Preparation of Polymeric Nanoparticles by Flow Ultrasonic Emulsification*

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The work is dedicated to the production of polymer suspensions using ultrasonic dispergation in a flow mode. An apparatus was designed on the basis of a Russian flow ultrasonicator. The applicability of this apparatus for obtaining aqueous dispersions of polymeric micro- and nanoparticles by means of one-step emulsification followed by solvent extraction / evaporation was demonstrated. The influence of the process parameters on the characteristics of the obtained suspensions was studied. The particle size distribution and the average size of the resulting particles were evaluated by using Delsa Nano S, Beckman Coulter laser analyzer (USA). The dependence of the average diameter of the suspension particles on the stabilizer concentration and on the change of the phases feed rate was shown. When polyvinyl alcohol was used as a stabilizer in the concentration range 0.5–2%, the average particle size was 30–400 nm. The feed rates of the aqueous and organic phases affect the nature of the particle size distribution.

Keywords: *polymeric microspheres ultrasonic flow emulsification, one-step emulsification, flow systems, polymer dispersion.*

Introduction

The interest in applying polymeric micro- and nanoparticles as carriers of active agents for creating the prolonged dosage forms and target delivery drugs constantly increases.

One of methods for obtaining polymeric suspensions of micro- and nanoparticles is extraction/evaporation of the solvent [1]. The method includes the following stages: obtaining a polymer solution, emulsification of this solution by an aqueous solution of a surfactant and solvent removal. The preparation of polymeric suspensions is carried out both in the periodic and continuous modes. Paddle stirrers, homogenizers and ultrasonic dispergators are used as dispergating devices. The size of polymeric particles in polymeric dispersions is in the range from 100 nm to 100 μm [2].

Ultrasonic dispergation of organic solutions of polymers in aqueous media is carried out most often in the periodic mode. Polymeric suspensions have a wide distribution of particles by sizes, and their average diameter is 1–5 μm [3–12]. In a number of works it was suggested to use flowing ultrasonic dispergators of a special design. This allowed obtaining polymeric suspensions

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in the continuous mode. The particles had an average size of 1 micron and narrow distribution [13–15]. Such design is promising for obtaining sterile stable suspensions, and it is suitable for their introduction into the industry.

This work presents data on obtaining polymeric suspensions by single-stage dispergation with the use of a flowing ultrasonic dispergator produced in Russia followed by extraction/evaporation of the solvent.

Experimental

In order to obtain dispersions of polymeric nanoparticles we used a copolymer of lactic and glycolic acids – PLGA (75:25) Resomer RG 755 S (Evonik Industries, Germany) as a polymer, an organic solvent – dichloromethane (GOST 9968-86) and a stabilizer – Polyvinyl Alcohol BF-08 (Chang Chun Petrochemical Co. Ltd, Taiwan).

In order to obtain polymeric nanoparticles dispersions we used the installation (see Figures 1 and 2) consisting of a MOD MEF 92 ultrasonic flowing dispergator (MELFIZ-ultrazvuk LLC, Russia), V 2015/YZ1515X peristaltic pumps (SHENCHEN Lab, China) and a RITM-01 magnetic stirrer without heating (Akvilon, Russia).

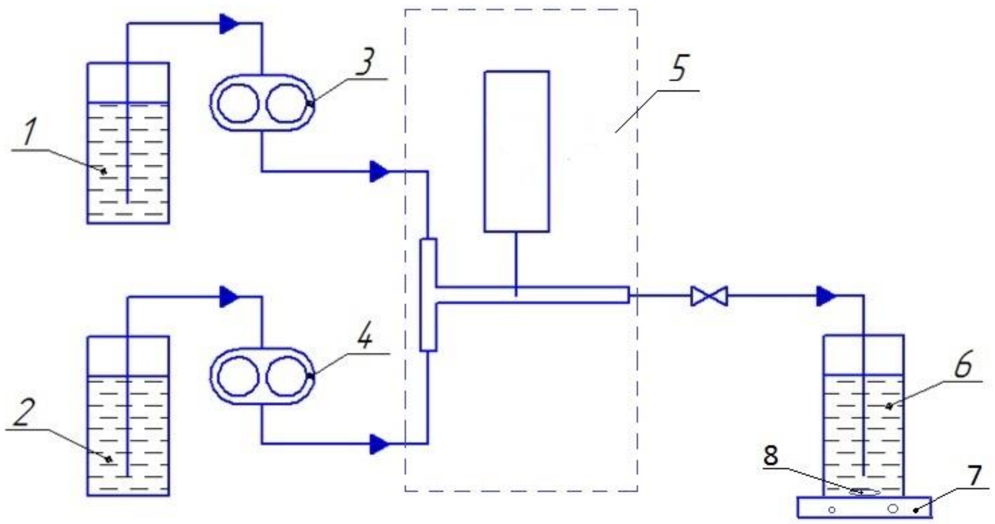


Figure 1. Schematic diagram of installation for obtaining polymeric particles based on MOD MEF 92 ultrasonic flowing homogenizer: *1* and *2* – containers with starting reagents, *3* and *4* – peristaltic pumps, *5* – flowing ultrasonic dispergator, *6* – intake vessel, *7* – magnetic stirrer, *8* – magnetic stir bar.

Figure 2. Installations for obtaining polymeric particles based on MOD MEF 92 ultrasonic flowing homogenizer.

Aqueous dispersions of polymeric nanoparticles were obtained by the following method. An aqueous solution of polyvinyl alcohol (PVA) and an organic solution of PLGA in methylene chloride were supplied by means of pumps 3 and 4 to the working camera of flowing dispergator 5, in which they were mixed and treated by ultrasound (600 W power). The obtained dispersion was collected in intake vessel 6 placed on magnetic stirrer 7. The dispersion was stirred for 12–14 h for complete solvent removal and particles hardening.

The obtained dispersions were analyzed, and the average particle size and particle size distribution were estimated with use of a Delsa Nano S laser analyzer of particles (Beckman Coulter, USA).

Results and Discussion

Dispersions of nanoparticles of lactic and glycolic acids copolymer were obtained by dispergating PLGA copolymer solution in the aqueous phase. On the basis of literature data [15] PVA concentration was chosen to be equal to 0.5%. The polymer concentration was chosen to be in the range 0.05–0.4% mass/mass, which is recommended for obtaining polymeric dispersions of biotechnological application. Preliminarily, the influence of the copolymer concentration in the initial solution on the average diameter of the particles was studied. It can be seen (Table 1) that the average diameter of the particles varies slightly and is equal to 350.0 ± 17.5 nm. For further studies, PLGA concentration in the organic phase was chosen to be equal to 0.1% mass/mass.

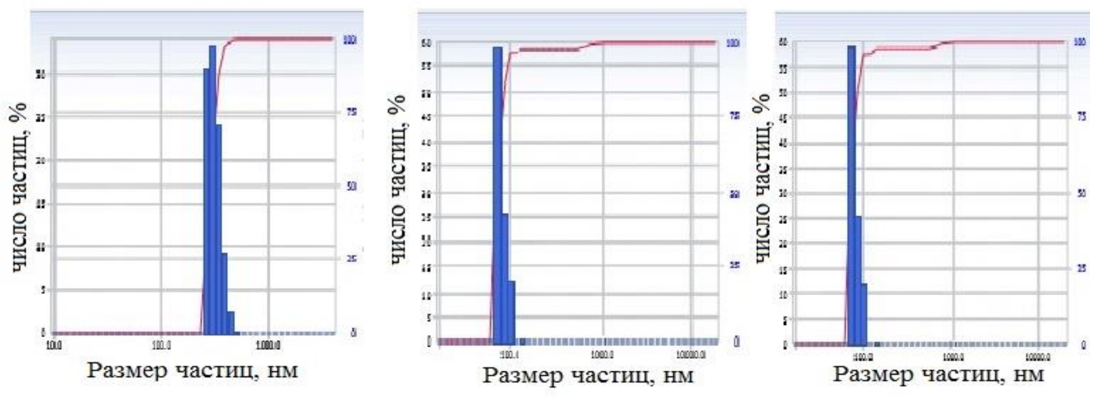
Table 1. Dependence of average diameter of polymeric nanoparticles on polymer concentration at the ratio of the supply rates of the organic and water phases (ml/min) 7:150

Parameters	PLGA concentration in the organic phase, % mass/mass			
	0.05	0.1	0.2	0.4
Average diameter, nm	316.0 ± 15.8	386.0 ± 19.3	353.0 ± 17.6	328.0 ± 16.4

The average diameter and particle size distribution in the polymeric suspensions depend on the variation of the supply rates of the phases and on PVA concentration. When PVA concentration is varied in the range from 0.5 to 2.0%, polymeric dispersions with an average diameter of particles from 30 to 400 nm are formed (Table 2, Figure 3). An increase in the supply rate of the organic phase in the range chosen for the study practically does not affect the average diameter of the particles and their size distribution. In all the studies the particles in polymeric suspensions had narrow sizes distribution.

Table 2. Dependence of the average diameter of the polymeric nanoparticles (nm) on the stabilizer concentration and on the ratio of the phases supply rates

PVA concentration in the water phase	Ratio of organic phase/water phase supply rates (ml/min)		
	7:150	**10:150**	**13:150**
0.5%	394.4 ± 19.7	304.2 ± 15.2	260.0 ± 13.0
1.0%	99.5 ± 4.9	142.7 ± 7.1	108.0 ± 5.4
2.0%	81.0 ± 4.0	32.6 ± 1.6	50.0 ± 2.5



a b c

Figure 3. Distribution of particle sizes at various PVA concentrations (ratio of organic phase/water phase supply rates (ml/min): 7:150): a – 0.5% PVA, b – 1.0% PVA, c – 2.0% PVA.

[число частиц means The number of particles; размер частиц, нм means Particle size, nm]

When using the PVA solution with a concentration of 1.0% as a dispersion medium, polymeric dispersions with particle sizes in the range from 100 to 150 nm (Figure 4) were obtained. These particles are of the greatest interest as drug carriers [11].

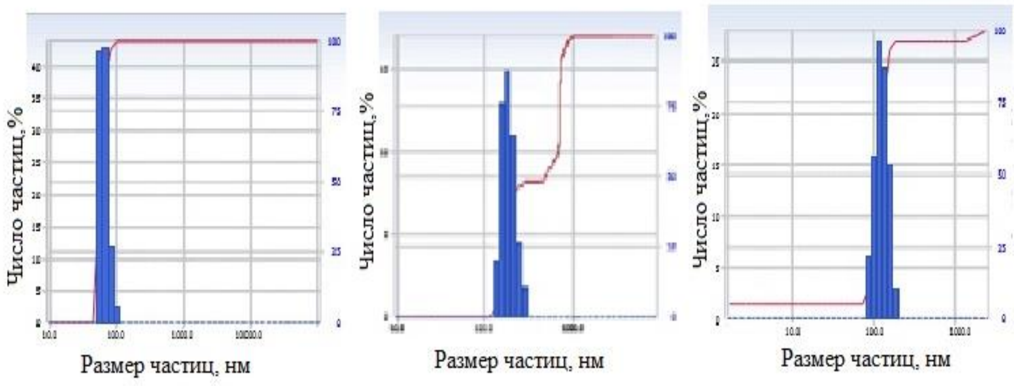


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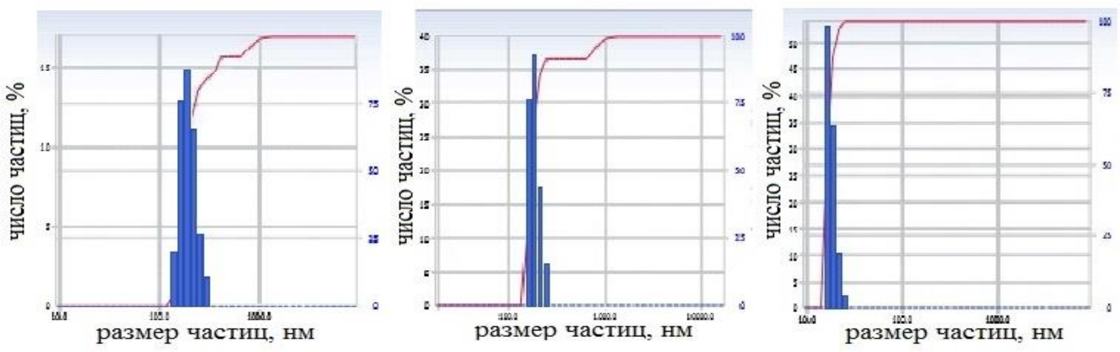
Figure 4. Size distribution of particles upon dispergation in 1% PVA
at different ratios of organic phase/water phase supply rates (ml/min):
a – 7:150, b – 10:150, c – 13:150.
[число частиц means The number of particles; размер частиц, нм means Particle size, nm]

Varying the supply rate of the aqueous phase from 150 to 220 ml/min resulted in reduction of the average diameter of the particles from 300 to 30 nm (Table 3, Figure 5).

Table 3. Dependence of the average diameter of the polymeric nanoparticles on the ratio of the phases supply rates

Parameters	**Ratio of organic phase/water phase supply rates (ml/min)**		
	10:150	10:180	10:220
Average diameter of particles, nm	280.0 ± 14.0	170.0 ± 8.5	33.0 ± 1.6



a b c

Figure 5. Size distribution of particles upon dispergation in 1% PVA
at different ratios of organic phase/water phase supply rates (ml/min): a – 10:150, b – 10:180, c – 10:220.
[число частиц means The number of particles; размер частиц, нм means Particle size, nm]

Conclusion

Ultrasonic dispergation of organic solutions of polymers in aqueous media in the flowing (continuous) mode allowed obtaining polymeric suspensions with a narrow particle size distribution. The average diameter of the particles depending on the composition of the organic and water phases and the rates of their supply is in the range from 30 to 400 nm.

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