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Tailored Synthesis of Polyesters by Dispersion Ring-Opening Polymerization of ε-Caprolactone and Lactides

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SUMMARY: Polyester microspheres were synthesized by anionic and/or pseudoanionic ring-opening polymerizations of lactides and ε-caprolactone, yielding particles with number average diameters up to 6.5 μm and with a narrow diameter polidispersity ($\overline{D}_w / \overline{D}_n$), which for the properly determined polymerization conditions did not exceed 1.2. Depending on the polymerization conditions (nature of initiator, initial monomer and initiator concentrations) it was possible to obtain polylactides with $\overline{M}_n$ in the region from 8 000 to 270 000 and poly(ε-caprolactone) with $\overline{M}_n$ from 3 000 to 106 000. Molecular weight polydispersities of high molecular weight polyesters were narrow ($1.05 \leq \overline{M}_w / \overline{M}_n \leq 1.3$). It was found that in investigated polymerizations the microspheres are formed at the early monomer conversion and the main part of propagation proceeds in the monomer swollen particles, in which all growing macromolecules are located. Partial degradation of polyesters in microspheres, treated with KOH in ethanol in presence of surfactants, yielded particles with diameters close to those of the parent ones. Surface layers of these microspheres were rich in carboxylic groups suitable for covalent immobilization of compounds with primary amino groups. Partially hydrolyzed microspheres were used for preparation of suspensions of nonaggregated particles in the water-based media. Poly(ε-caprolactone) microspheres suspended in water were loaded with a drug, ethul salicylate, yielding particles with content of the bioactive compound up to 34 wt%.

Introduction

Mechanisms of ionic and pseudoionic polymerizations in solution and in bulk are known quite well and recently these processes have been comprehensively reviewed in several monographs[1-3)]. Thus, before beginning studies of other types of ionic and pseudoionic polymerization, one has to ask himself, whether there is any justification for such research. Answer results from following facts. Ionic and pseudoionic polymerizations, in solution and

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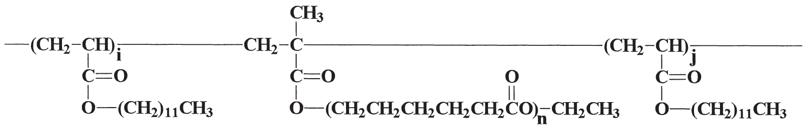
in bulk, have some disadvantages. Viscosity of polymerizing mixtures is often very high what leads to difficulties in control of mass and heat transfer and eventually, to problems due to possible local overheating of the polymerization mixture and to other related effects. After polymerizations in solution polymers have to be isolated, usually by precipitation, and the resulting mixed organic waste has to be processed (e.g. by purification or incineration). These disadvantages are strongly reduced in the case of polymerizations carried out in dispersed media. Viscosities of polymeric latexes, even with high load of solids, are relatively low[4)]. Polymers can be isolated by centrifugation or, in the case of organic media with density much lower than density of microspheres, by simple sedimentation under gravitational forces. Moreover, suspensions of polymeric particles or isolated polymer powders can be considered often as final products used for painting and for other processes of surface modification.

Recently, anionic dispersion polymerization was extensively studies by El-Aasser et al.[5-7)]. We were interested in pseudoanionic and anionic dispersion polymerizations of lactides and ε-caprolactone. In this chapter results of our studies on syntheses, modification, characterization, and potential application are summarized.

Requirements for ionic and pseudoionic polymerizations leading to microspheres

Ionic and pseudoionic polymerizations are carried out in organic media with dielectric constants much lower than dielectric constant of water. In these media ionic stabilization is ineffective and thus, microspheres have to be stabilized solely by steric interactions. Block and/or graft copolymers (or oligomers), used as steric stabilizers, usually have the following structure. One block is made of polymer segments soluble in a reaction medium whereas the second one assures the efficient and strong adsorption of copolymer molecules onto the surface of microspheres. Microspheres produced in the presence of these surfactants have hairy surfaces. During collision of such particles the soluble segments of stabilizers overlap and the increasing local concentration of stabilizing segments leads to the increasing osmotic pressure, creating the repulsive force.

Poly(ε-caprolactone) and polylactide microspheres were synthesized in a mixture of 1,4-dioxane:heptane (1:4 v/v for lactides and 1:9 for ε-caprolactone), a solvent for monomers and initiators but nonsolvent for polymers. Graft copolymer with poly(docecyl acrylate) main chain and with poly(ε-caprolactone) grafts (poly(DA-CL)), shown in Scheme 1, was used as surfactant. Poly(DA-CL) was obtained in a three-step process comprising the pseudoanionic polymerization of ε-caprolactone yielding poly(ε-caprolactone) macromolecules terminated with -OH groups, the conversion of poly(ε-caprolactone) into macromonomer in reaction with methacryloyl chloride, and eventually, the radical copolymerization of synthesized macromonomer with dodecyl acrylate. Detailed description of synthetic procedures is given in our earlier papers$^{8-12)}$. Molecular weight of poly(DA-CL) surface active agents used for syntheses of poly(ε-caprolactone) and polylactide microspheres was varied from 21 000 to 60 000. Molecular weight of poly(ε-caprolactone) grafts in these copolymers was in the region from 1 000 to 9 000.



$$-(CH_2-\underset{\underset{O-(CH_2)_{11}CH_3}{|}}{\underset{C=O}{\underset{|}{CH}}})_i-CH_2-\overset{CH_3}{\overset{|}{\underset{\underset{O-(CH_2CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}O)_n-CH_2CH_3}{|}}{\underset{C=O}{\underset{|}{C}}}}}-(CH_2-\underset{\underset{O-(CH_2)_{11}CH_3}{|}}{\underset{C=O}{\underset{|}{CH}}})_j-$$

Poly(DA-CL)

Syntheses of microspheres

Poly(ε-caprolactone) and polylactide microspheres were synthesized in dry solvents and monomers purified as it was described earlier$^{8-10)}$. Monomers, solvents, surface active agent (poly(DA-CL)), and initiators (diethylaluminum ethoxide and/or sodium trimethylsilanolate in the case of ε-caprolactone and tin(II) 2-ethylhexanoate in the case of lactides) were introduced into a reactor under nitrogen. Polymerizations were carried out with stirring (magnetic stirrer, 60 rev/min) at room temperature (for ε-caprolactone) or at 95 °C (in the case of lactides). In a typical synthesis 100 ml of 1,4-dioxane:heptane mixture, 5.5 g of ε-caprolactone (or 4 g of lactide), poly(DA-CL) (4 wt% with respect to monomer), and initiator were used. Time of polymerization was varied from 45 min to 2 h depending on the concentration of initiator. After required time, the suspension of microspheres was added to heptane, particles were isolated by sedimentation under gravitational forces, and washed with heptane. In heptane microspheres were stored for several months and when necessary used for other experiments.

Diameters and diameter distributions of microspheres

Diameters of poly(ε-caprolactone) and polylactide microspheres were almost independent from concentration of surface active agent[9,11,13]. However, we found that the ratio of molecular weights of poly(ε-caprolactone) grafts and poly(docecyl acrylate) chain in poly(DA-CL) strongly affects diameter polydispersity parameter of microspheres[9,11,15]. Dependence of $\overline{D}_w / \overline{D}_n$ on $\overline{M}_n(\varepsilon - \text{caprolactone}) / \overline{M}_n(\text{dodecylacrylate})$ for polylactide (poly(L-lactide) and poly(D,L-lactide)) microspheres is shown in Figure 1. The lowest polydispersity of diameters was for values of $\overline{M}_n(\varepsilon - \text{caprolactone}) / \overline{M}_n(\text{dodecylacrylate})$ close to 0.4.

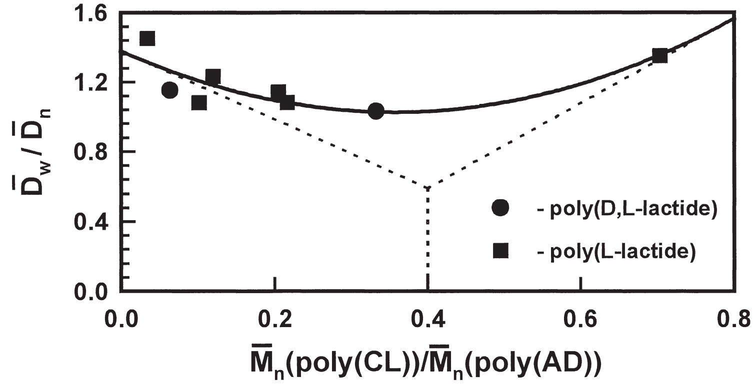


Figure 1 Dependence of $\overline{D}_w / \overline{D}_n$ on $\overline{M}_n(\varepsilon - \text{caprolactone}) / \overline{M}_n(\text{dodecylacrylate})$ for poly(D,L-lactide) and poly(L-lactide) microspheres.

Number average diameters of polylactide microspheres obtained by dispersion ring-opening polymerization initiated with tin(II) 2-ethylhexanoate were in the region from 2 μm to 3.5 μm. Variations of chemical composition and concentration of surface active agent changed the yield of microspheres but to much lesser extent their diameters. Syntheses with high initial monomer concentrations (higher than 0.45 mol/l) were not possible due to the limited monomer solubility. Thus, microspheres with larger diameters, up to 6.5 μm and with $\overline{D}_w / \overline{D}_n \leq 1.2$, were synthesized by a stepwise monomer addition. Dependence of $\overline{D}_n$ and $\overline{D}_w / \overline{D}_n$ on total concentration of introduced monomer ($[\text{L,L-Lc}]_{tot}$) is illustrated in Figure 2.

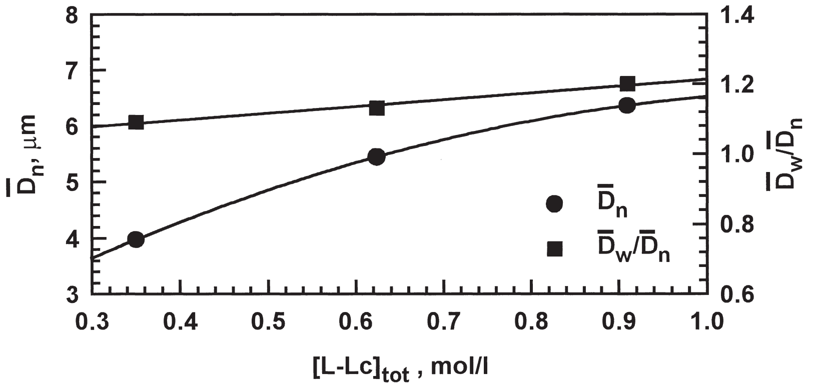


Figure 2 Dependence of $\overline{D}_n$ and $\overline{D}_n$ on $[L\text{-}Lc]_{tot}$. [Tin(II) 2-ethylhexanoate] = $5.7 \cdot 10^{-3}$ mol/l, [poly(DA-CL)] = 1.7 g/l, $\overline{D}_n$ (poly(CL)/ $\overline{M}_n$ (poly(DA-CL)) = 0.18.

Formation of microspheres

Narrow diameter distributions suggest that either all particles are nucleated at the early stage of polymerization or that each particle stops to growth after achieving a certain size. The latter seems to be less probable. However, we wanted to check in the independent experiment whether all microspheres are nucleated at the beginning of polymerization. For this purpose, a number of microspheres in a given volume of suspension was measured at various monomer conversions. Microscopic pictures of suspension samples placed in the Burkit cell were recorded by camera and analyzed using a personal computer. Dependencies of concentrations of microspheres on the normalized monomer conversion equal $([M]_0 - [M])/([M]_0 - [M]_e)$ (where $[M]$, $[M]_0$, and $[M]_e$ denote the actual, initial, and equilibrium monomer concentrations, respectively) are given in Figure 3. Plots in Figure 3 indicate that regardless whether dispersion polymerizations were initiated with the ionic ($(CH_3)_3SiONa$) or pseudoionic ($(CH_3CH_2)_2AlOCH_2CH_3$, tin(II) 2-ethylhexanoate) initiators all microspheres were nucleated at monomer conversions lower than 30 % and that at the later stages of polymerizations aggregation of microspheres was absent.

It was difficult to count microspheres at monomer conversions lower than 20%. At these stages of polymerization particles were too small for observation in the Burkit cell, under optical microscope. Thus, in an independent experiment, the partition of macromolecules with growing centers between solution and solid phase (microspheres) was performed for dispersion polymerization of ε-caprolactone initiated with $(CH_3CH_2)_2AlOCH_2CH_3$ [10]. Dependence of concentration of active species (initiator and growing centers) in solution on monomer conversion is shown in Figure 4.

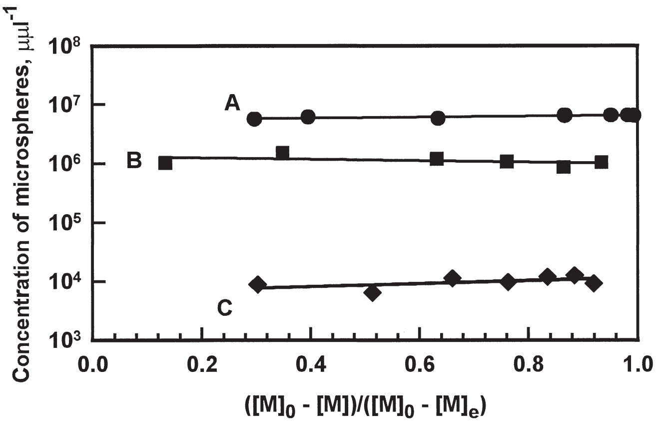


Figure 3 Dependence of concentration of microspheres on normalized monomer conversion. A - [ε-caprolactone]$_0$ = $4.3 \cdot 10^{-1}$ mol/l, $[(CH_3CH_2)_2AlOCH_2CH_3]_0$ = $5.60 \cdot 10^{-3}$ mol/l; B - [ε-caprolactone]$_0$ = $4.2 \cdot 10^{-1}$ mol/l, $[(CH_3)_3SiONa]_0$ = $1.83 \cdot 10^{-3}$ mol/l; C - [L-lactide]$_0$ = $4.4 \cdot 10^{-1}$ mol/l, [Tin(II) 2-ethylhexanoate]$_0$ = $7.16 \cdot 10^{-4}$ mol/l

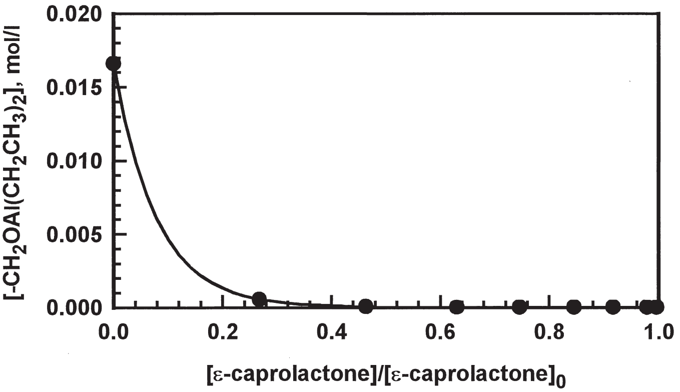


Figure 4 Dependence of solution concentration of active species on monomer conversion for polymerization of ε-caprolactone initiated with $CH_3CH_2OAl(CH_2CH_3)_2$ and carried out in 1,4-dioxane:heptane (1:9 v/v); [ε-caprolactone]$_0$ = $4.1 \cdot 10^{-1}$ mol/l, $[CH_3CH_2OAl(CH_2CH_3)_2]_0$ = $1.66 \cdot 10^{-2}$ mol/l.

Molecular Weights and Molecular Weight Distributions of Poly(CL) and Poly(Lc) Synthesized by Dispersion Ring-Opening Polymerizations

Polylactides were synthesized with tin(II) 2-ethylhexanoate used as an initiator. Polymers with $\overline{M}_n$ up to 270 000 and with a narrow molecular weight distributions ($\overline{M}_w/\overline{M}_n \leq 1.11$) were obtained. Dispersion polymerizations of ε-caprolactone are quasi-living and $\overline{M}_n$ can be predicted from ratios of the initial monomer and initiator concentrations:

$$\overline{M}_n(\text{calcd}) = [\text{CL}]_0 \text{FW(CL)}/[\text{I}]_0 \tag{1}$$

In this formula $\overline{M}_n$(calcd) denotes the calculated molecular weight of poly(CL), $[CL]_0$ and $[I]_0$ are the initial monomer and initiator concentrations, respectively, FW(CL) denotes the formula weight of ε-caprolactone (equal 114.14).

Initiation and the first propagation steps of investigated polymerization of ε-caprolactone occur in solution, before nucleation of microspheres, and the rates of propagation in solution are much lower than in particles[10)]. Thus, if monomer conversion during nucleation step is significant and macromolecules with short chains are formed, the obtained polymers have broad molecular weight distributions.

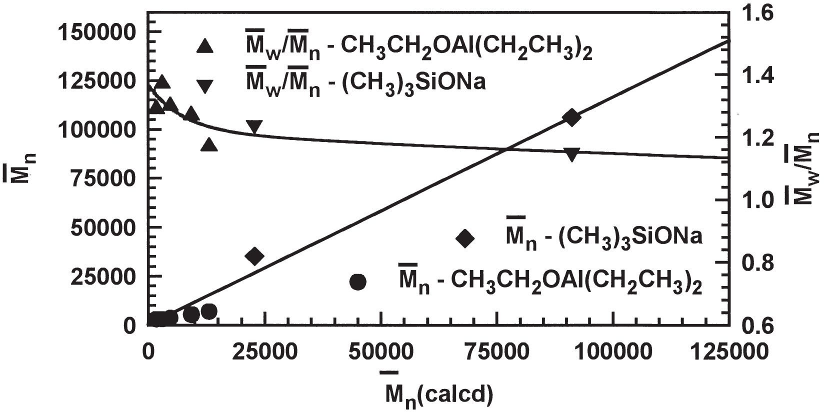


Figure 5 Dependencies of $\overline{M}_n$ and $\overline{M}_w/\overline{M}_n$ on $\overline{M}$(calcd) for polymerizations of ε-caprolactone initiated with $CH_3CH_2OAl(CH_2CH_3)_2$ and/or $(CH_3)_3SiONa$.

Poly(CL) and Poly(L-Lc) Microspheres with -COOH Groups in the Surface Layer

Biodegradable polyester microspheres with functional (e.g. carboxylate) groups in the surface layer, suitable for covalent immobilization of bioactive compounds are needed for various medical applications. Poly(CL) and poly(L-Lc) microspheres synthesized during ring-opening polymerization of cyclic esters contain macromolecules with -OH end-groups. Surface concentration of these groups is rather low.

A method, consisting on partial hydrolysis of particles transferred from heptane into ethanol containing KOH and surface active agent (Triton X-405, SDS, and/or ammonium sulfobetaine-2) was developed with purpose to convert these microspheres into particles with –COOH groups. Hydrolysis was carried out for 1 h and thereafter, microspheres were transferred into water by centrifugation and resuspension. The modified microspheres were characterized by SEM, QELS, conductometric titration, and electrophoretic mobility. Values of isoelectric point were at pH equal 2.9 and 4.4 for poly(L-Lc) and poly(CL) microspheres, respectively, i.e. in the region typical for polyelectrolytes with carboxylic groups. Diameters of microspheres were not affected significantly by the process of partial hydrolysis. In a model reaction it was found that poly(L-Lc) microspheres stabilized with SDS are suitable for covalent immobilization of 6-aminoquinoline (6AQ), a fluorescent label. A Lagmuir-type plot for this attachment (dependence of the reciprocal surface concentration of attached 6AQ ($1/\Gamma_{6AQ}$) on the reciprocal concentration of 6AQ in solution (1/[6AQ]) is shown in Figure 6. Intercept and slope in this plot are equal $1/\Gamma_{6AQ}(\max)$ and $1/(K_P\Gamma_{6AQ}(\max))$, respectively; $\Gamma_{6AQ}(\max)$ and K_P denote the maximal surface concentration of attached 6AQ and the partition equilibrium constant of 6AQ between the surface layer of microspheres and solvent, respectively. For plot in Figure 6 $\Gamma_{6AQ}(\max) = 0.451$ mg/m^2 and $K_P = 0.581$ l/g.

Microspheres with –COOH groups in the surface layer, forming stable suspensions in the water-based media, were used as matrices for loading with lipophilic drugs. For example, the slow addition of ethyl salicylate to the suspension of poly(CL) microspheres in ethanol/water mixture (7:3 v/v) yielded particles loaded up to 34 % (wt/wt) with this drug.

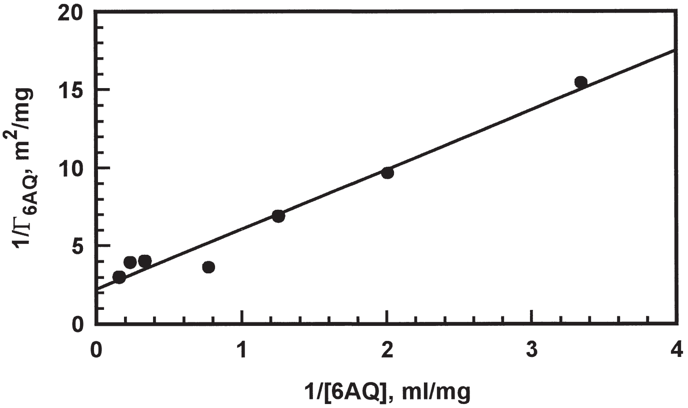


Figure 6 Langmuir plot for attachment of 6AQ to poly(L-Lc) microspheres. Concentration of microspheres 1.08 g/l.

Conclusions

Polyester microspheres with diameters up to 6.5 µm and with a narrow diameter polydispesity were obtained in the pseudoanionic and anionic ring-opening polymerizations of lactides and ε-caprolactone. In these processes poly(L-lactide) and poly(ε-caprolactone) with $\overline{M}_n$ up to 270 000 and 106 000, respectively and with the narrow molecular weight distribition were obtained. Partial hydrolysis of microspheres (without changing their diameters) yielded particles forming colloidally stable suspensions in the water-based media. These particles, with carboxylic groups in their surface layers, were suitable for covalent immobilization of compounds with primary amino groups. Poly((ε-caprolactone) microspheres were loaded with lipophilic drugs. In the case of ethyl salicylate the degree of loading reached 34 %.

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