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Preparation of poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) particles in O/W emulsion

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Abstract

In the present paper, we investigate the preparation of polymeric particles based on the biodegradable polyester poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV). A new technique for PHBV particle preparation has been developed. This method utilizes the thermoreversible gelation of PHBV in toluene. Particles have been obtained by the secondary dispersion technique in a three-step procedure: (a) preparation of PHBV solution in toluene; (b) preparation of O/W emulsion by ultrasound followed by the gel formation in toluene/PHBV droplets; and (c) toluene extraction. In the present study we investigated the influence of the stabilizer type and its concentration in the aqueous phase, ultrasound power, and PHBV concentration in toluene on the size and stability of the formed droplets as well as the final PHBV particles. It has been found that PEO/PS block copolymers are the best stabilizers for the present system as compared to conventional tensides such as SDS or CTAB. It has been found that PEO/PS block copolymers allow obtaining PHBV particles with a regular shape and controlled dimensions after toluene extraction. The minimal size of the PHBV particles obtained by this technique was ca. 100 nm. The obtained particles exhibit a relatively broad particle size distribution and the particle shape is strongly affected by the block copolymer composition, ultrasound power and the way of toluene extraction.

Keywords: Biodegradable particles; Thermoreversible gelation

1. Introduction

Recently, biodegradable materials have received increasing interest due to the ecological and the recycling reasons. Among numerous bio-polymers microbial polyesters which belong to the group of poly(hydroxy alkanoates) (PHA) have been intensively investigated by a numerous research groups. It has been established that a large number of different repeat units are found in these reserve materials, depending on the bacterial species and the ingested substrate. Such polyesters are biocompatible and can be bio-degraded under environmental conditions. Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) (Fig. 1) found numerous applications in medicine (implants [1], drug delivery systems [2,3], tissue engineering [4,5]) due to its attractive properties.

Recently, PHBV has been used for the preparation of the matrices with a controlled porosity for tissue engineering. The literature reports demonstrate that PHBV sustained the fibroblast cell proliferation rate similar to that observed in the collagen sponges [6]. The porous PHBV materials have been found to be adequate as substrates for the cell structures. No acute inflammation, abscess formation or tissue necrosis was observed in the tissues adjusted to the implant materials [7,8]. Considering the attractive features of PHBV mentioned above it might be an attractive material for the drug delivery systems. In this case this polymer should be present in the form of particles with desired size and morphology. Sendil et al. prepared PHBV microparticles by using a double emulsion (w/o/w), solvent evaporation technique [9]. PHBV particles with diameter from 400 to 500 nm with loaded tetracycline have been prepared by using PVA and gelatine as stabilizers. In this study chloroform has been applied as a good solvent for PHBV and the polymer particles have been obtained after solvent evaporation from the double emulsion (w/o/w). Similar technique was used for the preparation of the enzyme-loaded PHBV capsules [10]. It has been found that the increase of the stabilizer concentration (PVA) and PHBV concentration resulted in a decrease of the particle size from 450 to 200 nm. It has been

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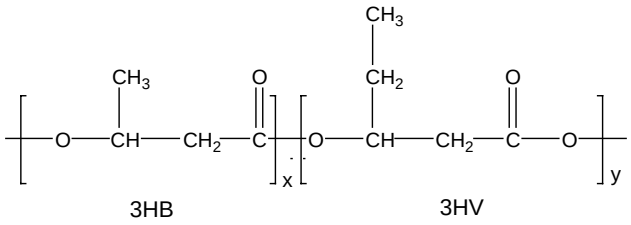
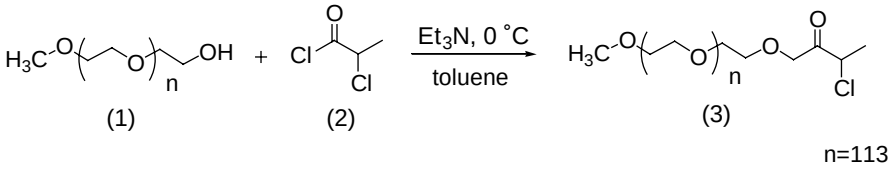


Fig. 1. Chemical structure of PHBV.



Scheme 1. Synthesis of the PEO macroinitiator [12].

also mentioned that low molecular weight PHBV led to the decrease of the particle size.

The aim of the present study was to prepare PHBV particles from the nanometer to micrometer range by a modified secondary dispersion technique. Recently, it has been reported that PHBV can undergo the thermoreversible gelation in toluene [11]. Hot PHBV solutions (ca. 80 °C) became transparent gels after cooling to room temperature. In present paper this physical gelation process was performed in a small droplets leading to the formation of PHBV gel beads swollen in toluene and after toluene extraction PHBV particles can be obtained. It is believed that this principally new method can offer numerous advantages especially in obtaining of the porous PHBV particles with defined size and morphology. Also improved incorporation of the hydrophobic drugs or inorganic materials might be possible leading to the formation of high-performance systems for the diagnostics or the controlled drug delivery.

2. Experimental

2.1. Materials

PHBV was received from Aldrich with following characteristics: hydroxyvalerate (HV) content 7.5 wt%; $M_n = 1.257 \times 10^5$ g/mol, $M_w = 4.205 \times 10^5$ g/mol and $M_z = 7.106 \times 10^5$ g/mol; polydispersity index 3.344. Toluene was obtained from Biesterfeld and used as received.

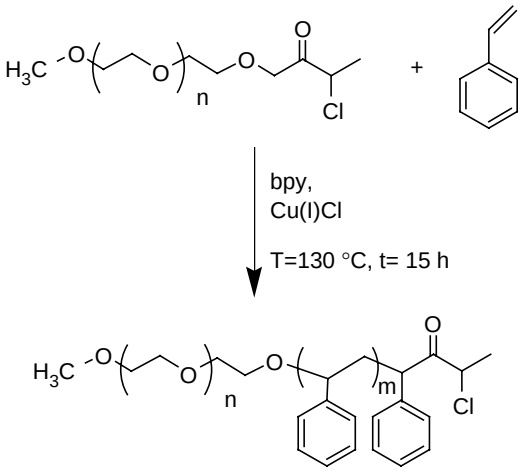
Poly(ethylene oxide)methyl ether (1) ($M_w = 5000$ g/mol) (Aldrich), 2-chlorpropionyl chloride (97%) (2) (Aldrich), copper(I)chloride (Aldrich), 2,2′-dipyridyl (99+%) (Acros) (bpy) were used as received. Triethylamin and toluene were both distilled over KOH. Styrene was distilled under reduced pressure over CaH_2.

Stabilizers *N*-cetyl-*N*,*N*,*N*-trimethylammoniumbromide (CTAB) (Merck), sodiumdodecylsulfate (SDS) (98%, Aldrich), poly(vinyl alcohol) (PVA) ($M_w = 100{,}000$ g/mol, Aldrich), hydroxypropyl cellulose (HPC) ($M_w = 100{,}000$ g/mol, Aldrich), Tween 80® (Merck), Disperbyk-180® (D-180) (BYK Chemie) were used as received.

2.2. Synthesis of PEO/PS block copolymers

The PEO macroinitiator was prepared according to the literature [12] (see Scheme 1). The functionality was determined by the ^{1}H NMR spectra.

The general polymerization procedure has been set as follows (see Scheme 2). A Schlenk flask was charged with the macroinitator (3), ligand (bpy) and CuCl (ratio 1:5:2) and different amounts of styrene (Table 1). The flask was subjected to three freeze–thaw cycles and sealed off under argon. The polymerization was carried out under argon at 130 °C for 15 h. The resulting reaction mixture was cooled down with liquid nitrogen, dissolved in $CHCl_3$ and the polymer was precipitated into cold *n*-hexane. To remove the copper ions the contaminated polymers were dissolved in chloroform and passed



Scheme 2. Synthesis of the amphiphilic block copolymers.

Table 1
Ingredients used for preparation of PEO/PS block copolymers

	Macroinitiator (mmol)	Ligand (mmol)	Cucl (mmol)	Styrene (mmol)	Conversion (%)
PEO/PS 1:2	0.1	0.5	0.2	24	59
PEO/PS 1:4	0.1	0.5	0.2	48	51
PEO/PS 1:6	0.1	0.5	0.2	72	48

Table 2
Molecular weight and composition of PEO/PS block copolymers

	M_n (g/mol)	D	$M_{n(PEO)}$:$M_{n(PS)}$	Composition
PEO/PS 1:2	14,500	1.32	PEO_1-*block*-$PS_{1.8}$	PEO_{113}-*block*-PS_{90}
PEO/PS 1:4	26,300	1.4	PEO_1-*block*-$PS_{4.1}$	PEO_{113}-*block*-PS_{203}
PEO/PS 1:4	37,000	1.36	PEO_1-*block*-$PS_{6.3}$	PEO_{113}-*block*-PS_{307}

D, polydispersity index (M_w/M_n).

through an aluminium oxide column. The monomer conversion was determined gravimetrically.

Table 2 shows the molecular weight polydispersity index and composition of obtained block copolymers.

2.3. Preparation of PHBV solutions in toluene

The solutions were prepared by dissolving of an appropriate amount of PHBV in toluene at ca. 90 °C.

2.4. Preparation of emulsions

The O/W emulsions have been prepared by the dispergation of PHBV/toluene solution in the water/surfactant mixture at 70 °C by means of the ultrasound (Branson Sonifier). The ultrasonic agitation was applied for 10 min and ultrasonic power was varied from 80 to 320 W.

2.5. Solvent extraction

Toluene has been removed from the particles by means of the extraction with ethanol and this procedure was repeated three times.

2.6. Analytical methods

2.6.1. Molecular weight determination

The molecular weight and molecular weight distributions for PEO/PS block copolymers were measured using SEC (detector type—Knauer differential refractometer; column type—SDV 8×300 mm^2 with polystyrene as filler material). Measurements were performed with THF as eluent, polystyrene standards have been used for column calibration.

2.6.2. Dynamic light scattering

A commercial laser light scattering (LLS) spectrometer (ALV/DLS/SLS-5000) equipped with an ALV-5000/EPP multiple digital time correlator and laser goniometer system ALV/CGS-8F S/N 025 was used with a helium–neon laser (Uniphase 1145P, output power of 22 mW and wavelength of 632.8 nm) as the light source.

2.6.3. Analytical centrifuge

The stability measurements were performed with the separation analyser LUMiFuge 114 (L.U.M. GmbH, Germany). The measurements were made in the glass cuvettes at acceleration velocity 3000 rpm. The slope of the sedimentation curves was used to compare the stability of the samples.

2.6.4. Scanning electron microscopy

SEM images were taken with Gemini microscope (Zeiss, Germany). The samples were prepared in the following manner. PHBV dispersions were diluted with distilled water, dropped onto the aluminium support and dried at room temperature. PHBV particles have been covered by a thin gold layer prior to measurements. Pictures were taken at voltage of 4 kV.

3. Results and discussion

The conformational properties of bacterial polyesters have been intensively investigated by different working groups [13–15]. These studies include SANS [13], X-ray analysis [14], molecular modelling investigations [15] and have been focused on poly(3-hydroxybutyrate) (PHB). The solution properties of PHB have been studied by Marchessault et al. [16] by means of

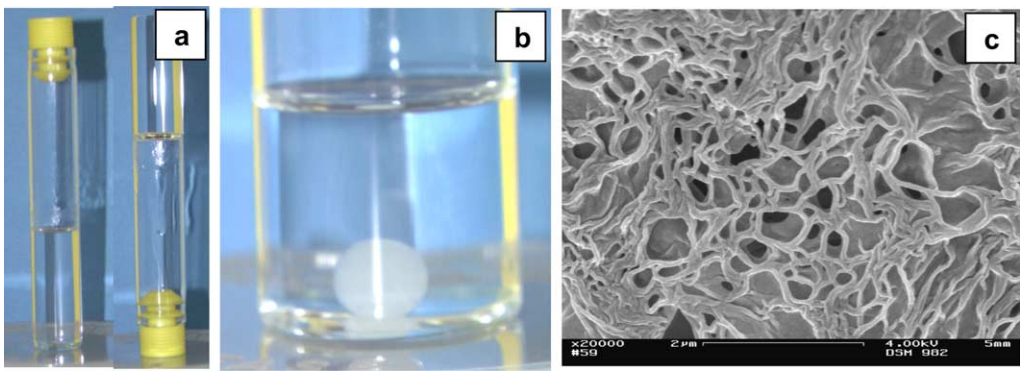


Fig. 2. Photograph of PHBV solution in toluene at $T=70$ °C (left) and formed gel after cooling down to $T=25$ °C (a); photograph of PHBV/toluene gel bead formed after injection of hot solution into cold water (b); SEM image of internal structure of PHBV bead after toluene extraction (c).

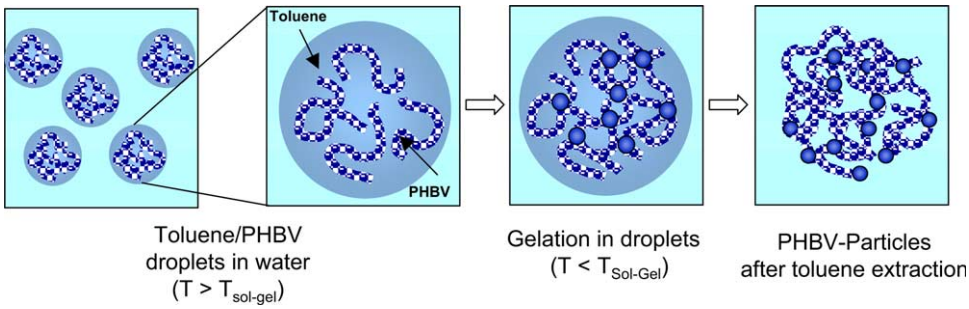


Fig. 3. Schematic representation of PHBV particle formation in O/W emulsion.

intrinsic viscosity, sedimentation analysis and optical rotary dispersion experiments in chloroform, ethylene dichloride, and trifluoroethanol. Authors report that the type of the solvent influences the chain conformation and it changes from coil to the partially helical structure. The polymer conformational transitions play also an important role in the formation of biopolymer gels and networks which have been intensively investigated [17–19]. Recently, it has been reported that PHBV can be dissolved in hot toluene and form physical gels in after cooling to room temperature (Fig. 2) [11]. It has been assumed that the gelation process in PHBV–toluene system proceeds in the following way. PHBV chains are in the random-coil conformation at a given temperature and concentration and later on form partial helices after being cooled. If the temperature still decreases, the helices aggregate into multiple junctions forming a three-dimensional network. This effect is fully reversible and can open new possibilities for the design of biomaterials on PHBV-basis with defined dimensions and morphologies. This includes preparation of membranes, fibres or particles, which can be suitable for medical applications.

In the present work thermoreversible gelation of PHBV in toluene has been used for the preparation of secondary dispersion of PHBV particles of sub-micrometer size. Fig. 3 demonstrates the way of PHBV particle formation.

At the first stage PHBV solution in toluene heated above the gelation temperature (T=70 °C) can be dispersed by the ultrasound in water and formed droplets are stabilized by the surfactant to avoid coalescence (stage 1, Fig. 3). Later by cooling down the system gelation process takes place in droplets what leads to formation of PHBV network swollen by toluene and the droplets become a gel particles (stage 2). Finally, toluene can be removed by the extraction with ethanol and PHBV particles are formed (stage 3). Since ethanol and water are non-solvents for PHBV one can expect the formation of porous structures after toluene removal.

3.1. Preparation and properties of emulsions

3.1.1. Influence of stabilizer type

For the preparation of the PHBV particles by the method described above it is essentially important to prepare stable O/W emulsions and to avoid the droplet coalescence during gelation process. For that reason a number of stabilizers have been tested and as an evaluation criterion the particle size of obtained toluene/PHBV droplets has been defined. Fig. 4 shows the results of the dynamic light scattering measurements performed for different systems at least 10 min after redispergation by ultrasound at 70 °C and cooling to room temperature.

Fig. 4 indicates that the diameter of gelled toluene/PHBV droplets obtained after dispergation in water deviates from 250 to 850 nm. The best results have been obtained by using PEO/PS block copolymers which allow preparation of the toluene/PHBV droplets in range of 200–450 nm. It is obvious from Fig. 4 that the chemical composition of block copolymers influences the size of obtained droplets. Increase of the hydrophobic segment length leads to the formation of smaller droplets. In addition, block copolymers provide a long-term stability for O/W emulsions and DLS measurements indicate no change of the droplet size for a minimum of 5 h. In the case of low molecular weight stabilizers (SDS, CTAB) as well as water-soluble polymers (PVA, HPC) the formation of aggregates has been detected. The stabilization mechanism by PEO/PS block copolymers seems to be effective due to the orientation of the polymer chains at the water-droplet interface where hydrophobic PS block shifts toward toluene phase and water-soluble PEO block remains in aqueous phase. That is why a PEO brush-like layer is formed providing effective sterical stabilization to the colloidal system. Increase of the PS block length leads to the formation of smaller droplets (Fig. 4) probably due to a better adsorption of these hydrophobic segments of oil-water interface. Based on this results further

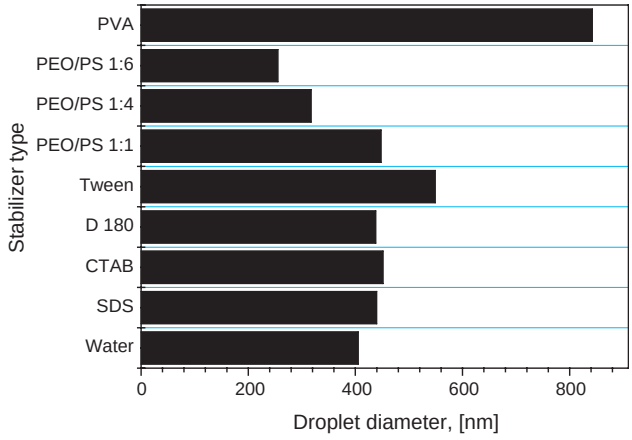


Fig. 4. Influence of stabilizer type on size of obtained PHBV/toluene particles (stabilizer concentration, 2.5 wt%; US-power, 160 W; c_{PHBV}=10 g/l).

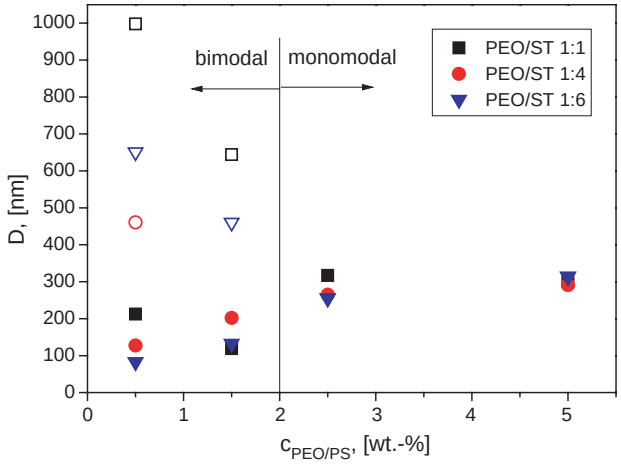


Fig. 5. Size of PHBV/toluene particles as a function of PEO/PS block copolymer composition and concentration in aqueous phase. The solid and open symbols at low copolymer concentrations indicate small and large particles, respectively, detected by DLS (US-power, 160 W; $c_{PHBV} = 10$ g/l).

investigations have been performed with PEO/PS block copolymers as the most effective stabilizers.

The influence of the block copolymer concentration in aqueous phase on the size of formed toluene/PHBV droplets has been investigated. Fig. 5 demonstrates the particle diameters measured by DLS for three copolymer types.

As a general trend for all copolymer types one can define the formation of two types of particles (bimodal particle size distribution) at low copolymer concentration in water. This effect can be explained in the way that not enough stabilizer is present in the system and this leads to partial droplet coalescence and the formation of large particles. Increase of the copolymer concentration leads to the gradual decrease of large droplets size (open symbols in Fig. 5) and after some critical value monomodal particle size distribution has been detected. Similar effect has been reported by Baran et al. [10] where increase of PVA concentration in the system led to the decrease of emulsion droplets containing PHBV chains. It is interesting to note that if copolymer concentration reaches 3 wt% there is no considerable change of the droplet diameter with further increase of copolymer concentration. In this case also block copolymer composition does not influence the final size of the toluene/PHBV droplets.

To evaluate the stability of obtained emulsions they were treated by the analytical centrifuge. The stability of emulsions was investigated by sedimentation method developed by Lerche et al. [20]. In the special centrifuge an integrated optoelectronic sensor system allows spatial and temporal changes of light transmission during the rotation to be detected. In contrast to other approaches [21] the local transmission is determined over the entire sample length simultaneously. Throughout the measurement, transmission profiles are recorded and sedimentation process can be depicted as a time course of the relative position of the boundary between supernatant and sediment (resolution better than 100 μm) or of the transmission averaged over the entire or a chosen part of the sample length. On the basis of obtained data the sedimentation constants, the packing density, etc. can be derived.

Fig. 6 shows the experimentally determined transmission–time curves (Fig. 6(a)) and the sedimentation velocity of toluene/PHBV droplets prepared with different PEO/PS 1:4 contents calculated from the slope of the transmission–time curves (Fig. 6(b)).

The obtained sedimentation velocity data indicate that the increase of the stabilizer concentration increases the stability of the emulsion, so the formation of large droplets or aggregates is hindered.

The influence of ultrasound power on the size of obtained toluene/PHBV droplets has been investigated. Fig. 7 indicates that the increase of the ultrasound power leads to a linear increase of the droplet diameter. This surprising result can be explained in the following way. During ultrasonic agitation a small toluene/PHBV droplets are formed and if the total surface area is larger than the area, which can be effectively protected by stabilizer the reversible process (droplet coalescence) takes place. It seems that by the increasing ultrasound power at constant stabilizer concentration the droplet coalescence is the dominating process and this leads to the formation of larger droplets.

Fig. 8(a) indicates that PHBV concentration in toluene has some influence on the droplet size at high stabilizer concentration. However, the experimental results indicate

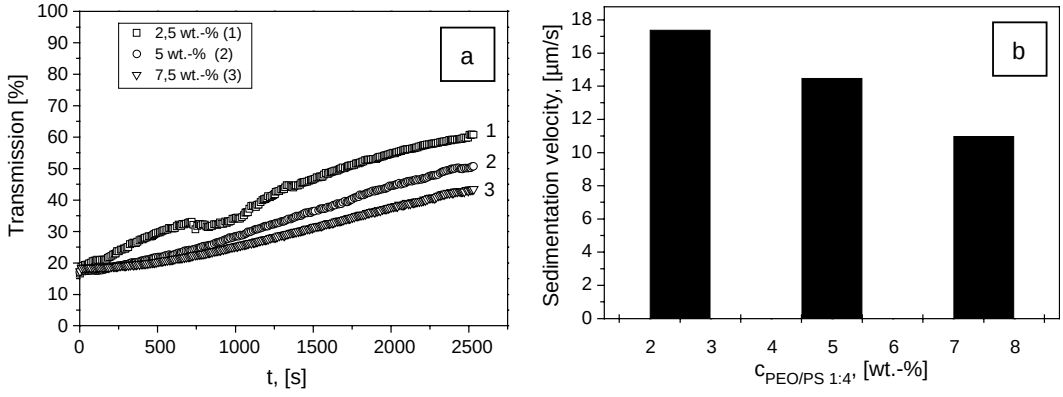


Fig. 6. Transmission–time curves (a) and calculated there from sedimentation velocity values (b) for W/O emulsions prepared with different PEO/PS 1:4 concentrations (measurement performed at rotation speed 2000 rpm, $c_{PHBV} = 10$ g/l).

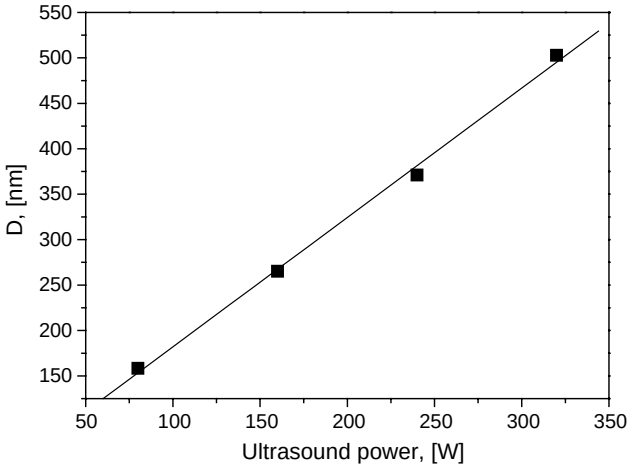


Fig. 7. (a) Droplet size as a function of ultrasound power ($c_{PEO/ST1:4}$ = 2.5 wt%; c_{PHBV} = 10 g/l).

that the increase of droplet size with the increasing PHBV concentration in toluene was not significant. By the increasing of PHBV concentration up to 30 g/l even smaller droplets with average diameter 250 nm have been obtained. Generally, it can be expected that the increase of PHBV concentration should increase the viscosity of the toluene/PHBV phase leading to the formation of droplets with larger dimensions [10,22].

The viscosity of PHBV solutions in toluene has been investigated and the polymer concentrations as well as the temperature have been varied. The experimentally obtained specific viscosity data are summarized in Fig. 8(b) for four PHBV concentrations in toluene. Fig. 4 shows that the specific viscosity increases with the increase of PHBV concentration in the system in accordance with our expectations. Solid arrow in Fig. 8(b) indicates the viscosity difference for polymer solutions at 70 °C (at this temperature redispergation has been performed). From Fig. 8(b) one can recognize that in case of all solutions at certain temperature there is a rapid increase of the viscosity (dashed arrow used to guide the eye), which can be related to the beginning of gelation process and formation of the aggregates in solution. Despite the remarkable viscosity change with PHBV concentration the size of the obtained droplets does not vary strongly as indicated in Fig. 8(a). It seems that within selected PHBV concentration range the viscosity of the oil phase does not influence strongly the dimensions of obtained droplets and the ultrasound power is high enough to prepare highly dispersed system.

3.2. PHBV particles preparation by solvent extraction

As it was mentioned earlier, after preparation of stable emulsions toluene has been removed from the droplets by the extraction with ethanol and the morphology of obtained PHBV particles has been investigated by electron microscopy. Fig. 9 shows typical images of PHBV particles prepared in the presence of SDS and CTAB as stabilizers.

It is obvious that after toluene extraction PHBV particles without well defined morphology have been formed. They partly stick together forming larger aggregates visible clearly in SEM images. In case if PEO/PS block copolymers have been used as the stabilizers spherical PHBV particles with average diameters 100–300 nm have been obtained. To check the influence of the copolymer concentration on the morphology of the obtained PHBV particles, electron microscopy studies have been performed for the systems prepared with different concentrations of PEO/PS 1:4. SEM images presented in Fig. 10 indicate that at low stabilizer concentrations particles collapse and form large aggregates without defined morphology due to the lack of stabilization. The gradual increase in stabilizer concentration leads to the formation of regular spherical particles with the average diameter 130 nm. There is a good correlation with the DLS measurements presented in Fig. 7. The PHBV/toluene droplet size was 160 nm and removal of toluene leads to smaller PHBV particles. Further increase of the stabilizer content led to the decrease of the particle dimensions to 80–100 nm, but the particle size distribution became broad. This fact does not correlate with the DLS measurements, which show no considerable change of the droplet size with increase of the stabilizer concentration. One can expect that the broadening of particle size distribution is caused by the droplet aggregation and the fusion during toluene removal.

It has been found that the ultrasound power has strong impact on the morphology of the obtained PHBV particles.

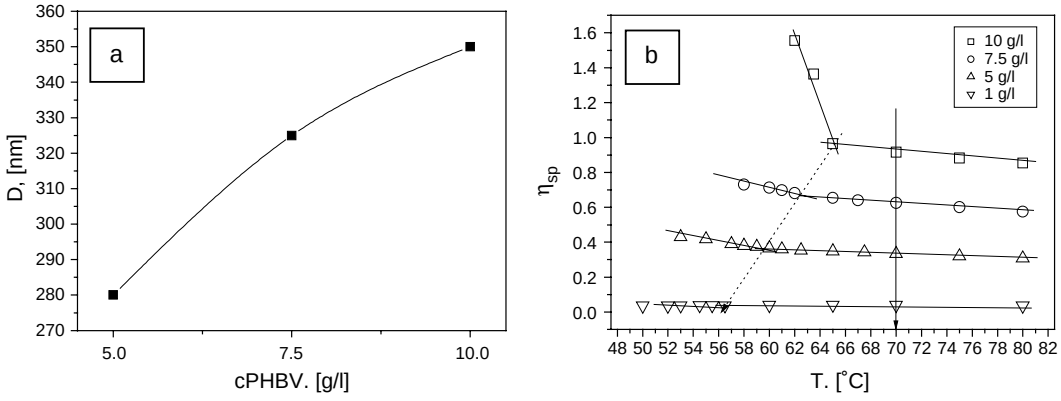


Fig. 8. (a) Droplet size as a function of PHBV concentration in toluene phase ($c_{PEO/ST1:4}$ = 7.5 wt%; US-power, 80 W); (b) specific viscosity data for PHBV solutions in toluene as a function of temperature (solid lines are to guide the eye).

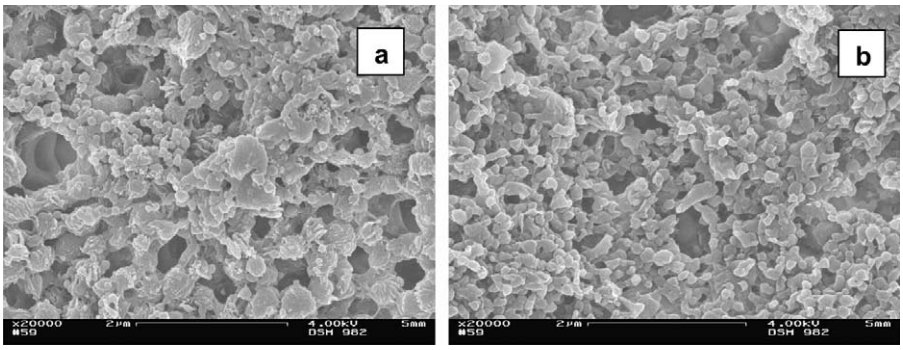


Fig. 9. SEM images of PHBV particles after toluene extraction with ethanol: (a) SDS, (b) CTAB (2.5 wt% stabilizator, US-power, 240 W, c(PHBV) = 7.5 g/l).

Fig. 11 shows images of the samples prepared by different sonication grades. It is obvious that the increase of ultrasound power leads to the formation of PHBV particles without defined morphology and a strong particle aggregation takes place. This effect is in accordance with the DLS measurements presented in Fig. 7 and it seems that high ultrasound power causes the particle collision and the formation of the aggregates which undergo fusion during toluene extraction.

The influence of PHBV concentration in toluene droplets on the morphology of final PHBV particles is shown in Fig. 12. Increase of PHBV concentration leads to the formation of large particles of micrometer range. Extremely high PHBV concentration in toluene (30 g/l) results in the formation of the particles with loop-like morphology and the amount of micrometer-large beads increases. This observation is again contrary to the DLS measurements presented in Fig. 8(a) where PHBV concentration in toluene weakly influences the average dimensions of the formed droplets. This effect is probably caused by the hindered diffusion of toluene from formed gel droplets during the extraction process. This can also lead to the partial particle destabilization and aggregation in water–ethanol medium.

In summary, the size and morphology of PHBV particles strongly depend on the way of the PHBV/toluene droplet preparation and solvent removal stage. As most important parameters one can define the stabilizer concentration, the ultrasound power and PHBV concentration in toluene phase. It is believed that the gelation inside of the formed droplets helps to ‘freeze’ the droplets and prevent to some extent the coalescence process. The process of PHBV particle preparation described in present study is comparable to the models developed by Desgouilles et al. [23] for poly(lactic acid) (PLA) and ethylcellulose (EC). In that case PLA and EC particles have been formed by the evaporation of ethylacetate from O/W emulsion. However, in present case the formation of

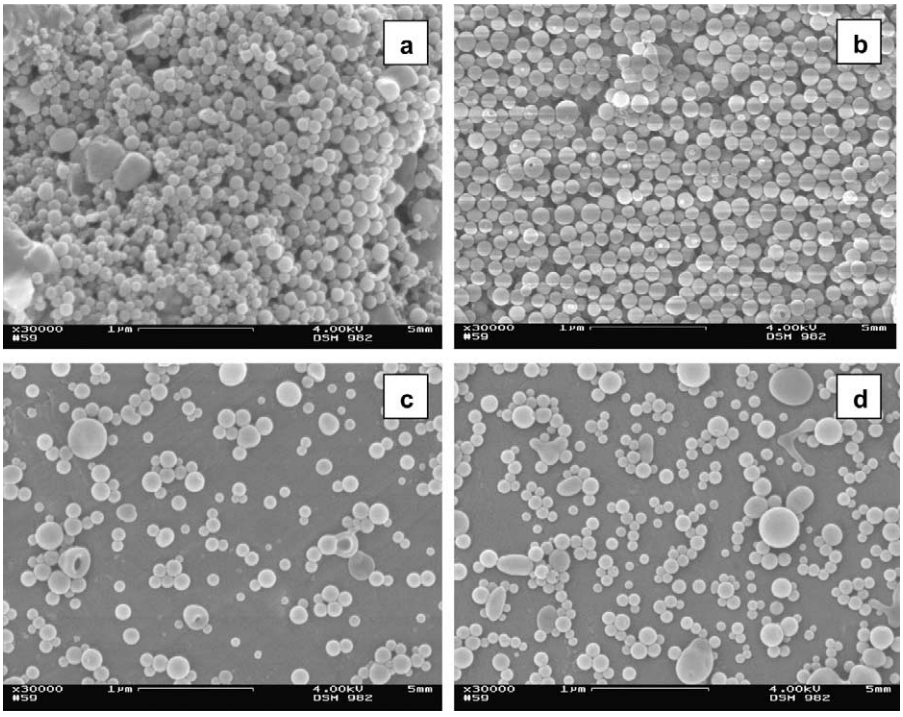


Fig. 10. SEM images of PHBV particles prepared at different concentrations of PEO/PS 1:4: (a) 1.5 wt%; (b) 2.5 wt%; (c) 7.5 wt%; (d) 10 wt% (c_{PHBV} = 10 g/l, US-power, 80 W).

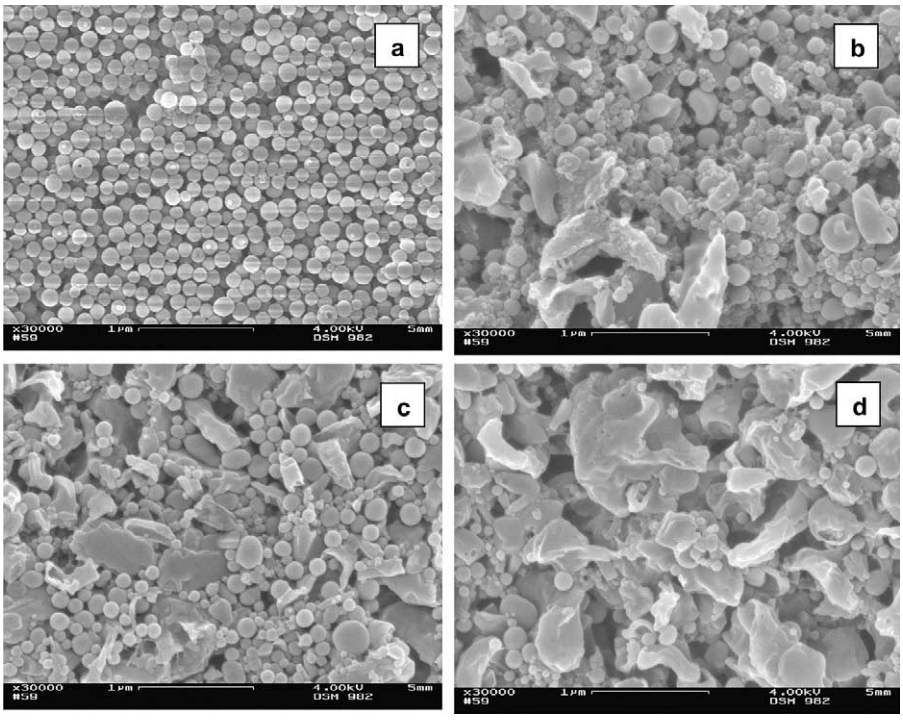


Fig. 11. SEM images of PHBV particles prepared at different ultrasound power, (a) 80 W; (b) 160 W; (c) 240 W; (d) 320 W ($c_{PEO/PS1:4}$ = 7.5 wt%, c_{PHBV} = 10 g/l).

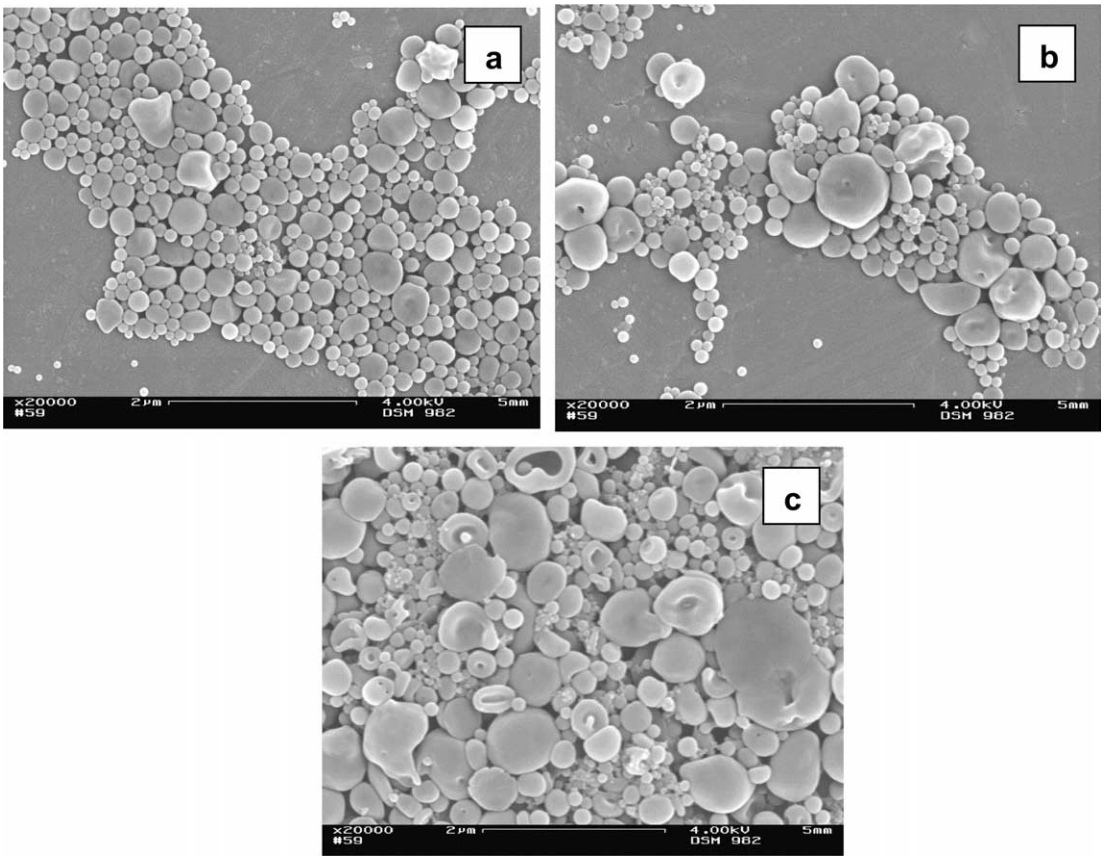


Fig. 12. SEM images of PHBV particles prepared at different PHBV concentrations in toluene phase: (a) 5 g/l; (b) 10 g/l; (c) 30 g/l ($c_{PEO/ST1:4}$ = 7.5 wt%, US-power, 80 W).

PHBV particles from emulsion droplets without aggregation and coalescence was possible at low stabilizer concentrations and low ultrasonic power (PLA-model). At high block copolymer concentration and PHBV contents in toluene phase a mechanism similar to EC-model was observed. The shrinkage of PHBV/toluene droplets due to the solvent removal in this case led to the instability, droplet aggregation and formation of large PHBV particles followed by the broadening of particle size distribution.

By following the mechanism of the particle preparation used in present work one can expect that obtained PHBV spheres are to some extent porous. The voids can be formed during toluene extraction from the gelled droplets. To confirm this TEM investigations are in progress. The porosity of the PHBV particles should have strong impact on their hydrolytic or enzymatic degradation kinetics. This will control the release of the active compounds and, therefore, determine the validity of such particles as containers for delivery purpose.

4. Conclusions

A new method for the preparation of the biodegradable particles from bio-polyester poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) has been developed. This method utilizes the thermoreversible gelation of PHBV in toluene and the particles have been obtained in three-step procedure: (a) preparation of PHBV solution in toluene; (b) preparation of O/W emulsion by ultrasound followed by the gel formation in toluene/PHBV droplets; and (c) toluene extraction. It has been shown that the PEO/PS block copolymers are effective stabilizers for toluene/PHBV emulsion in water comparing to the conventional tensides or water-soluble polymers. The properties of O/W emulsions have been studied in terms of the droplet size and the colloidal stability. It has been found that the increase of block copolymer concentration in water decreases the droplet size and increases the colloidal stability. The increase of ultrasound power led to the opposite effect—gradual increase of the droplet size. It has been also demonstrated that at higher ultrasonication power particles with non-spherical morphology have been formed. Toluene extraction from the obtained emulsions led to the formation of PHBV particles. The dimension of the obtained particles is in the range 80–300 nm. The particle size distribution becomes broader with the increase of the stabilizer concentration. The increase of the PHBV concentration in toluene leads to the formation of the micrometer-large beads and the particle size distribution is getting broader.

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