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Note

Submicronparticles from biodegradable polymers

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Abstract

The objective was to prepare small particles in the nm range with poly(D,L-lactide) and poly(D,L-lactide-co-glycolide) applying the spontaneous emulsification process. Polymer parameters as well as process parameters were investigated. The results show that spontaneous emulsification is a simple method to produce small particles in the 200–1000 nm range. A major drawback is the limitation to very restricted conditions, e.g. molecular weight up to 30.000 g/mole, glycolide content in the copolymer up to 30 mole% and concentration of the polymer solution lower than or equal to 1% (w/v).

Keywords: Poly(D,L-lactide); Poly(D,L-lactide-co-glycolide); Submicronparticles

Drug loaded microcapsules from biodegradable polymers on the basis of lactic acid (polylactides and their copolymers with diglycolide) are well known. They were used therapeutically in the case of parenteral drug release systems to control the active agent delivery. Microparticles can be administered intramuscularly or subcutaneously. Medicinal therapies often require intravenous drug application and transport via blood circulation demanding particles in the nm range. Microparticles are not suitable in this case because of their size in the μm-range. Therefore intravenous administration is an application field for submicron- and nanoparticles (1–1000 nm). Microencapsulation methods usually applied (coacervation, spraying and solvent evaporation processes) allow the production of particles up to 1 μm. That's why a nanoprecipitation process ('spontaneous emulsification') (Fessi et al., 1989; Bodmeier et al., 1991; Fessi et al., 1992) was chosen to generate particles smaller than 1 μm. Possibilities and limitations of this process concerning applying a broad range of polylactide and their copolymers with diglycolide were investigated.

Poly(D,L-lactide) (PDLLA) was synthesized by ring-opening polymerization of D,L-dilactide in a horizontal kneading reactor with discharge screw at 175 °C in the presence of tin octonoate as initiator (Fig. 1) (Rafler and Dahlmann, 1990, 1992). The copolyesters of lactic and glycolic acid (PGDLLA), containing up to 50 mole% glycolic acid units, were prepared applying similar reaction conditions (Fig. 2). The polymers were extracted with methanol to separate unreacted monomers and dried in vacuum, subsequently.

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D,L-dilactide and glycolide were purchased from Boehringer (Ingelheim, Germany). The molecular weights of the polymers were estimated by viscosimetry using the corresponding Kuhn-Mark-Houwink equation and gel permeation chromatography (Dahlmann et al., 1990).

Scheme 1 presents the nanoprecipitation process. The polymeric wall material is dissolved in a semipolar water-miscible organic solvent (e.g. acetone or mixtures of acetone and ethanol). The process is limited to water-miscible solvents because of the demanded high diffusion rate to initiate spontaneous emulsification (Quintanar-Guerrero et al., 1998). Optionally an active agent is dispersed in the polymer solution (high speed stirring) or dissolved in the polymer solvent. Various amounts of the resulting solution/dispersion (15–50 ml) are poured into 50 ml of the continuous aqueous phase (distilled water with or without surfactant). Mixing was carried out applying different conditions (magnetic stirrer, electric stirrer, static mixer as well as without mixing). Small particles are formed instantaneously because of

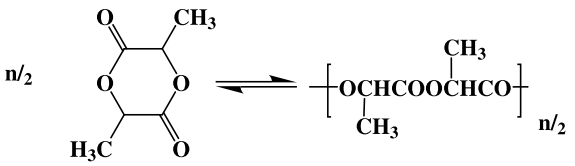


Fig. 1. Ring-opening polymerization of PDLLA.

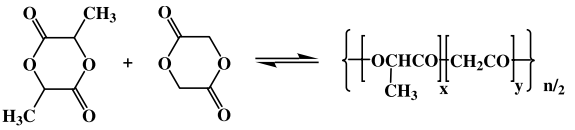
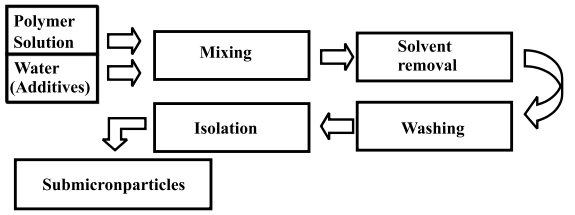


Fig. 2. Ring-opening polymerization of PGDLLA.



Scheme 1. Nanoprecipitation to produce small particles.

rapid solvent diffusion. The mechanism has been explained by interfacial turbulences generated during the solvent displacement (Fessi et al., 1989; Quintanar-Guerrero et al., 1998). The solvents were removed subsequently by evaporation (raising temperature, vacuum) or cross-flow-filtration. Particles were washed two times with water and isolated applying centrifugation, membrane filtration as well as freeze drying processes. Solvents and other chemicals are supplied by different german companies, e.g. Carl Roth (Karlsruhe) and Merck (Darmstadt). They were used as received (p.a. grade).

The particles were characterized by laser diffraction with a particle size analyser (5-Helos, Sympatec GmbH, Clausthal-Zellerfeld, Germany) and by scanning electron microscopy (Joel-JSM 6330 F (Kontron, München, Germany)).

A broad range of polylactides (based on L- as well as D,L-lactic acid, respectively) and their copolymers with diglycolide were investigated to produce small particles applying the nanoprecipitation process. Only PDLLA and copolymers of D,L-lactic acid with diglycolide could be used because of the limited solubility of those polymers in suitable, water-miscible solvents. Copolymers with glycolide can contain up to 30 mole% diglycolide for the same (solubility) reasons. Suitable polymer solvents are especially acetone or mixtures of acetone with ethanol.

Homopolymers and copolymers with different molecular weights were used (Table 1). The concentration as well as the volume of the added polymer solution were varied. There are limitations concerning the molecular weight of the suitable polymers. Polymers with molecular weights M_n up to 30.000 g/mole can be applied. Polymers like that allow to produce particles in the submicron range with the nanoprecipitation process (Figs. 3–6). Figs. 3 and 4 present the volume particle size distribution of the resulting particles. The particle size ranges between 200 and 1000 nm. So the resulting particles are rather submicronparticles than true nanoparticles (< 100 nm). There are no differences concerning particle size and distribution between the polymers and the copolymers of lactic acid. The particle size was confirmed by scanning electron microscopy (Figs.

Table 1
Applied polymers and copolymers

Polymer/ copolymer	Copolymer content (mole%)	Molecular weight (g/mole)	Concentration polymer solution (% (w/v))	Dosage polymer solution (ml)	Result
PDLLA	–	78.000	1	25	Agglomeration, lumps
		52.000	1	25	Agglomeration, lumps
		32.800	10	25	Agglomeration, fibres
		32.800	5	25	Agglomeration, fibres
		32.800	1	15	Small particles
		32.800	1	25	Small particles
		32.800	1	35	Small particles, agglomerates
		32.800	1	50	Small particles, agglomerates
		12.300	10	25	Agglomerates, fibres
		12.300	5	25	Agglomerates, fibres
		12.300	1	15	Small particles
		12.300	1	25	Small particles
		12.300	1	35	Small particles, agglomerates
		12.300	1	50	Small particles, agglomerates
PDGLLA	30	27.400	1	25	Small particles
	25	25.900	1	25	Small particles
	10	29.800	1	25	Small particles

5 and 6). The surface of the particles is smooth, there are no holes. No agglomeration occurs, the particles are separately in the continuous phase.

The size of the particles is significantly affected by the concentration of the polymer solution. There are only very diluted polymer solutions applicable (1% w/v). The use of higher concentrated polymer solutions results in agglomeration of the primary particles, formation of fibers or lumps. The phase ratio between aqueous and organic phase is limited to 1:1. Phase ratios with higher part of the organic phase also results in agglomeration of the primary particles. The lower the concentration of the organic phase and the lower the content of the organic phase in the continuous phase the smaller the resulting particles are. The particle size can be reduced up to 100–500 nm in that way. According to Quintanar-Guerrero et al. (1998) the increase of particle size was determined by the viscosity of the system (organic and/or continuous water phase).

The dispersing of the polymer solution into the aqueous continuous phase can be carried out by static as well as dynamic stirrers. Particle size and distribution are independent on the kind of stirrers and their stirring rate as expected because of the particle forming mechanism.

Different kinds of additives were used to reduce the particle size, e.g. emulsifiers (TWEEN®-type) and stabilizers (e.g. polyvinyl alcohol or gelatin). There are no significant differences observable (Table 2). It is also possible to use the water phase without additives but this results in the formation of agglomerates (Table 2).

The stability of the particle dispersion is noticeable. Particle size and distribution of different particle dispersions were observed. No increase in particle size was estimated in the course of several weeks on condition that the organic solvent was

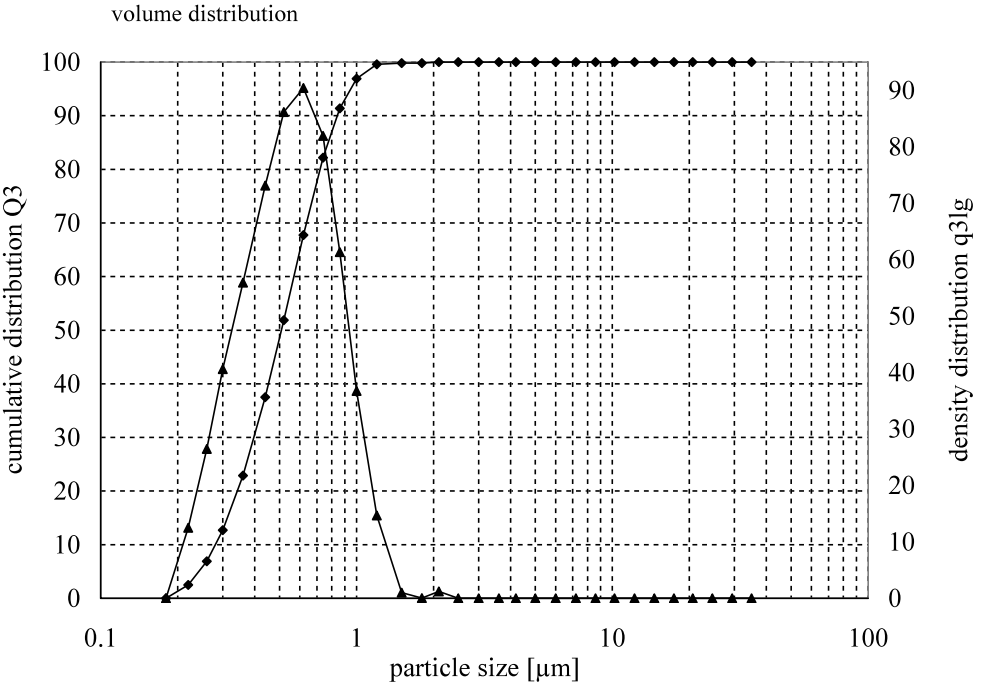


Fig. 3. Particle size distribution (volume) of PGDLLA after solvent exchange.

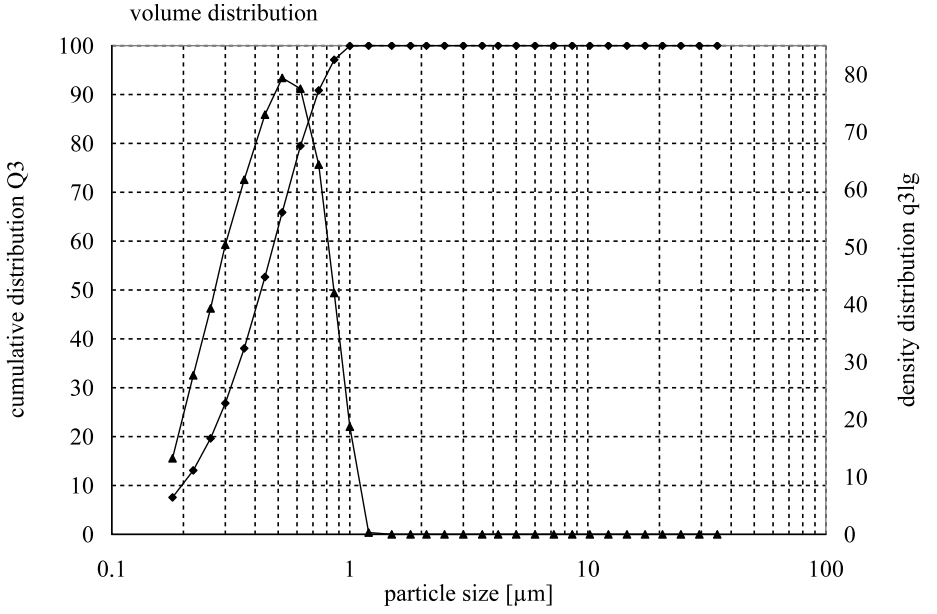


Fig. 4. Particle size distribution (volume) of PDLLA after solvent exchange.

Table 2
Particle size in dependence on additives

Water additive	Volume particle size distribution [μm]			
	X_5	X_{50}	X_{95}	Maximum
–	0.28	5.66	25.07	0.55/20
TWEEN 20® (0, 1%)	0.23	0.49	0.90	0.55
TWEEN 20® (1%)	0.22	0.58	1.61	0.85
Polyvinyl alcohol (0, 1%)	0.27	0.93	1.99	1.50
Gelatin (0, 1%)	0.27	0.60	2.03	1.47

Polymer: PDLLA, polymer solution concentration: 1% w/v, 25 ml of polymer solution.

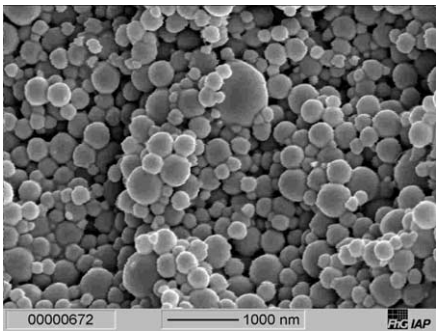


Fig. 5. Scanning electron micrograph of PGDLLA-submicron-particles.

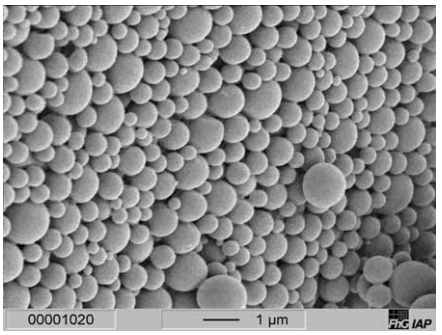


Fig. 6. Scanning electron micrograph of PDLLA-submicron-particles.

removed completely. For this reason a conventional solvent evaporation process was compared to a cross-flow-filtration process. Solvent evaporation by temperature raising resulted in agglomeration of the primary particles. A similar observation was made applying vacuum for this reason. By contrast application of cross-flow-filtration didn't cause agglomeration.

Because of the polymer nature (hydrolytic degradation) and for applicational reasons it is necessary to separate the submicronparticles. The separation of the submicronparticles is problematic. Normally used separation processes such as filtration or centrifugation are not applicable. A possibility to solve this problem is freeze drying. Scale- or membrane-like agglomerates (100–500 μm) were obtained using that 'drying process'. The formed agglomerates are very stable. In the end a redispergation into primary particles is not possible.

References

Bodmeier, R., Chen, H., Tyle, P., Jarosz, P., 1991. Spontaneous formation of drug-containing acrylic nanoparticles. Journal of Microencapsulation 8, 161–170.

Dahlmann, J., Rafler, G., Fechner, K., et al., 1990. Synthesis and properties of biodegradable aliphatic polyesters. British Polymer Journal 23, 235–240.

Fessi, H., Puisieux, F., Devissaguet, J.Ph., Ammoury, N., Benita, S., 1989. Nanocapsule formation by interfacial polymer deposition following solvent displacement. International Journal of Pharmaceutics 55, R1–R4.

Fessi, H.C., Devissaguet, J.-P., Puisieux, F., Thies, C., 1992. Process for the preparation of dispersible colloidal systems of a substance in the form of nanoparticles. US Patent US. 5, 118–528, 2 June.

Quintanar-Guerrero, D., Allémann, E., Fessi, H., Doelker, E., 1998. Preparation techniques and mechanisms of formation of biodegradable nanoparticles from preformed polymers. Drug Development and Industrial Pharmacy 24, 1113–1128.

Rafler, G., Dahlmann, J., 1990. Biologisch abbaubare Polymere. 2. Mitt.: Zur Homo- und Copolymerisation von D,L-Dilactid. Acta Polymerica 41, 611–617.

Rafler, G., Dahlmann, J., 1992. Biodegradable polymers. 6th comm. polymerization of ε-caprolactone. Acta Polymerica 43, 91–95.