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Dispersion polymerization of dilactide and ε-caprolactone

Summary — Ring-opening polymerization of dilactide and ε-caprolactone carried on in 1,4-dioxane — heptane mixed solvent in the presence of poly(dodecyl acrylate)-*g*-poly(ε-caprolactone) surface active agent led to formation of polyesters shaped into microspheres with diameters from 0.6 to 7.4 μm and with small diameter polydispersity factor ($\overline{D}_w/\overline{D}_n$). Studies of the mechanism of particle formation revealed that all growing chains became incorporated into microspheres at the very beginning, when monomer conversion was low (≤10%) and that the number of the initially formed microspheres did not change with time. Thus, subsequent monomer additions resulted in increasing volumes of particles without affecting their number in suspension. It has been found also that in the polymerization of dilactide the average number of propagating macromolecules per microsphere was independent from the initial initiator concentration and the increased initiator concentration resulted in increased number of particles. This observation conformed to the model illustrating formation and growth of microspheres according to which new particles are formed by collision of two polyester chains with molecular weight exceeding the critical ones and subsequently other chains are incorporated into existing particles by accretion. Thus, by selection of the required initial initiator and total monomer concentration (introduced in one or in more steps to the polymerizing mixture) it was possible tailoring of particle concentration and particle diameters.
Key words: dispersion ring-opening polymerization, dilactide, ε-caprolactone, microspheres formation, microspheres diameter, diameter polydispersity factor.

Common way leading to products made of polymers includes two stages. The first one consists on polymer synthesis and the second one on shaping the synthesized polymer (by molding, casting, spinning, *etc.*) into the desired object. However, it is worth noting that Nature usually uses another approach. In most instances in plants and in animals the synthesis of macromolecules and formation of desired elements are closely combined. For example, lipids, cellulose, lignin and starch molecules synthesized within particular cells are immediately incorporated into cell walls and membranes or into energy storing granules [1—3]. Similarly, collagen molecules are synthesized directly on site of bone, cartilage and skin formation.

In the domain of synthetic polymers the reaction-injection-molding (RIM) processes are examples of a combined synthesis and final product formation [4]. However, this method can be used for production of the relatively large objects (with linear dimensions of few millimeters or larger).

Recently, there is growing interest in synthesis and studies of properties of inorganic and organic — including polymeric — nano- and microparticles. These small and preferably uniform particles can be used as building blocks of the assemblies with interesting material properties.

Until now majority of studies were related to synthesis of nano- and microparticles that were not biodegradable. The extensively investigated processes of emulsion, miniemulsion and microemulsion polymerizations dealt with vinyl polymers, *i.e.* with polymers with exclusively carbon-carbon bonds in the main chains. Such polymers are resistant towards hydrolytic and enzymatic degradation. It is worth noting, however, that for many applications — especially in biology and

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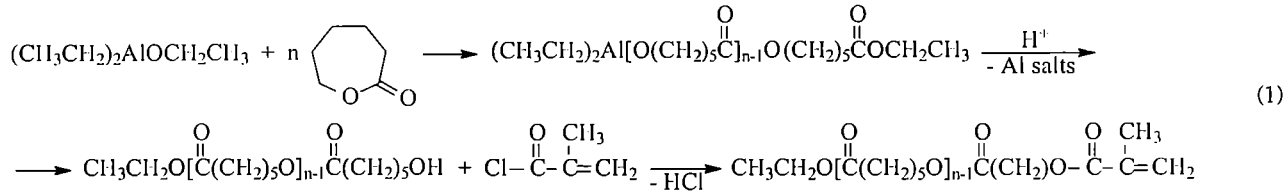
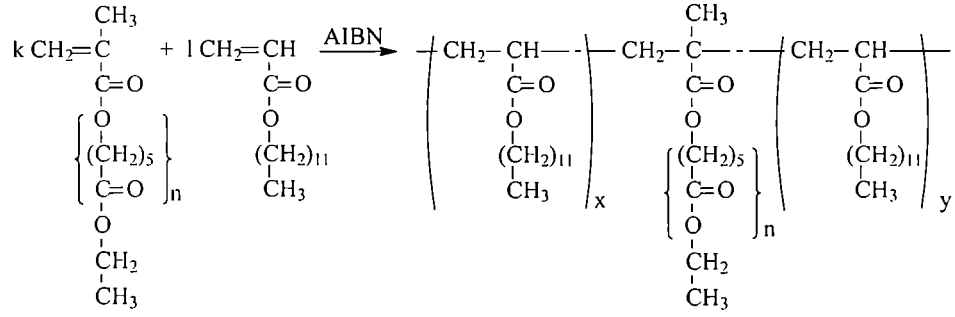
medicine — the biodegradable nano- and microspheres would be very useful.

In the last ten years we investigated pseudoanionic and anionic ring-opening polymerization of ε-caprolactone and dilactide leading to product in form of microspheres [5—14]. In this paper we would like to summarize the most important findings of our studies.



(1)



(2)

Scheme A. Synthesis of poly(dodecyl acrylate)-g-poly(ε-caprolactone) (I)

SYNTHESIS OF POLY(ε-CAPROLACTONE) AND POLYLACTIDE MICROSPHERES BY RING-OPENING POLYMERIZATION

Microspheres can be obtained directly in the heterogeneous polymerization only in presence of the appropriate surface active compounds that are added to the polymerizing mixture and/or are formed *in situ* [15]. Depending on their chemical structure, the mentioned above surface active compounds prevent aggregation and coalescence of microspheres either due to the electrostatic repulsion or to the steric hindrance occuring when two particles are brought close to each other.

Ring-opening polymerizations of dilactide and ε-caprolactone has to be carried on in the nonprotic organic media. Using of protic media either leads to termination or to an extensive chain transfer. The medium should be a solvent for initiator and monomer and nonsolvent for polymer. We found that the best properties have mixtures of heptane and 1,4-dioxane [5]. Dielectric constant of the mentioned above mixtures is much lower than dielectric constant of water. Therefore, dissociation of ions in these organic media is inefficient and surface charge at the particle-liquid interface is very low making any electrostatic stabilization ineffective. Thus, dispersion polymerization of cyclic esters leading to microspheres has to be carried on in the presence of steric stabilizers. As stabilizers we used poly(dodecyl acrylate)-*g*-poly(ε-caprolactone) copolymers [(I) in Scheme A] in which poly(ε-caprolactone) anchored stabilizer molecules to surface of particles and poly(dodecyl acrylate) segments provided stabilization in the hydrocarbone rich medium [5—8]. Detailed synthesis of the stabilizing compound has been described elsewhere [5]. Its structure is illustrated in Scheme A.

Molecular weight ($\overline{M}_n$) of poly(dodecyl acrylate)-*g*-poly(ε-caprolactone) used for stabilization of suspension of polyester microspheres was in the range from 30 000 to 40 000. Molecular weight ($\overline{M}_n$) of poly(ε-caprolactone) grafts was varied from 1 000 to 10 000.

Synthesis of polydilactide and poly(ε-caprolactone) microspheres was described in our earlier papers [5—8]. Here we give only short recipes:

Synthesis of poly(D,L-dilactide) microspheres

D,L-dilactide 4 g
Stannous octoate 0.2 g
Poly(dodecyl acrylate)-*g*-poly(ε-caprolactone) 0.16 g
1,4-Dioxane:heptane (1:4 v/v) 100 mL

Polymerization at 95°C, under argon, with stirring 60 revolutions per min carried on for 2 h. Poly(D,L-dilactide) microspheres were purified from unreacted monomer by fractionated sedimentation and washing with heptane. Particles with number average diameter $\overline{D}_n$ = 3.14 μm and diameter polydispersity factor (*DPF*), *i.e.*, $\overline{D}_w/\overline{D}_n$ = 1.05 were obtained.

Synthesis of poly(ε-caprolactone) microspheres

ε-Caprolactone 5.50 g
Diethylaluminum ethoxide 0.1 g
Poly(dodecyl acrylate)-*g*-poly(ε-caprolactone) 0.22 g
1,4-Dioxane:heptane (1:9 v/v) 100 mL

Polymerization at 25°C, under argon, with stirring 60 revolutions per min carried on for 1 h. After polymerization particles isolated by sedimentation were washed with fresh portions of heptane. Diameter and *DPF* of obtained microspheres were equal $\overline{D}_n$ = 0.63 μm and $\overline{D}_w/\overline{D}_n$ = 1.04.

DIAMETERS OF POLYDILACTIDE MICROSPHERES SYNTHESIZED BY DISPERSION RING-OPENING POLYMERIZATION AND OBTAINED BY OTHER METHODS FROM EARLIER SYNTHESIZED POLYMERS

Examples given in the previous section indicated that dispersion ring-opening polymerization of dilactide and ε-caprolactone yielded particles with a narrow diameter distribution. Thus, it was interesting to compare *DPF* values characterizing these particles with *DPF* of microspheres obtained in traditional way from the earlier synthesized polymers. The comparison was made for poly(L,L-dilactide) microspheres.

Poly(L,L-dilactide) microspheres were synthesized according to the general recipe given in the previous section. Initial L,L-dilactide and initiator (stannous octoate) concentrations were equal $3.50 \cdot 10^{-1}$ mol/L and $5.70 \cdot 10^{-3}$ mol/L, respectively. Concentration of surface active compound (I) ($\overline{M}_n$ = 62 000) was 1.67 g/L. Molecular weight of poly(ε-caprolactone) grafts in copolymer was 11 000.

Microspheres from emulsion of polymer solution by solvent evaporation method were prepared from polymer with $\overline{M}_n$ = 9 300 and $\overline{M}_n/\overline{M}_w$ = 1.06. Particles were obtained from solution of poly(L,L-dilactide) in CH_2Cl_2 (1 g of polymer in 1 mL of CH_2Cl_2) slowly added to 150 mL of water containing poly(vinyl alcohol) (1% wt/v) and emulsified by stirring at 170 rev/min. Stirring was continued for 30 min. After this time CH_2Cl_2 evaporated from the mixture. Finally, poly(L,L-dilactide) microspheres were isolated by sedimentation.

Poly(L,L-dilactide) solution in ε-caprolactone (polymer concentration 1 g/mL) was used for preparation of microspheres from emulsion of polymer solution by solvent extraction method; 10 mL of this solution was dispersed by sonication or by mixing in 40 mL of heptane containing Span 85 (3% wt/v). Then, this solution was poured into isopropanol containing polyvinylpyrrolidone (5% wt/v). ε-Caprolactone was extracted with intensive mixing from emulsion droplets into the isopropanol rich solvent. After washing with isopropanol and water, both containing polyvinylpyrrolidone (0.1% wt/v), the microspheres were isolated by centrifugation.

Values of number averaged diameters ($\overline{D}_n$) and of *DPF* for microspheres obtained using various presented above methods are collected in Table 1.

Data in Table 1 indicate that diameters of microspheres synthesized by ring-opening polymerization are much smaller than diameters of particles obtained by other methods. Much more important, however, is that

Table 1. Number averaged diameters ($\overline{D}_n$) and *DPF* values ($\overline{D}_w/\overline{D}_n$) for poly(L,L-dilactide) microspheres obtained by ring-opening polymerization or from earlier synthesized poly(L,L-dilactide) emulsion by solvent evaporation and solvent extraction methods

Method	$\overline{D}_n$, μm	*DPF* ($\overline{D}_w/\overline{D}_n$)
By ring-opening dispersion polymerization	3.6	1.07
From polymer emulsion by solvent evaporation	34.4	2.68
From polymer emulsion by solvent extraction	20.0	2.06

DPF values of microspheres synthesized by dispersion polymerization was very small too. Thus, we became interested in understanding features of the mechanism allowing formation of particles with so narrow diameter distribution.

MECHANISM OF MICROSPHERES FORMATION IN DISPERSION POLYMERIZATION OF DILACTIDE AND ε-CAPROLACTONE

We noticed that initially, during polymerizations for which the recipes were given above, the polymerizing mixture was in form of a clear solution. However, after a short period this mixture became turbid indicating formation of microspheres. The first question for which we wanted to find an answer was whether after induction period all propagating active centers were located in microspheres or whether a significant fraction of them remained in solution. Figure 1, based on our earlier studies [8], illustrates relation between changes of molecular

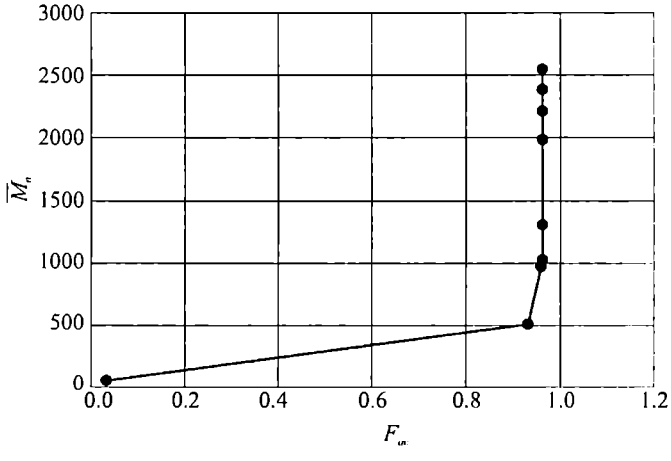


Fig. 1. Dispersion polymerization of ε-caprolactone, molecular weight of poly(ε-caprolactone) formed in microspheres ($\overline{M}_n$) as function of the fraction of active centers in microspheres (F_{ac}). Polymerization conditions: $[\varepsilon\text{-caprolactone}]_0 = 4.1 \cdot 10^{-1}$ mol/L, $[(CH_3CH_2)_2AlOCH_2CH_3]_0 = 1.66 \cdot 10^{-2}$ mol/L (based on data from [8])

weight of poly(ε-caprolactone) formed in microspheres during dispersion polymerization and fraction of active centers inside of these microspheres.

Plot in Figure 1 indicates that in dispersion polymerization of ε-caprolactone the main increase of molecular weight occurred when all active centers were inside of microspheres (propagation in dispersed phase). It has to be noted that only 150 seconds after beginning of the polymerization (the whole process was monitored for 2 700 seconds) 96% of active centers was already inside of particles.

It was important also to find out whether all microspheres formed at the beginning remained isolated or particle aggregation and coalescence occurred at later stages of the polymerization. Figure 2 illustrates relations between concentrations of microspheres (expressed as number of particles in unit volume) and monomer conversion. Plots were made for dispersion ring-opening polymerization of L,L-dilactide initiated with stannous octoate (C) and for polymerizations of ε-caprolactone initiated with anionic [$(CH_3)_3SiONa$] (B) and pseudoanionic [$(CH_3CH_2)_2AlOCH_2CH_3$] (A) initiators.

From plots in Figure 2 it follows that in all studied processes the number of microspheres formed at the early stage did not change during the later stages.

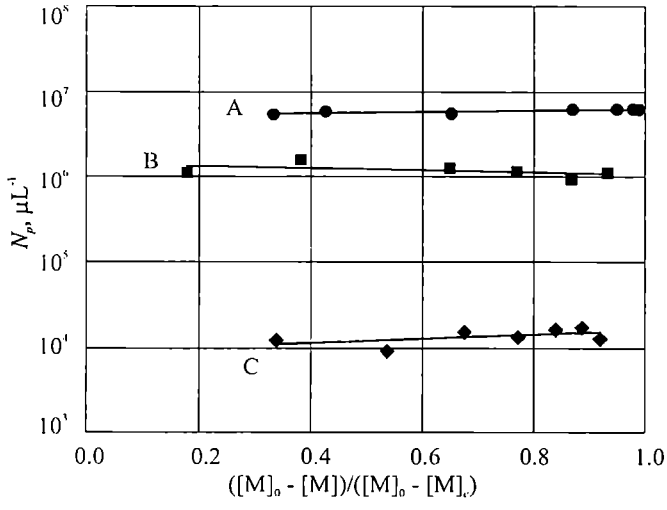
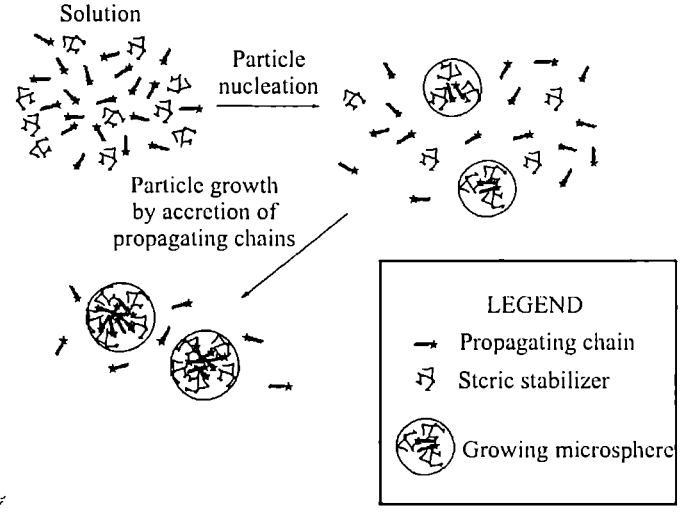


Fig. 2. Dependence of concentration of microspheres (number of particles in unit volume, $N_p \cdot \mu L^{-1}$) on normalized monomer conversion: A — [ε-caprolactone]$_0$ = $4.3 \cdot 10^{-1}$ mol/L, [$(CH_3CH_2)_2AlOCH_2CH_3$]$_0$ = $5.60 \cdot 10^{-3}$ mol/L; B — [ε-caprolactone]$_0$ = $4.2 \cdot 10^{-1}$ mol/L, [$(CH_3)_3SiONa$]$_0$ = $1.83 \cdot 10^{-3}$ mol/L; C — [L,L-dilactide]$_0$ = $2.7 \cdot 10^{-1}$ mol/L, [Tin(II) 2-ethylhexanoate]$_0$ = $7.16 \cdot 10^{-4}$ mol/L

With purpose to understand better the process of particle formation we analyzed also the relation between concentration of active centers created during initiation and number of propagating chains per microsphere. Remembering that in dispersion polymerization of cyclic esters all microspheres are formed during the initial period, when propagating chains are short (*cf.* Figure 1), it was reasonable to propose the following scheme (Scheme B) illustrating disappearance of molecular chains from solution and nucleation of microspheres (particles).



Scheme B. The mechanism of microspheres formation

According to Scheme B the rate of microsphere formation (dN/dt) should be proportional to square of propagating chain concentration (n^2).

$$\frac{dN}{dt} = \frac{1}{2} k_1 n^2 \tag{1}$$

where: *parameter k_1 denotes the rate constant of nucleation of microspheres, coefficient 1/2 indicates that aggregation of two chains nucleates one particle.*

It is important to remember also that propagating chains disappear from solution not only during nucleation of new microspheres but also by adsorption onto the already existing ones. Rate of the latter process should be proportional to the concentration of propagating chains and concentration of particles (n and N, respectively) and to the average surface of microsphere ($\overline{S}$). The average volume of microsphere ($\overline{V}$) is proportional to the ratio of the number of chains in microspheres and number of them:

$$\overline{V} = \frac{n_0 - n}{N} \tag{2}$$

where: n_0 — *initial concentration of chains, n — concentration of chains at the moment when N particles are present in the system.*

Remembering that surface of sphere is proportional to its volume in the power 2/3 we wrote the following differential equation describing changes of chains concentration in solution:

$$\frac{dn}{dt} = -k_1 n^2 - k_2\left(\frac{n_0 - n}{N}\right)^{2/3} Nn \qquad (3)$$

where: k_2 — *rate constant of microspheres growth by chain accretion.*

Solution of the set of equations (1) and (3) allowed calculation of the number of chains per microsphere. Figure 3 illustrates calculated dependence of the number of chains per microsphere on time. Values of kinetic parameters used for calculations and n_0 are given in the caption for Fig. 3. Plots in Fig. 3 revealed that number of propagating chains in the average microsphere formed according to Scheme B should be independent on the initial chain concentration.

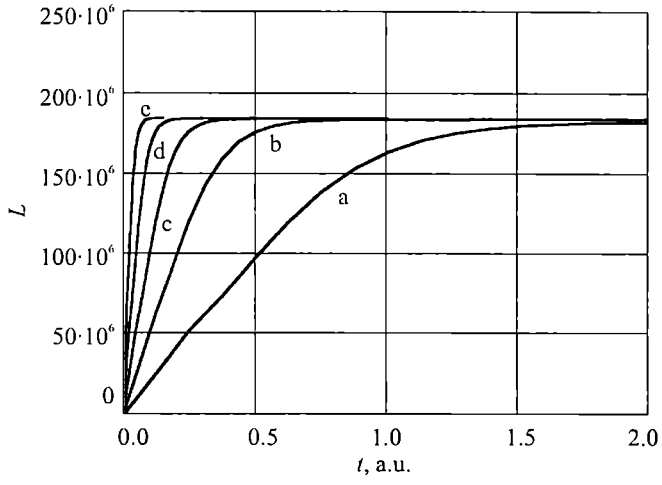


Fig. 3. Number of propagating chains per microsphere (L) as a function of time (t). Calculations based on equations (1) and (3), values of kinetic parameters: k_1 = 300 L/mol·s and $k_2/k_1 = 7.36 \cdot 10^4$. Initial concentrations of chains: a — $1.0 \cdot 10^{-3}$ mol/L, b — $2.5 \cdot 10^{-3}$ mol/L, c — $5.01 \cdot 10^{-3}$ mol/L, d — $1.0 \cdot 10^{-2}$ mol/L, e — $2.0 \cdot 10^{-2}$ mol/L

Dependence of the number of propagating chains per microsphere determined experimentally for poly(L,L-dilactide) particles obtained in dispersion polymerization initiated with 2,2-dibutyl-2-stanna-1,3-dioxepane is shown in Fig. 4.

Plot in Figure 4 reveals that, like in calculations based on Scheme B (*cf.* Fig. 3), the averaged number of propagating chains per microsphere is essentially independent on concentration of initiator.

Rapid formation of microspheres (each containing the same number of propagating chains) during the early stage of polymerization and absence of particle coagulation allowed easy control of diameters of microspheres. Remembering that each particle contains the same number of growing macromolecules, the average volume of microsphere ($\overline{V_n}$) should be proportional to the ratio of concentration of polymerized monomer

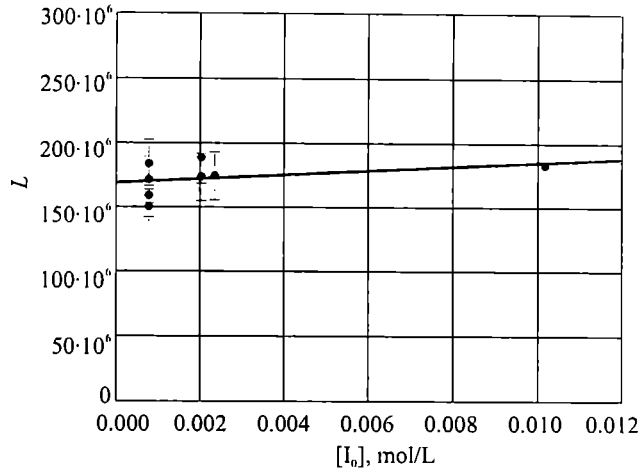


Fig. 4. Number of propagating chains per microsphere (L) as a function of initiator concentration [I_0] registered for dispersion polymerization of L,L-dilactide initiated with 2,2-dibutyl-2-stanna-1,3-dioxepane; initial monomer concentration was $3.5 \cdot 10^{-1}$ mol/L

($[M]_0 - [M]_e$) to concentration of growing chains [P^*] that were assembled into microspheres:

$$\overline{V_n} \sim \frac{[M]_0 - [M]_e}{[P^*]} \qquad (4)$$

where: $[M]_0$ *and* $[M]_e$ — *the initial and equilibrium monomer concentrations, respectively.*

Thus, radii of microspheres should depend on concentration of monomer and initiated chains according to the following formula:

$$\overline{D_n} \sim \left(\frac{[M]_0 - [M]_e}{[P^*]}\right)^{1/3} \qquad (5)$$

In dispersion polymerization of dilactide carried on with new monomer portions added after polymerizing the first ones, the value of [P^*] (concentration of growing chains that formed particles) is constant during the whole polymerization process.

We showed earlier (*cf.* Fig. 2) that in dispersion polymerization of dilactide coagulation of particles that could change number of propagating chains per microsphere was absent. Thus, in dilactide polymerization with new monomer additions after consumption of the already added ones the diameters of microspheres ($\overline{D_n}$) should be proportional only to $([M]_0 - [M]_e)^{1/3}$, where $[M]_0$ denotes the total concentration of monomer added.

An example of experimentally registered dependence of D_n on $([M]_0 - [M]_e)^{1/3}$ for dispersion polymerization of L,L-dilactide initiated with stannous octoate is shown in Fig. 5. Indeed, as it was expected the addition of required amounts of monomer allowed synthesis of microspheres with predictable diameters. The nonlinear least square method was used to find value of $[M]_e$ ensuring the best fit of experimental data:

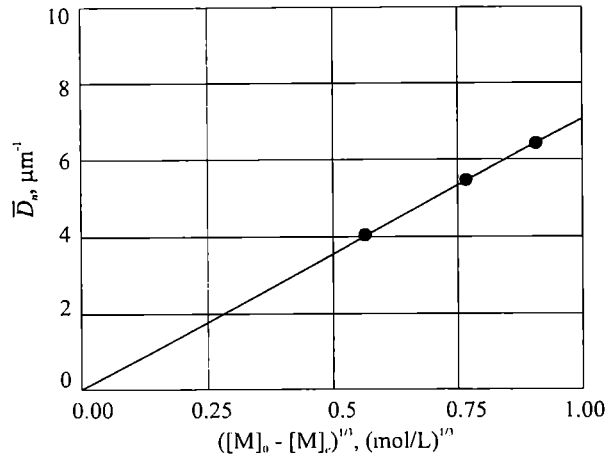


Fig. 5. Dependence of $\overline{D}_n$ on $([M]_0 - [M]_e)^{1/3}$ for dispersion polymerization of L,L-dilactide initiated with stannous octoate (initial initiator concentration $5.70 \cdot 10^{-3}$ mol/L)

$$\overline{D}_n \sim ([M]_0 - [M]_e)^{1/3} \quad (6)$$

The best fit corresponding to proportionality of $\overline{D}_n$ to $([M]_0 - [M]_e)^{1/3}$ was found for the equilibrium concentration of L,L-dilactide $[M]_e$ = 0.17 mol/L. According to Duda and Penczek [16], for the polymerization of D,L-dilactide carried out in 1,4-dioxane at 95°C the equilibrium monomer concentration equals $7.7 \cdot 10^{-2}$ mol/L. However, it is rather obvious that for polymerization in dispersed system the equilibrium monomer concentration averaged over the whole volume comprising two phases (swollen particles and liquid medium) may differ from that for the polymerization in solution; namely, for dispersion polymerization the value of $[M]_e$ is affected by local monomer equilibrium concentration within microspheres and by monomer partition between particles and medium.

CONCLUSIONS

Dispersion ring-opening polymerization of ε-caprolactone and dilactide proceeds with formation of microspheres at the early stage of monomer conversion. Experimental findings conform to assumption that initiation proceeds in solution. Then, when growing macromolecules reach the critical length they form nuclei of microspheres, later rapidly growing by accretion of propagating chains from solution. Regardless of the concentration of initiated chains each microsphere contains the same number of propagating species. Thus, during later stages of polymerization all particles grow with the same rate and their diameter distribution is narrow — much narrower than for microspheres obtained by standard methods from earlier synthesized polymers. Proper selection of the initial monomer concentration in dispersion polymerization ε-caprolactone and dilactide allows controlling of diameters of microspheres. Particles with diameters from *ca.* 0.6 to 7 μm can be easily obtained by this method.

ACKNOWLEDGMENT

This work was supported by grant of Polish Committee for Scientific Research No 3 T09A 05118.

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