Self-assembly of double hydrophobic block copolymers in water–ethanol mixtures: from micelles to thermoresponsive micellar gels†

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Micellization and micellar gel formation of poly(styrene)-block-poly(methyl methacrylate) [PS-*b*-PMMA] are demonstrated in a water–ethanol solvent mixture; full hydration of the PMMA causes a large radius of gyration resulting in micellar gel formation at only 1 wt% polymer concentration.

The self-assembly of well-defined block copolymers can be used for the construction of a variety of nanostructures, including spherical micelles, worm-like micelles and vesicles, depending on the block lengths and ratios as well as the chemical composition.[1] The self-assembly process can be further controlled by selection of the non-solvent and/or the use of solvent mixtures.[2] However, for obvious reasons, the use of aqueous solvent mixtures has only been reported for the self-assembly of amphiphilic block copolymers until now.

The introduction of a thermoresponsive segment in block copolymers facilitates stimuli-responsive self-assembly behavior. The majority of such reported block copolymers self-assemble at elevated temperatures based on the lower critical solution temperature (LCST) transition.[3] In contrast, only a limited number of examples were reported on the upper critical solution temperature (UCST) induced switching of micelles, mostly based on poly(betaine)s.[3a,4] Such switchable block copolymers have also been applied for the preparation of thermoresponsive micellar gels based on LCST[5] and UCST,[6] which are relevant for, *e.g.*, drug delivery and tissue engineering.[5a,7]

Here, we demonstrate for the first time micellization and thermoresponsive gelation of a double hydrophobic block copolymer, namely poly(styrene)-block-poly(methyl methacrylate) [PS-*b*-PMMA], in an ethanol–water mixture. Even though the enhanced solubility of poly(methyl methacrylate) [PMMA] in ethanol–water mixtures is known with a solubility maximum at 20 wt% water,[8] this property seems to have been forgotten and has never been exploited for self-assembly purposes. Until now, the self-assembly of PS-*b*-PMMA, and other double hydrophobic block copolymers, has only been reported in organic solvent mixtures[9] as well as a hydrophobic ionic liquid.[10] Clearly, the use of ethanol–water solvent mixtures would be beneficial based on their low toxicity.

PS-*b*-PMMA block copolymers were prepared by anionic polymerization using diphenylethylene to reduce the reactivity of the living polystyrene chain ends before proceeding with the methyl methacrylate polymerization, as described elsewhere (Table 1).[11] The micellization of PS-*b*-PMMA-I was investigated in an ethanol–water 80/20 wt% mixture at different concentrations. Only after heating to ~120 °C in a closed vial, *i.e.* above the glass transition, did the dispersed solid polymer form a micellar solution. After cooling to room temperature, translucent micellar solutions were obtained with 0.2 wt% and 0.5 wt% polymer while micellar gels were obtained with 1 wt% and 2 wt% polymer as indicated by the vial inversion test (Fig. 1, top). In fact, a 1 wt% polymer content is exceptionally low for micellar gel formation compared to other reported micellar gels that require at least 8 wt% triblock copolymer[5,6a,b] or 5 wt% pentablock copolymer.[6c] The micelles obtained at 0.2 wt% concentration of PS-*b*-PMMA-I in the ethanol–water 80/20 wt% mixture were investigated by transmission electron microscopy [TEM] revealing clustered spherical micelles (Fig. 1, bottom left). Cryogenic TEM [cryo-TEM] demonstrated the presence of individual spherical micelles indicating that the clustering is due to solvent evaporation. This evaporation additionally causes the collapse of the PMMA shell in the dry state as also illustrated by the radius (R) of the micelles that was determined to be ~15 nm by TEM and 20–30 nm by cryo-TEM, respectively. The formation of spherical micelles is rather surprising when taking into account the degree of polymerization [DP] of both blocks. The similar molar masses of the PS and PMMA blocks would be expected to lead to worm-like micelles rather than spherical micelles indicating that the hydrodynamic radius of the PMMA block in the ethanol–water 80/20 wt% mixture is relatively large. Spherical

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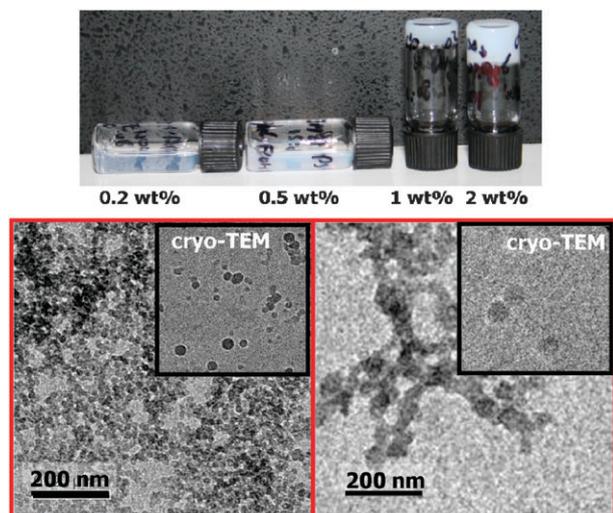[b] *Dutch Polymer Institute (DPI), P.O. Box 902, 5600 AX Eindhoven, The Netherlands*
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Table 1 Structural details of the investigated block copolymers

Polymer	$M_n{}^a$/kDa	PDI^a	DP$_{PS}{}^b$	DP$_{PMMA}{}^b$
PS-*b*-PMMA-I	13.9	1.16	88	80
PS-*b*-PMMA-II	291.2	1.23	112	2800

^{a} Determined by size exclusion chromatography. ^{b} Determined by ^{1}H NMR spectroscopy.

Fig. 1 Top: pictures of the vial inversion test for micellar solutions of PS-*b*-PMMA-I in an ethanol–water 80/20 wt% mixture with different polymer concentrations. Bottom: TEM images of PS-*b*-PMMA-I (left) and PS-*b*-PMMA-II (right) micelles at 0.2 wt% concentration. The insets show the corresponding cryo-TEM images (same scale).

micelles with a R of 20 nm were also found by cryo-TEM for a similar block copolymer in an ionic liquid indicating similar swelling of the PMMA chains in both media.[10b] The micelles of PS-*b*-PMMA-II in the ethanol–water 80/20 wt% mixture showed an even stronger tendency to cluster in TEM compared to PS-*b*-PMMA-I while cryo-TEM revealed the presence of individual spherical micelles in solution. This more pronounced clustering might indicate stronger interactions between the larger PMMA blocks. The R was found to be ~ 35 nm with TEM and ~ 67 nm with cryo-TEM again demonstrating the collapse of the PMMA in the dry state.

The micellization procedure of PS-*b*-PMMA-I in the ethanol–water 80/20 wt% mixture yielded a freely flowing micellar solution at elevated temperatures, which upon cooling formed a micellar gel. This thermoresponsive behavior was evaluated for a gel with 4 wt% of PS-*b*-PMMA-I (Fig. 2).
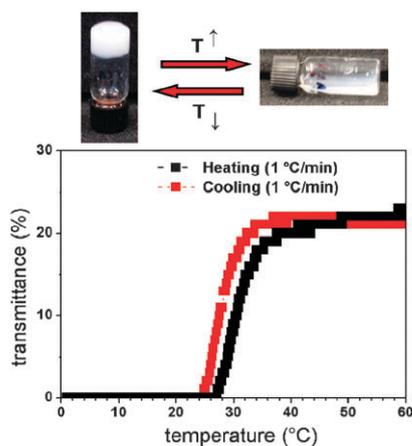

Fig. 2 Top: vial inversion test for the micellar gel of PS-*b*-PMMA-I in an ethanol–water 80/20 wt% mixture with 4 wt% polymer indicative of the thermoresponsive behavior. Bottom: transmittance *versus* temperature plot for the same micellar gel.

Turbidimetry revealed 0% transmittance at temperatures below 25 °C indicative of micellar gel formation. Upon heating, the transmittance increased up to 20% indicating the gel–sol transition between 25 °C and 40 °C. During the transition, the PMMA chains pass the UCST,[8b] *i.e.* the PMMA chains undergo a transition from a collapsed state to a solvated state, resulting in solubilization of the micelles. This thermoresponsive transition between a micellar gel and a micellar solution is fully reversible, although some hysteresis is observed. Upon heating the mid-point of the transition is passed at 30 °C while upon cooling this point of the transition is observed at 23 °C. This hysteresis indicates that solvation of the PMMA chains is based on favorable interactions, presumably between water and the ester groups of PMMA, making it more difficult to dehydrate the polymer compared to the hydration process.

In contrast to PS-*b*-PMMA-I, micellar solutions of PS-*b*-PMMA-II in the ethanol–water 80/20 wt% mixture phase separated into a gel fraction and a clear soluble fraction upon cooling (Fig. 3). At elevated temperatures, the gel fraction redissolves and a translucent micellar solution is obtained. Surprisingly, the gel fraction is more compact and rigid at 2 wt% polymer concentration compared to 1 wt%. This observation indicates the presence of strong interactions between the PMMA micellar coronas at low temperatures in the ethanol–water 80/20 wt% solvent mixture causing aggregation of the micelles resulting in the formation of a gel fraction.

Nevertheless, the questions remain as to why PS-*b*-PMMA-I forms spherical micelles and why a micellar gel is already formed with 1 wt% polymer concentration in water–ethanol (80/20 wt%). The answer to both questions appears to be related to the radius of gyration [R_g] of the PMMA, which was investigated by small angle neutron scattering (SANS). In addition, the hydration state of the polymer might influence the solution properties of PMMA in the ethanol–water 80/20 wt% mixture. Previously, the enhanced solubility of PMMA in isopropanol–water (80/20 vol%) was ascribed to hydrogen bonding between water and the carbonyl groups of PMMA[12] while it was opposingly reported that the solubility of PMMA in *tert*-butanol–water is facilitated by specific interactions between the polymer and *tert*-butanol.[13]

To understand the solubility of PMMA in the water–ethanol solvent mixture, SANS measurements were conducted on solutions of PMMA with different molecular weights in an ethanol-d$_6$–D$_2$O 80/20 wt% mixture. The structural details of the investigated PMMA samples are listed in Table 2. The SANS scattering curves are typical for random coils in solution indicating the absence of anisotropy in the dissolved PMMA chains (Fig. 4). The experimental data were mathematically modeled using a random coil form factor and the resulting R_g values are listed in Table 2 (see ESI† for further
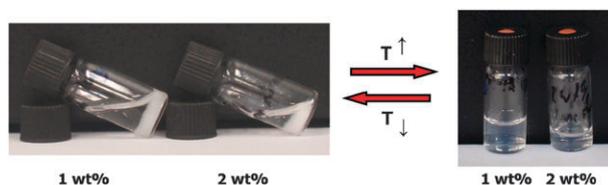

Fig. 3 Pictures of the thermoreversible micellar gel formation of PS-*b*-PMMA-II in ethanol–water 80/20 wt%.

Table 2 Molar mass of PMMA and R_g obtained by SANS

Polymer	$M_n{}^a$/kDa	PDI^a	$R_g{}^b$/Å
PMMA-14K^c	13.8	1.18	23.7
PMMA-27K^c	27.4	1.43	35.3
PMMA-84K^d	84.2^d	1.02^d	60.3^e

^{a} Determined by size exclusion chromatography. ^{b} Obtained by the FISH analysis program. ^{c} Prepared by ATRP.[14] ^{d} Obtained from PSS. ^{e} Measured at 40 °C to ensure solubility of the polymer.
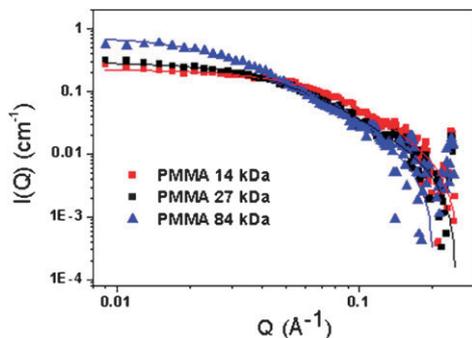
Fig. 4 SANS scattering curves for PMMA with different molecular weights in an ethanol-d$_6$–D$_2$O 80/20 wt% solvent mixture. Scattered data points represent the measurement data while the solid lines are the fits for a random coil model using the FISH analysis program.

information). The best fit to the data was obtained with incorporating one D$_2$O molecule per methyl methacrylate repeating unit clearly indicating full hydration of the polymer.

The R_g value for PMMA with a M_n of 2030 kDa (PDI = 1.20) was reported to be 39 Å in 1-chlorobutane[15] and the R_g of PMMA with a M_n of 105 kDa (PDI = 1.05) was found to be 34 Å in acetonitrile.[16] Based on these literature data it can be concluded that PMMA is significantly swollen in ethanol–water 80/20 wt% since a similar R_g of 35.3 Å was found for PMMA-27K with a M_n of only 28 kDa. Swelling of PMMA in the ethanol–water 80/20 wt% mixture is proposed to be due to the full hydration shell that causes an expansion of the polymer chain.

In summary, the self-assembly of double hydrophobic PS-b-PMMA block copolymers is demonstrated in an ethanol–water 80/20 wt% solvent mixture. At polymer concentrations below 1 wt%, individual spherical micelles are obtained with equal sizes of both blocks due to the relatively large R_g of the fully hydrated PMMA chains as revealed by SANS. Increasing the polymer concentration to as little as 1 wt% resulted in the formation of a thermoresponsive micellar gel due to the relatively large R_g of the PMMA block facilitating interactions between the individual micelles. The mechanical properties of the reported micellar gels and the effects of, e.g., the ethanol–water ratio and PS-b-PMMA block copolymer composition on the self-assembly process will be interesting subjects for future studies. The reported strategy represents an environmentally friendly approach for the micellization of double hydrophobic block copolymers and the formation of responsive materials using low-toxicity solvents.

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