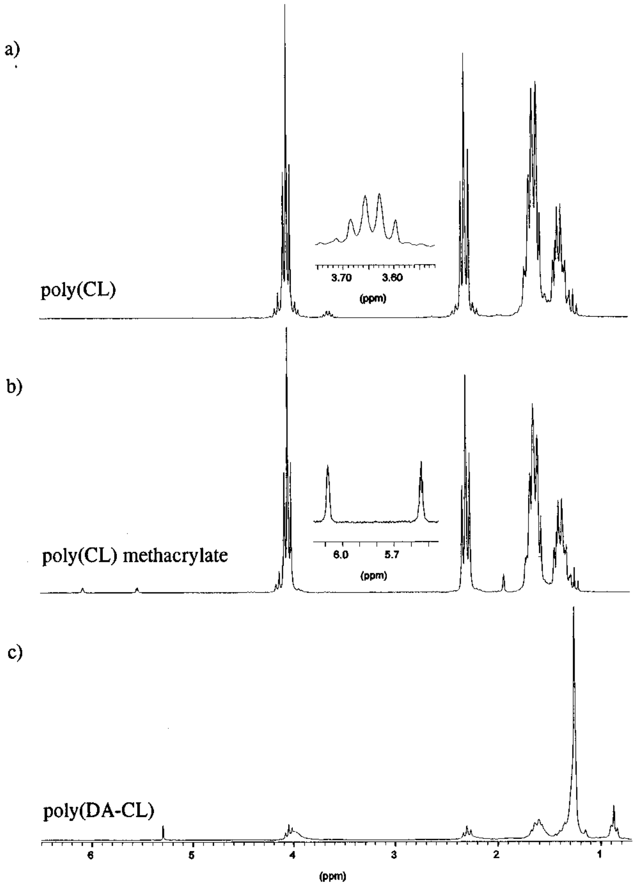


Figure 1. ^{1}H NMR spectra of ω-hydroxypoly(ϵ-caprolactone) (a); poly(ϵ-caprolactone) methacrylate (b), and poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) (c).

nor poly(CL) absorbs light and that the observed variations of measured optical density (OD) could be related solely to the changes of light scattering by micelles. Plots of OD$_{320}$ vs concentrations of poly(DA−CL) in the 1,4-dioxane−heptane mixture are collected in Figure 2. We found that, for all samples with copolymer concentrations lower then 5 g/L, the values of OD$_{320}$ did not differ significantly from 0. For higher concentrations, the values of OD$_{320}$ increased, indicating the formation of micelles. The higher the concentration of micelles is and the larger they are, the more efficient is the light scattering and the higher the apparent OD$_{320}$ is. From the plots collected in Figure 2, it follows that the tendency for micellization, characterized by dOD_{320}/d*c*, is very sensitive to the composition of poly(DA−CL).

The lowest concentration of micellization was observed for the K5 sample (parameters characterizing the poly(DA−CL) samples: K1, K3, K5, K8, and K10 are given in Table 2). Poly(dodecyl acrylate) is well soluble in the 1,4-dioxane:heptane mixture. Poly(CL) with molecular weights up to ca. 1500 is also soluble in this solvent, however, further increasing the molecular weight results in decreasing the solubility of poly(CL). Thus, the observed concentrations of micellization increased in the order K5 < K3 < K1, as expected. The reversal of the order for copolymers K8 and K10, with poly(CL) grafts over 5000, is probably due to the fact that the poly(CL) chains with lengths over the certain critical one collapse and, in copolymers, become embedded in the poly(dodecyl acrylate) fragments of their own macromolecules. This is typical, for example, for solutions of many proteins in the water-based media when the hydrophobic portions of proteins are hidden inside the hydrophilic envelopes, strongly reducing the tendency of protein macromolecules for aggregation.

Poly(L,L-lactide) Microspheres. Diameters and Diameter Distributions of the Poly(L,L-lactide) Microspheres. Poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone)s with various compositions (K1, K3, K5, K8, and K10 samples) were used as surfactants for the syntheses of poly(L,L-lactide) microspheres. Details of the polymerization procedures, isolation, and purification of microspheres were described in our earlier paper on the polymerization of D,L-lactide.[12] Here, we recall them only briefly. Solutions of initiator (tin(II) 2-ethylhexanoate) and of the surface active agent were prepared in ampules equipped with Teflon stopcocks by using the vacuum line technique. The monomer was introduced into the reactor connected to the source of dry argon. Then, the solution of the surface agent was added. After thermostating the monomer solution at 95 °C, the solution with initiator was added. The initial concentrations of monomer, initiator, and surface-active agent were equal to 2.77×10^{-1} mol/L, 4.9×10^{-3} mol/L, and 1.6 g/L, respectively. Polymerizations were carried out with stirring (60 rev/min) for 2 h. Thereafter, the mixtures were rapidly cooled to ca. 50 °C by addition of cold heptane. Crystals of unreacted monomer were removed by fractional sedimentation and washing the product with fresh portions of heptane.

The SEM micrographs of the microspheres, obtained using surface active agents with various $\bar{M}_n$'s of poly(CL) grafts and various values of $\overline{NG}$ per one macromolecule of surfactant, are given in Figures 3−7. The yields of the microspheres (after purification), number-average particle diameters ($\bar{D}_n$), and diameter polydispersity indexes ($\bar{D}_v/\bar{D}_n$, where $\bar{D}_v$ denotes the volume-average diameter) are collected in Table 3. Figures 3−7 and the data in Table 3 indicate that the diameters and diameter distributions strongly depend on the nature of the surface-active agent. The most uniform microspheres (with the lowest value of the diameter polydispersity index $\bar{D}_v/\bar{D}_n = 1.08$) were obtained for the K5 sample of poly(DA−CL). In the case of syntheses carried out in the presence of K1 and K3 surfactant, a significant part of the polymer precipitated in the form of coagulum.

In all syntheses, the yields of poly(L,L-lactide) were lower than 50%. Polymerization of lactides is an equilibrium process. According to Duda and Penczek,[26] for the polymerization of (D,L-lactide) carried out in 1,4-dioxane at 95 °C, the equilibrium monomer concentration is equal to 7.7×10^{-2} mol/L. Thus, at these conditions, for the initial monomer concentration equal to 2.77×10^{-1} mol/L (concentration of L,L-lactide in the syntheses described in this paper), the maximal yield of poly(D,L-lactide) could reach 72%. At the moment, we do not know to which extent the equilibrium monomer concentration in the polymerization of L,L-lactide in dispersion differs from the equilibrium concentration of D,L-lactide in solution; nevertheless, it is reasonable to expect that also in dispersion the yield of polymer will be lower than 100%.

We were also interested in the dependence of the diameters and diameter distributions of poly(L,L-lactide) microspheres synthesized with various concentrations of the surface active agent. For these studies, we selected copolymer K5, which allowed synthesis of the most uniform microspheres. A series of syntheses were carried out with constant starting monomer and initiator concentrations equal to 2.77×10^{-1} and 4.9×10^{-3}

Table 1. Molecular weights of ω-hydroxy-poly(ϵ-caprolactone) and poly(ϵ-caprolactone) Methacrylate

		ω-hydroxy-poly(ϵ-caprolactone), g/mol			poly(ϵ-caprolactone) methacrylate, g/mol			
		GPC			GPC			
sample	$114[CL]_0/[I]_0$	$\bar{M}_n$	$\bar{M}_w/\bar{M}_n$	$\bar{M}_n$ NMR	$\bar{M}_n$	$\bar{M}_w/\bar{M}_n$	$\bar{M}_n$ NMR	$\bar{M}_n$ (VPO)
CL1	930	1 240	1.12	1 060	1 340	1.10	1 700	970
CL3	2 400	3 290	1.09	2 900	3 010	1.10	3 800	3 200
CL5	5 100	3 490	1.17	4 000	3 440	1.19	4 600	4 700
CL8	8 400	6 100	1.13	6 000	5 910	1.13	9 900	5 400
CL10	11 100	8 780	1.25		7 480	1.18		9 000

Table 2. Parameters Characterizing Poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone)

sample	$\bar{M}_n$,[a] g/mol	f_{CL}	$\bar{N}\bar{G}$[b]	N[c]
K1	29 300	0.23	6.9	13.6
K3	29 800	0.20	1.9	25.6
K5	26 400	0.24	1.3	31.4
K8	32 300	0.19	1.1	96.5
K10	21 800	0.23	0.6	125

[a] Osmometrically. [b] $\bar{N}\bar{G}$ was calculated according to eq 1 and using for CL blocks $\bar{M}_n$ determined tonometrically (cf. Table 1). [c] Number of dodecyl acrylate units per one poly(ϵ-caprolactone) graft.

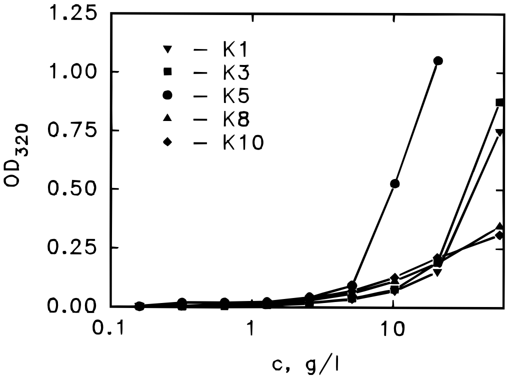


Figure 2. Dependence of the optical density at 320 nm (OD_{320}) on the concentration of poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) samples (K1, K3, K5, K8, and K10). Conditions: 1,4-dioxane:heptane (1:4 v/v) solvent, 1-cm cell.

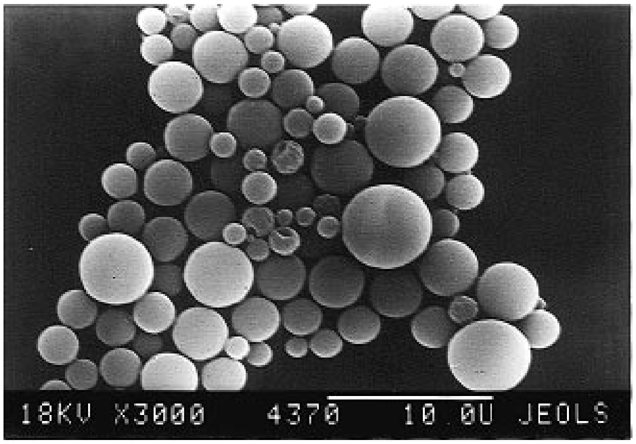


Figure 3. SEM micrograph of poly(L,L-lactide) microspheres obtained in the presence of K1 surfactant.

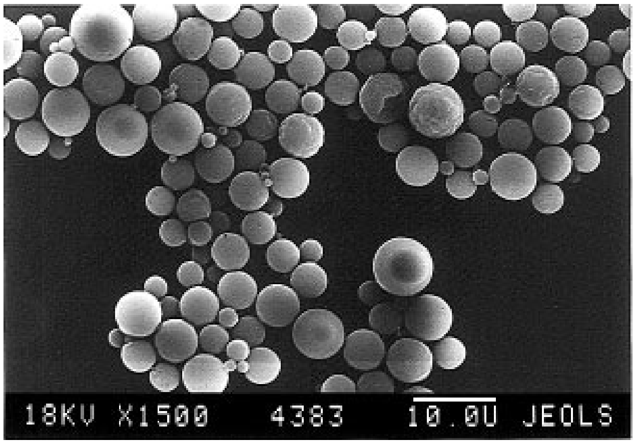


Figure 4. SEM micrograph of poly(L,L-lactide) microspheres obtained in the presence of K3 surfactant.

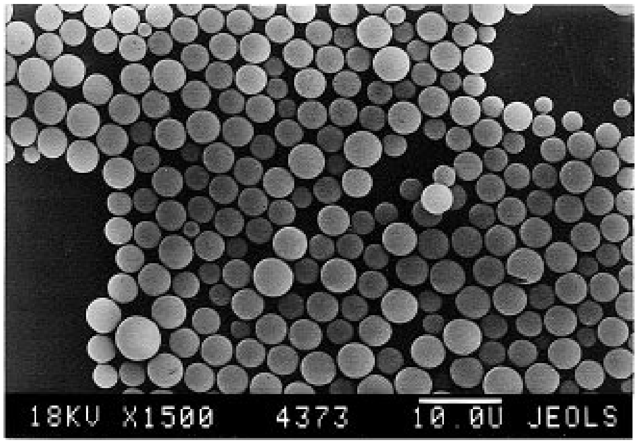


Figure 5. SEM micrograph of poly(L,L-lactide) microspheres obtained in the presence of K5 surfactant.

mol/L, respectively, and with the concentration of the surface-active agent varied from 10^{-1} to 1.6 g/L. The yields of poly(L,L-lactide) in the form of microspheres and the values of the number-average diameters ($\bar{D}_n$) and of the diameter polydispersity index ($\bar{D}_v/\bar{D}_n$) for particles obtained in these syntheses are given in Table 4. It became evident that the decreasing concentration of K5 results in a slightly increased diameter of microspheres produced in significantly lower yield. For concentrations of K5 surfactant lower than 4×10^{-1} g/L, the major part of poly(L,L-lactide) was in the form of the shapeless product. However, it is worth noticing that, for the fraction in the form of microspheres, the diameter polydispersity was low and essentially independent of the concentration of the surfactant.

Molecular Weights, Molecular Weight Distributions, and Optical Purities of Poly(L,L-lactide) in Microspheres. All polymerizations were carried out with the same initial monomer and initiator concentrations ($[\text{L,L-lactide}]_0 = 2.77 \times 10^{-1}$ mol/L, $[\text{tin(II) 2-ethylhexanoate}]_0 = 4.9 \times 10^{-3}$ mol/L), thus, we could see whether the changes of composition and concentration of the surface-active agent influence the molecular weights and molecular weight distributions of the poly(L,L-lactides) in microspheres.

From the ^{1}H NMR spectra of dissolved microspheres, we concluded (calculations were based on the signal at 1.25 ppm of the CH_2 groups of dodecyl moiety and signals at 1.58 ppm of the CH_3 groups of poly(L,L-lactide)) that the admixture of surface active agents did

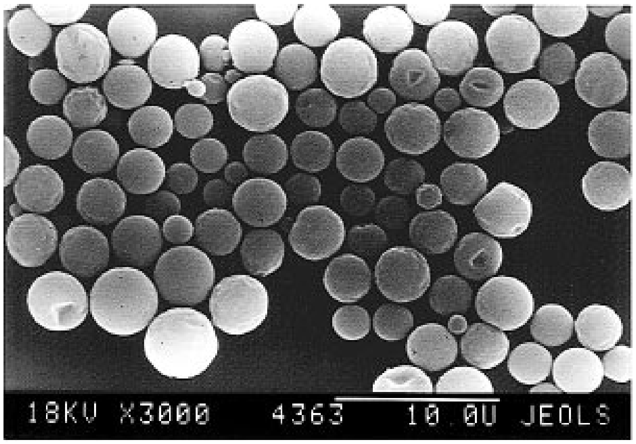


Figure 6. SEM micrograph of poly(L,L-lactide) microspheres obtained in the presence of K8 surfactant.

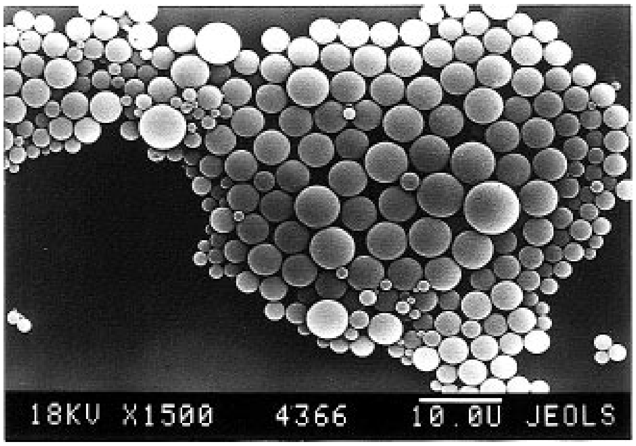


Figure 7. SEM micrograph of poly(L,L-lactide) microspheres obtained in the presence of K10 surfactant.

Table 3. Yields, Number-Average Diameters ($\bar{D}_n$), and Diameter Polydispersity Indexes ($\bar{D}_v/\bar{D}_n$) of Poly(L,L-lactide) Microspheres Obtained in the Dispersion Polymerization of L,L-Lactide with Poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) Surface-Active Agents (K1−K10)

surface-active agent	yield, %	$\bar{D}_n$, μm	$\bar{D}_v/\bar{D}_n$
K1	18.5	2.46	1.45
K3	33.0	4.07	1.23
K5	40.5	3.44	1.08
K8	50.0	2.73	1.14
K10	48.5	2.85	1.35

Table 4. Yields, Number-Average Diameters ($\bar{D}_n$), and Diameter Polydispersity Indexes ($\bar{D}_v/\bar{D}_n$) of the Poly(L,L-lactide) Microspheres Obtained in the Dispersion Polymerization of L,L-Lactide Carried Out in the Presence of Various Concentrations of Poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) Surface-Active Agents K5

[K5] g/L	yield, %	$\bar{D}_n$, μm	$\bar{D}_v/\bar{D}_n$
1.6	41	3.44	1.08
8.0×10^{-1}	45	4.63	1.07
4.0×10^{-1}	33	3.68	1.06
2.0×10^{-1}	14	4.62	1.07
1.0×10^{-1}	11	4.87	1.06

not exceed 1 wt %. Prior to any analysis, samples of microspheres were dried under vacuum (10^{-3} mmHg) for at least 48 h, and in the ^{1}H NMR spectra of dissolved microspheres, the signals which could be assigned either to 1,4-dioxane or to heptane were absent.

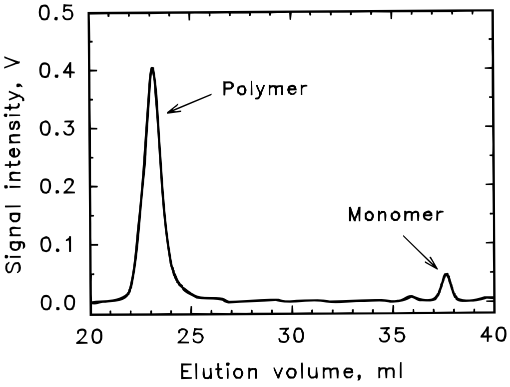


Figure 8. GPC trace of poly(L,L-lactide) from microspheres obtained in the presence of K5 surfactant ([K5] = 1.6 g/L).

Table 5. Molecular Weights ($\bar{M}_n$), Molecular Weight Polydispersities ($\bar{M}_w/\bar{M}_n$), Contents of Residual Monomer, Specific Optical Rotations, and Optical Purities of Poly(L,L-lactide) in Microspheres Obtained in the Dispersion Polymerization of L,L-Lactide Carried Out in the Presence of Various Poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) Surface-Active Agents (K1−K10)

surface-active agent	$\bar{M}_n$,[a] g/mol	$\bar{M}_w/\bar{M}_n$[a]	monomer, % wt	$[\alpha]^{25}_D$	$[\alpha]^{25}_D/\alpha(0)]^{25}_D$
K1	7 880	1.08	4.8	−143	91.7
K3	8 590	1.06	6.1	−144	92.3
K5	8 360	1.06	6.0	−142	91.0
K8	8 760	1.07	1.5	−148	94.9
K10	8 520	1.06	6.6	−145	92.9

[a] $\bar{M}_n$ and $\bar{M}_w/\bar{M}_n$ determined by GPC; calibration on poly(ϵ-caprolactones) with narrow molecular weight distribution.

Figure 8 illustrates the typical GPC trace of microspheres dissolved in THF. There are two peaks in this chromatogram: one at 23.1-mL elution volume corresponds to poly(L,L-lactide); the second at 37.6 mL is due to the remaining monomer. In independent measurements, we determined the refractive index increment (dn/dc) for L,L-lactide and poly(L,L-lactide) in THF. For L,L-lactide, $dn/dc = 0.0625$ mL/g; for poly(L,L-lactide), $dn/dc = 0.0558$ mL/g. Thus, for the quantitative determination of the residual monomer in microspheres, it is necessary to multiply the monomer signal by the correction factor $f = 0.0558/0.0625 = 0.89$. The molecular weight ($\bar{M}_n$), polydispersity parameter ($\bar{M}_w/\bar{M}_n$), and percentage of residual monomer are given in Table 5 and Table 6. From these data, it follows that the fraction of residual monomer and $\bar{M}_w/\bar{M}_n$ do not depend on the composition and/or concentration of poly(DA−CL). The fraction of residual monomer equals 5% ± 2%; the polydispersity of poly(L,L-lactide) $\bar{M}_w/\bar{M}_n \leq 1.08$.

We measured the specific optical rotation ($[\alpha]^{25}_D$) of several samples of poly(L,L-lactide) from microspheres. The results were corrected for optical rotation due to the presence of the residual monomer. According to Chabot et al.,[27] the specific optical rotation of 100% optically pure poly(L,L-lactide) is equal to $[\alpha]^{25}_D = -156$. Thus, we could evaluate the optical purity of poly(L,L-lactide) in synthesized microspheres. The data are collected in Table 6. The optical purity of poly(L,L-lactide), equal to 93% ± 1%, was very close to the optical purity of the monomer used for the synthesis (95.4%). This observation indicates that, during dispersion polymerization of L,L-lactide initiated with tin(II) 2-ethylhexanoate, like in the solution polymerizations initiated with tributyltin methoxide and tributyltin butoxide,[28] powdered Zn,[27] and cationic initiators[29] (polymer-

Table 6. Molecular Weights ($\bar{M}_n$), Molecular Weight Polydispersities ($\bar{M}_w/\bar{M}_n$), DSC Characteristics, and Contents of Residual Monomer in Microspheres Obtained in the Dispersion Polymerization of L,L-Lactide Carried Out in the Presence of Various Concentrations of Poly(dodecyl acrylate)-*g*-poly(ϵ-caprolactone) Surface-Active Agents K5

				T_g, °C					
[K5], g/L	$\bar{M}_n{}^a$ mol/g	$\bar{M}_w/\bar{M}_n{}^a$	monomer, % wt	first run	second run	ΔH_c, J/g first run	ΔH_m, J/g first run	ΔH_c, J/g second run	ΔH_m, J/g second run
1.6	8 340	1.06	6.0	42.4		−10.5	40.8	−8.0	33.9
8.0×10^{-1}	9 970	1.06	4.2	41.1	50.4	−30.4	28.5	−4.8	5.0
4.0×10^{-1}	10 870	1.06	2.4	45.4	53.8	−10.7	16.7	−4.4	3.1
2.0×10^{-1}	9 100	1.08	7.6	41.2	47.7	−26.2	27.5	−4.6	6.9
1.0×10^{-1}	10 690	1.07	7.6	40.8	45.4	−14.8	17.9	−0.9	1.9

[a] Determined by GPC with calibration based poly(CL) samples with narrow molecular weight distribution.

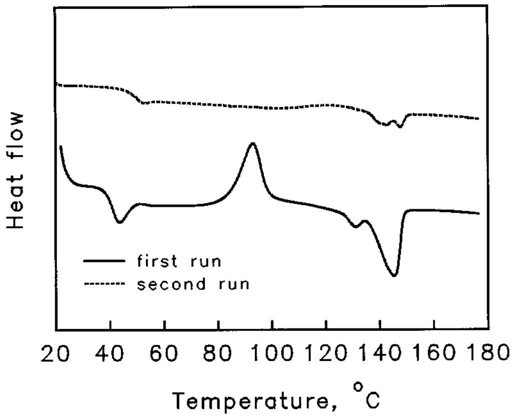


Figure 9. DSC traces of poly(L,L-lactide) microspheres obtained in the presence of K5 surfactant, [K5] = 8.0×10^{-1} g/L.

izations below 100 °C), propagation proceeds without significant racemization.

Thermal Characteristics of Poly(L,L-lactide) Microspheres. Poly(L,L-lactide) microspheres synthesized in the presence of various concentrations of K5 surfactant were analyzed by differential scanning calorimetry. Microspheres were produced in polymerizations carried out at 95 °C.[12] After polymerization, the suspension of microspheres was rapidly cooled to 55 °C, by addition of cold heptane. Microspheres were stored in heptane at room temperature. Before the DSC measurements, each sample was washed several times with heptane and then dried at room temperature under vacuum (at 10^{-3} mmHg) for 48 h. The typical DSC trace, registered for the poly(L,L-lactide) microspheres, is shown in Figure 9. The inflection point at 41 °C (T_g) corresponds to the glass transition of poly(L,L-lactide). Close to T_g could be observed an endothermic peak. This peak was attributed to the enthalpy relaxation effects reflecting the thermal history of the sample.[30] At 93.0 °C, there is a maximum of the exothermic peak corresponding to the "cold" crystallization (below the melting temperature) of amorphous poly(L,L-lactide). Finally, the complex endotherm with maxima at 131.8 and 145.3 °C corresponds to melting of the crystalline poly(L,L-lactide). The absolute value of the enthalpy of crystallization ($\Delta H_c = -30.4$ J/g)) is close to the enthalpy of melting ($\Delta H_m = 28.5$ J/g), indicating that, before the DSC run, essentially the whole polymer was amorphous. After the first DSC scan, the sample was cooled during 2 h to 40 °C and subsequently quenched rapidly in liquid nitrogen, and then the second scan was registered. In this scan, also shown in Figure 9, the inflection point corresponding to T_g is present at 50.4 °C, i.e., at a significantly higher temperature than during the first run. Absolute values of the enthalpies of crystallization and melting are again close to each other, $\Delta H_c = -4.8$ J/g and $\Delta H_m = 5$ J/g; however, each is much smaller than during the first run. Moreover, the maximum of the exothermic crystallization peak is at the higher temperature (at 121.6 °C). Apparently, before the second DSC run, the sample was in the amorphous state, like before the first one, however, some changes in its morphology made the cold crystallization more difficult. During polymerization, monomer diffuses into the growing particles swollen with 1,4-dioxane. After polymerization, the extensive washing of microspheres with heptane, followed by drying under high vacuum, yielded particles which according to the GPC and ^{1}H NMR analyses were free from the residual solvents and contained less than 1% surface-active agents. However, the drying under vacuum could lead to many internal defects (pores on the nanometer scale) in microspheres. During heating, in the course of the DSC analysis, the presence of such defects could facilitate cold crystallization. Melting should remove the mentioned defects, making cold crystallization more difficult. Similar DSC measurements were performed for microspheres synthesized in the presence of various concentrations of K5 surface-active agent. The values of T_g, the enthalpy of crystallization, and the enthalpy of melting in the first run and in the second run are collected in Table 6. From these data, it follows that the enthalpy of melting depends on the concentration of K5, surfactant used in the synthesis of microspheres. For lower concentrations of K5, the values of ΔH_m are lower. Apparently, the surface-active agent acts as a plasticizer.

Discussion

The diameters and diameter polydispersities of the poly(L,L-lactide) microspheres, obtained directly in the dispersion polymerization of L,L-lactide carried out in the presence of poly(DA−CL), strongly depend on the number and molecular weights of the poly(CL) grafts in these surface-active agents. The most uniform microspheres, with respect to their diameter, could be obtained in the systems with fast particle nucleation in the initial period of the polymerization, followed with a continuous size increase of growing particles, without particle coagulation.[31] Any system with nucleation extended for a significant fraction of time required for polymerization and/or with coagulation of primary particles formed during the initial period of polymerization would yield microspheres with the broad diameter distribution. In the dispersion polymerization of L,L-lactide, the coagulation of primary particles could be prevented by efficient adsorption of surfactant macromolecules, providing steric stabilization. The best stabilizers for the nonaqueous dispersions are considered to be the block and graft copolymers, with soluble blocks and blocks anchoring copolymer to the surface of the particles.[32] In systems without stabilizers, the stability ratio parameter (W) in Smoluchowski's equation describing the kinetics of aggregation equals 1.[33]

For concentrations of surfactants equal to or higher than the ccm's), W tends toward infinity, indicating the absence of aggregation.[32] Fitch et al. found that, for the emulsion polymerization of methyl methacrylate carried out at the conditions when the concentration of the surfactant (sodium dodecyl sulfate) was lower than 10% of ccm, the changes of the stability ratio parameter were proportional to the changes of the concentration of sodium dodecyl sulfate.[34,35]

These general rules also apply to the precipitation polymerization of L,L-lactide. In the case of graft copolymers K1, K3, K8, and K10, which even at concentrations up to 10 g/L in the 1,4-dioxane:heptane (1:4) mixture did not show significant tendency for micellization, the values of the $\bar{D}_v/\bar{D}_n$ polydispersity parameter are large (from 1.14 to 1.45), apparently due to the aggregation of primary particles. In the case of the polymerization carried out in the presence of copolymer K5, for which the micellization was clearly manifested with ccm = 5.1 g/L, the diameter distribution was narrow with $\bar{D}_v/\bar{D}_n = 1.08$.

The critical concentration of micellization of copolymer K5 is rather high, only 8-fold lower than the monomer concentration used in the synthesis (due to the limited solubility of L,L-lactide in the dioxane−heptane mixture, even at 95 °C, we could not use higher monomer concentrations). Thus, for practical reasons, we were interested in establishing how much it is possible to decrease the concentration of K5 surfactant without a significant reduction of the yield of microspheres. It is important to note that whereas the overall yield of poly(L,L-lactide) was 50%, the yield of microspheres (with respect to the initial monomer) was above 40% even for concentrations of K5 as low as 8×10^{-1} g/L. A further decrease of the concentration of K5 resulted in substantially decreasing the yield of microspheres, down to 11% for $[K5] = 1.0 \times 10^{-1}$ g/L. For monodisperse particles (the polydispersity of microspheres obtained in the presence of K5 surfactant is very low, cf. Table 4), one could write a simple relation between the total surface of particles present in 1 mL of the suspension of microspheres produced during polymerization ([S]), the density of poly(L,L-lactide) in the microspheres (d), the diameter of the microspheres (D), and the concentration of the microspheres in suspension after polymerization ([M]):

$$[S]d = 6[M]/D \qquad (2)$$

By remembering that the concentration of microspheres is equal to the initial monomer concentration $[M']_0$ (in g/mL) multiplied by the yield of microspheres (Y), one could replace eq 2 with the following expression:

$$[S]d = 6[M']_0Y/D \qquad (3)$$

In all experiments carried out with various concentrations of K5, the initial monomer concentration $[M']_0$ was equal to 4×10^{-2} g/mL. For these experiments, we calculated the values of $[S]d$ from eq 3 and plotted them as a function of the concentration of K5 in the polymerizing mixture (cf. Figure 10). Assuming that the density of poly(L,L-lactide) microspheres obtained in all syntheses was the same, the plot in Figure 10 represents the changes in [S] of the suspension of microspheres resulting from the changes of [K5]. The dependence of $[S]d$ on [K5] could be approximated with two straight lines. The initial steep line in Figure 10 was attributed mainly to the increasing yield of poly(L,L-lactide) in the form of microspheres (Y). Apparently, for $[K5] < 4 \times 10^{-1}$ g/L, the concentration of surfactant was insufficient for the stabilization of all primary particles, and some of them aggregated and precipitate in the form of coagulum. For higher concentrations of K5, the higher number of particles was stabilized. When the concentration of K5 was higher than 4×10^{-1} g/L, presumably all poly(L,L-lactide) was used up for the formation of microspheres. Further increasing [K5] resulted in smaller changes of [S], due to the decreasing diameter (D) of produced microspheres.

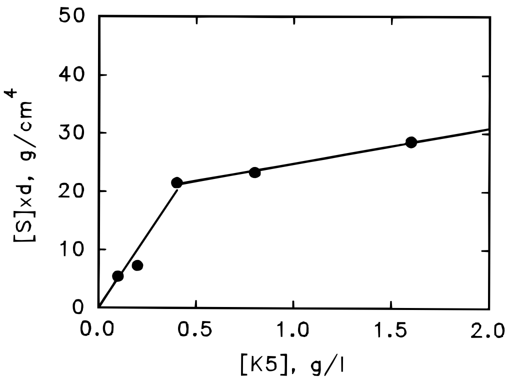


Figure 10. Dependence of $[S]d$ on [K5] ([S] denotes the surface of the poly(L,L-lactide) microspheres produced in 1 mL of reaction mixture; d denotes the density of the microspheres).

It is important to understand why, particularly, copolymer K5 gave solutions with the best manifested micellization (cf. Figure 2) and, when added to the dispersion, polymerization of L,L-lactide allowed us to obtain the most uniform microspheres. The fraction of poly(CL) in all copolymers was almost the same (cf. Table 2). The difference was in the molecular weight of the poly(CL) grafts, the molecular weight of poly(dodecyl acrylate) segments, and the average number of grafts per copolymer macromolecule. Apparently, many poly(CL) grafts in K1 and K3 copolymers were too short, and macromolecules with these grafts and poly(dodecyl acrylate) main chain were soluble in mixed solvent rich in hydrocarbon (1,4-dioxane:heptane mixture, 1:4 v/v). Anchoring of the macromolecules of these copolymers onto the surface of the microspheres was inefficient. In effect, polymerizations carried out in the presence of these compounds yield, in addition to microspheres, some coagulum. In the case of copolymer K5, with the average number of poly(CL) grafts per one copolymer macromolecule equal to 1.3, there was apparently the proper balance between the poly(dodecyl acrylate) segments soluble in the reaction medium and the insoluble poly(CL) grafts. In polymers K8 and K10, with $\overline{NG}$ equal to 1.1 and 0.6, respectively, only a fraction of macromolecules is equipped with poly(CL) grafts needed for anchoring them at the solvent−microsphere interface. Therefore, at any concentration of K8 and K10, the effective concentration of macromolecules suitable to form micelles in the 1,4-dioxane:heptane (1:4 v/v) mixed solvent was significantly lower. Moreover, because all copolymers have similar molecular weights, the longer the poly(CL) chains are, the shorter the poly(dodecyl acrylate) segments are. Copolymers with shorter poly(dodecyl acrylate) segments are poorer stabilizers. The inefficient stabilization could lead to fusion of growing microspheres and, in effect, to the broad polydispersities of their diameters.

The ^{1}H spectra of dissolved microspheres indicated that the weight fraction of poly(DA−CL) in these particles was lower than 1% and that microspheres are free from residual 1,4-dioxane and heptane. In spite of the eventual low content of poly(DA−CL) in the microspheres, we observed the dependence of thermal properties of these particles on the concentration of K5 surfactant during polymerization. A detailed quantitative analysis of the DSC traces of poly(L,L-lactide) microspheres is difficult because surfactants are heterogeneous and polymeric particles also contain some amounts of monomer, with the melting temperature (T_m = 93 °C) being in the region in which the effects of cold crystallization of polymer are observed. However, it is clear that the poly(L,L-lactide) microspheres obtained in the presence of various concentrations of copolymer K5, with exception of particles synthesized with the highest concentration of K5 ([K5] = 1.6 g/L), were in the amorphous state ($|\Delta H_c| \approx \Delta H_m|$). For microspheres produced with [K5] = 1.6 g/L, the value of the enthalpy of melting was significantly higher than the absolute value of the enthalpy of cold crystallization and indicated that, before the DSC run, these particles were, at least partially, crystalline. Apparently, in microspheres produced with the highest concentrations of K5 surfactant, the internal structure was loose enough to allow for easy crystallization below T_m. This is evident also from a comparison of the second DSC runs, when all samples had exactly the same thermal history. Again, for microspheres synthesized with [K5] = 1.6 g/L, the cold crystallization was relatively easy and $|\Delta H_m| > \Delta H_c|$. However, poly(L,L-lactide) in microspheres obtained with lower concentrations of K5 was apparently internally more rigid, less prone to crystallization during cooling between runs and during the second DSC run, and characterized with ΔH_m lower for lower concentrations of K5.

Our studies indicate that the selection of poly(DA−CL) with proper composition (K5 sample) allows us to synthesize directly the poly(L,L-lactide) microspheres with low diameter polydispersity and with low molecular polydispersity of constituting polymer. There is a narrow concentration region of K5 surfactant (from 4 × 10^{-1} to 8 × 10^{-1} g/L) allowing us to obtain essentially all poly(L,L-lactide) in the form of amorphous microspheres with low tendency for cold crystallization.

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