

Diblock Copolymer Micelles with Ionic Amphiphilic Corona

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Summary: Aqueous dispersions of diblock copolymer micelles with homogeneous hydrophobic core (polystyrene) and heterogeneous amphiphilic corona from ionic N-ethyl-4-vinylpyridinium bromide (EVP) and hydrophobic 4-vinylpyridine (4VP) units have been prepared at pH 9. The structure and dispersion stability of micelles as function of the ratio and distribution pattern of ionic and hydrophobic units in corona have been systematically studied by means of transmission electron microscopy, static and dynamic light scattering, UV-spectrophotometry techniques. It was shown that gradual decrease of the quantity of EVP-units in corona had no impact on micelle structure until its fraction was above 0.7. When EVP-fraction dropped below this point noticeable changes in micelle mass and dimensions were observed. In the case of random distribution of 4VP and EVP units these changes were moderate in value and jump-like in character. In the case of microarm (starlike) distribution of 4VP and EVP blocks changes were large in value and monotonous in character. The presented results may be of certain use for design of polymer micelles with nanosegregated corona.

Keywords: amphiphilic; diblock copolymers; micelles; polyelectrolytes; self-assembly

Introduction

Self-assembly is a process of spontaneous reversible formation of organized structures via non-covalent interactions of the system components. Ionic amphiphilic diblock copolymers belong to self-assembling polymers. In aqueous media they spontaneously form micelles with insoluble hydrophobic core and lyophilizing ionic corona.^[1] These micelles are regarded as promising drug delivery vehicles and nanoreactors for synthesis and stabilization

of various nanoparticles because of their remarkable binding and solubilizing properties as well as enhanced disintegration resistance towards dilution.^[2,3]

In the simplest case polymer micelles consist from chemically uniform core and chemically uniform corona.^[1,2] A challenging task for polymer chemistry is creation of hierarchically organized polymer micelles, i.e. micelles with compartmentalized core and/or corona consisting of smaller structural units that differ in composition and properties. Such micelles would resemble globules of natural proteins with their microheterogeneous structure and may pave the way for design of smart multifunctional nanostructures.^[3] First examples of polymer micelles with segregated core or corona can be found in literature.^[4–9] Three ways of creation such micelles can be distinguished: synthesis of multiblock (primarily triblock) copolymers,^[4,5] synthesis of amphiphilic copolymers with a mixed (static and block)

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distribution of units of various polarity^[6,7] and joint micellization (hybridization) of several diblock copolymers with different chemical nature.^[8,9]

The present paper deals with two types of polymer micelles in aqueous media. Both types consist from hydrophobic homogeneous polystyrene (PS) core and heterogeneous corona formed by nonpolar 4-vinylpyridine (4VP) and charged N-ethyl-4-vinylpyridinium bromide (EVP) units. The first variable in our investigation is mole fraction of EVP units in corona, $\beta = [\text{EVP}]/([\text{EVP}] + [\text{4VP}]) = 0 \div 1$. The second variable is distribution pattern of charged and nonpolar units within corona. The first type of micelles consists from PS-block-poly(4-vinylpyridine-stat-N-ethyl-4-vinylpyridinium bromide) (PS-P(EVP/4VP)- β) block copolymers with random distribution of EVP and 4VP units along corona-forming block. Therefore, block copolymer micelles of the first type possess random distribution of EVP and 4VP units in corona. The second type includes hybrid (mixed) micelles from PS-block-poly(4-vinylpyridine) (PS-P4VP_[0]) and PS-block-poly(N-ethyl-4-vinylpyridinium bromide) (PS-PEVP) diblock copolymers. Here and below such micelles will be designated as PS-PEVP/PS-P4VP- β . Block copolymer micelles of the second type possess microarm (starlike) distribution of PEVP and P4VP blocks within corona. The purpose of the investigation is to find the influence of composition and distribution pattern of ionic and hydrophobic units in corona on micellar structure and properties. Micelle characteristics (mass, dimensions and aggregation stability) as a function of their composition β and distribution pattern have been systematically studied to find such correlations.

Experimental Part

Polymers

Diblock copolymers of PS-P4VP, PS-PEVP and PS-P(EVP/4VP)- β have been synthesized as described elsewhere.^[10] The

lengths of PS, P4VP, PEVP and P(EVP/4VP) blocks were equal 100 units, the polydispersity index for all diblock copolymers was 1.12. For PS-P(EVP/4VP)- β copolymers $\beta = 0.3 \div 1.0$. The initial PS-P4VP sample was synthesized and generously provided to us by Prof. Adi Eisenberg from McGill University, Montreal, Quebec, Canada.

Preparation of Micelle Dispersions

Aqueous dispersions of individual PS-P(EVP/4VP)- β micelles were prepared using the dialysis technique. Initially, PS-P(EVP/4VP)- β copolymers were dissolved in a mixed DMF/methanol (80/20 v/v) solvent and stirred for one day. After that, water was added to the mixture dropwise under vigorous stirring. When water content was 33 vol. %, the mixture was left for one day to reach the equilibrium. Another portion of water was added until its content was 67 vol. %. The mixture was stirred additionally for one day. Finally, the water-organic mixture was dialyzed against pure water during one week using membrane tubing to remove organic solvents. The concentration of PS-P(EVP/4VP)- β in final dispersion was determined from UV-spectrophotometry measurements at $\lambda = 257 \text{ nm}$.^[10]

To prepare aqueous dispersions of PS-PEVP/PS-P4VP- β micelles, individual PS-PEVP and PS-P4VP copolymers were initially dissolved in DMF/methanol (80/20 v/v) solvent and mixed at appropriate ratio $\beta = 0.05 \div 1.0$. All other steps were identical to that described above for PS-P(EVP/4VP)- β micelles. In our recent publication we have demonstrated the formation of hybrid micelles with joint PS-core and mixed PEVP/P4VP corona upon addition of water into above mentioned diblock copolymers mixture in DMF/methanol solvent. We have found that the micelle composition coincided or approached closely to the composition of the copolymer mixture.^[11] The PS-core of hybrid micelles “freezes” during the dialysis procedure thus fixing the micelle aggregation number and the structure of the core.^[12]

All experiments were performed at room temperature (25 °C) in TRIS buffer solution (0.01 M, pH 9) to keep the 4VP units completely uncharged and hydrophobic.^[13] To evaluate aggregation stability of micelles in saline media the micelle dispersions were mixed with NaCl aqueous solutions of appropriate concentration and vigorously stirred for one day. In the case of precipitation the insoluble phase was separated from the supernatant via ultracentrifugation during 15 min at 13000 rpm. The concentration of block copolymer micelles in supernatant was determined by UV-spectrophotometry technique at $\lambda = 257$ nm.

Measurements

Spectrophotometer measurements were performed at UV-VIS Lambda-25 spectrophotometer (Perkin-Elmer, USA) in 10 mm quartz cells. Static and dynamic light scattering measurements were performed using PhotoCorr-M light scattering spectrometer (PhotoCorr, Russia). A 25-mW He-Ne laser operating at 633 nm wavelength was used as a light source. Light scattering angles varied within $30 \div 150^\circ$. Refractive index increments were measured by a KMX-16 differential refractometer (Milton Roy, USA) with a 2-mW He-Ne laser as a light source, $\lambda = 633$ nm. All solutions were filtered two times through Millipore GS 0.45 μm prior to all light scattering measurements. Static light scattering data were treated by Zimm

method, extrapolating the obtained values of reduced intensity of scattered light to zero scattering angle. The negative staining technique was used for the transmission electron microscopy (TEM) studies. Samples were studied by use of Hitachi H-7000 microscope (Hitachi, Japan) using uranyl acetate as contrasting agent.

Results and Discussion

Chosen TEM microphotographs of PS-PEVP, PS-P(EVP/4VP)-0.17 and PS-PEVP/PS-P4VP-0.2 micelles are presented in Figure 1. One can easily notice the spherical morphology of all micelles. This result is expected since spherical morphology is characteristic for diblock copolymers when the core and corona forming blocks are of comparable lengths.^[14] One can find micelles in Figure 1a, 1b and 1c are of different size. This observation may reflect the strong influence of micelle composition and distribution pattern of ionic and non-ionic units in corona on micelle mass and dimensions. To follow this influence, methods of static and dynamic light scattering were applied.

Figure 2 shows the dependencies of weight-average molecular masses (M_w) and hydrodynamic radii (R_h) of PS-P(EVP/4VP)- β micelles as a function of β . (Note that values of M_w and R_h were obtained by extrapolation of corresponding

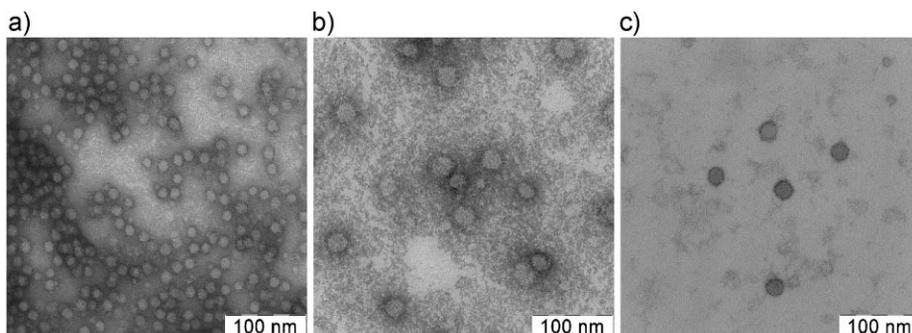


Figure 1.

TEM microphotographs of PS-PEVP (a), PS-P(EVP/4VP)-0.17 (b) and PS-PEVP/PS-P4VP-0.2 (c) from salt-free aqueous dispersions.

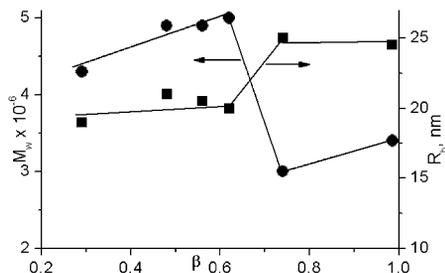


Figure 2.

Weight-average molecular weight M_w (●) and hydrodynamic radius R_h (■) of PS-P(EVP/4VP)- β micelles in 0.05 M NaCl aqueous dispersions as a function of β .

experimental data to zero concentration.) One can easily notice that mass and hydrodynamic radius of micelles change in a jump-like manner near $\beta \sim 0.6 \div 0.7$, while below and above this narrow region micelle characteristics change insignificantly.

Using the obtained data we have estimated other structural characteristics of the micelles: their weight-average aggregation number N_w , the radius of the PS-core (R_C) and the dimensions of the P(EVP/4VP)-corona (D). Aggregation number was calculated as $N_w = M_w/M_0$, where M_0 is a molecular mass of a single macromolecule. To calculate R_C we use the following equation:

$$R(\text{nm}) = \left(\frac{3M_{PS}P_{PS}N_w \times 10^{21}}{4\pi N_A \rho_{PS}} \right)^{1/3}$$

Here $M_{PS} = 104$ g/mol – molar mass of PS unit, $P_{PS} = 100$ – polymerization degree of PS-block, $\rho_{PS} = 1.04$ g/cm³ – density of amorphous PS in a solid state (it is supposed that

Table 1.

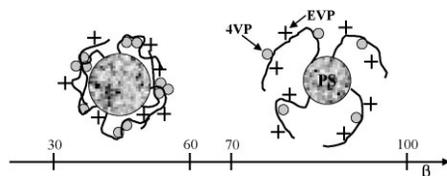
Structural characteristics of PS-P(EVP/4VP)- β micelles in 0.05 M NaCl aqueous dispersions.

β	N_w	R_C (nm)	D (nm)
0.29	180	9	9
0.48	190	9	12
0.56	180	9	12
0.62	180	9	11
0.74	100	7	18
1.0	100	7	16

PS-core of micelles does not contain water) and N_A – Avogadro's number. The corona dimensions were calculated as $D = R_h - R_C$. The results of calculations are summarized in Table 1 and their general qualitative interpretation is presented in Scheme 1 below.

When $\beta < 0.6$ micelles possess higher aggregation number (larger PS-core) and contracted corona. When $\beta > 0.7$ micelles possess lower aggregation number (smaller PS-core) and expanded corona (Table 1 and Scheme 1). We believe the reason of a jump is the reversion in the balance between nonpolar interactions of 4VP units and electrostatic interactions of EVP units in corona. At low β the structure of a micelle is determined by hydrophobic attraction of dominating 4VP-units. Such attraction manifests itself in local association of 4VP units in corona, which in turn, is accompanied by contraction of the corona and increase in micelle aggregation number (left micelle in Scheme 1). At high β the fraction of 4VP-units is low and the micelle structure is determined by the electrostatic repulsion of charged EVP units. The micelle “tries” to alleviate unfavorable electrostatic repulsion in corona. This is achieved by unfolding of P(4VP/EVP) chains (i.e. by expanding the corona) and decrease the aggregation number (right micelle in Scheme 1).

In the case of hybrid PS-PEVP/PS-P4VP- β micelles 4VP and EVP units are chemically bound into blocks per 100 units. These blocks are planted from joint PS-core in a star-like fashion. Because P4VP blocks are insoluble in water at pH 9 the hybrid micelles must have three-layered structure



Scheme 1.

Structural organization of PS-P(EVP/4VP)- β micelles in 0.05 M NaCl aqueous dispersions as a function of β .

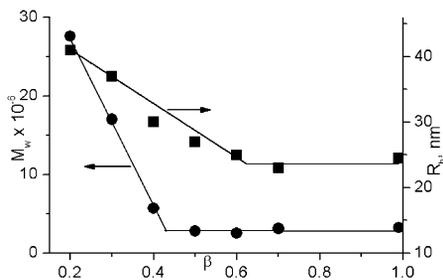


Figure 3.

Weight-average molecular weight M_w (●) and hydrodynamic radius R_h (■) of PS-PEVP/PS-P4VP- β micelles in 0.05 M NaCl aqueous dispersions as a function of β .

Table 2.

Structural characteristics of PS-PEVP/PS-P4VP- β micelles in 0.05 M NaCl aqueous dispersions.

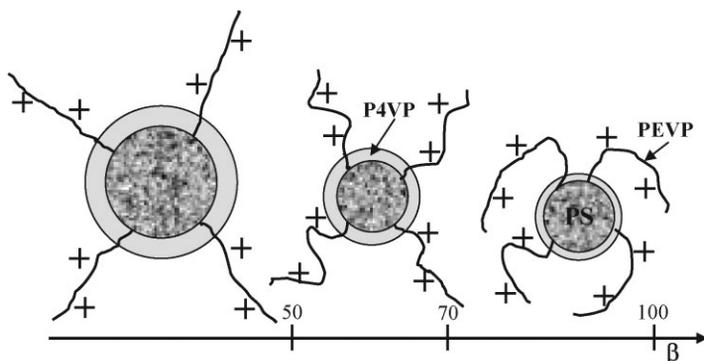
β	N_w ^{a)}	R_C (nm)	D (nm)
0.2	1200	17	24
0.3	700	14	23
0.4	230	10	20
0.5	110	8	20
0.6	90	7	18
0.7	110	8	14
1.0	100	7	15

^{a)}For hybrid micelles $M_o = \beta M_{o(\text{PS-PEVP})} + (1-\beta)M_{o(\text{PS-P4VP})}$, where $M_{o(\text{PS-PEVP})}$ and $M_{o(\text{PS-P4VP})}$ are molecular masses of individual diblock copolymers.

from the PS-core, intermediate shell form contracted P4VP blocks and the outer lyophilizing layer from charged PEVP blocks.^[9] For hybrid micelles the dependencies of M_w and R_h upon corona composition β are quite different from that for PS-P(EVP/4VP)- β micelles. As can be seen from Figure 3 both R_h and M_w values are constant at high β ($\beta \geq 0.7$ for R_h and $\beta \geq 0.5$ for M_w), while essentially and monotonously changing at low β ($\beta < 0.7$ for R_h and $\beta < 0.5$ for M_w). The calculated values of N_w , R_C and D are presented in Table 2, while the overall influence of β on structural characteristics of hybrid micelles is visualized in Scheme 2.

When $\beta \geq 0.7$ micelle characteristics are similar to that of pure PS-PEVP. The reason of micelle structural stability lies in domination of electrostatic repulsions of

PEVP units over hydrophobic attraction of PS and P4VP units. Nevertheless due to the collapse of P4VP blocks onto PS-core the specific area of core-corona interface per one PEVP-chain does increase. To shield the bare interface PEVP-chains start to elongate, this means the growth of D . The effect becomes noticeable at $\beta < 0.7$ (Table 2). When β drops below 0.5, the PS core also grows to diminish the specific area of the core-corona interface (Table 2). The growth of PS-core means the elongation of PS chains. Elongation of PS-chains amplifies the effect of PEVP elongation and enables to sustain micelle aggregation stability despite decreasing the “lyophilizing potential” of the corona. Contour lengths (25 nm) of PS and PEVP-chains define their elongation limit. From Table 2 one can see that when $\beta = 0.2$ the R_C and D



Scheme 2.

Structural organization of PS-PEVP/PS-P4VP- β micelles in 0.05 M NaCl aqueous dispersions as a function of β .

values are close to the limit. This point means the boundary of micelle phase stability. When β drops below 0.2, micelles precipitate.

Scheme 1 and 2 demonstrate the role of distribution pattern of ionic and hydrophobic units in corona on micelle structure as a function of corona composition. In the case of statistical distribution of 4VP and EVP units structural changes are moderate in values and jump-like in character (Scheme 1). In the case of microarm distribution of P4VP and PEVP blocks changes are large in values and monotonous in character. The origins of this difference lie in spatial segregation of ionic and nonionic units in the case of hybrid micelles. To prove this statement theoretical consideration of micelle structure is necessary. Such consideration is in progress now and its discussion will be presented in our nearest publications.

The micelle structure must determine the micelle properties. To illustrate this correlation we have examined the aggregation stability of micelles towards increasing the ionic strength of the solution. Figure 4 presents the diagram of micelle aggregation stability upon addition of NaCl. Here $[\text{NaCl}]^*$ is a threshold concentration, below it micelles are stable, and above it micelles quantitatively precipitate. So the area left and above the curve $[\text{NaCl}]^* - \beta$ corresponds to micelle precipitation (salting out), while the area right and below the

curve designates the micelle aggregation stability. As can be seen from Figure 4 for both types of micelles the value of $[\text{NaCl}]^*$ monotonously increases with increase of β . Above some threshold composition (β^*) micelles do not precipitate even at saturated NaCl concentrations, ca 5.5 M.

For PS-P(EVP/4VP)- β micelles $0.6 < \beta^*(1) < 0.7$, i.e. fits the region of micelle structural transformation. For hybrid PS-PEVP/PS-P4VP- β micelles $0.2 < \beta^*(2) < 0.3$, i.e. lies near the boundary of maximal core and corona chains elongation. Here we see the evident correlation between micelle structure and its ability to persist against salting out. Due to spatial segregation of ionic and nonpolar blocks in their corona hybrid micelles persist more efficiently against precipitation impact of adding salt.

Conclusion

We have systematically studied the influence of corona composition on structure and dispersion stability of diblock copolymer micelles with ionic amphiphilic corona in aqueous media. We have found that micelle structure is quite insensitive to variation of its composition within the range of $\beta = 0.7 \div 1.0$. When the fraction of charged units drops below this range the structural reorganization of micelles is observed. The reorganization allows to sustain micelle aggregation stability despite decreasing the lyophilizing capacity of the corona. The character of micelle structural reorganization depends upon the distribution pattern of ionic and hydrophobic units in corona and can be qualitatively explained by the interplay of electrostatic and hydrophobic interactions of polymer units within the micelle. We believe that our findings may be of certain importance for design of multifunctional polymeric micelles with heterogeneous microstructure.

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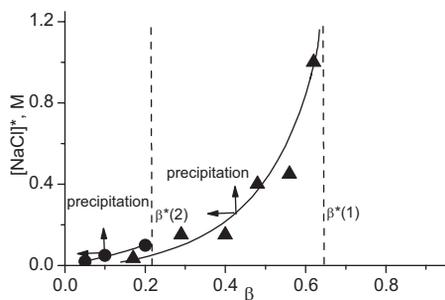


Figure 4.

Diagrams of dispersion stability of PS-P(EVP/4VP)- β (\blacktriangle) and PS-PEVP/PS-P4VP- β (\bullet) micelles in aqueous media in the presence of NaCl.

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