pH-sensitive Spherical Micelles with Core–Corona Structure Based on Graft-like Block Copolymer Containing Biodegradable ε-Caprolactone Branches

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pH-sensitive spherical micelles with obvious core–corona structure were fabricated by self-assembling of block copolymer of methylacrylic acid and macro-monomer FM [$CH_2{=}C(CH_3)$-$OOCH_2CH_2(OCOCH_2CH_2CH_2CH_2CH_2)_5OH$] (PMAA-*b*-PFM). Transmission electron microscopy and laser light scattering studies showed that micelles were nanoscale with narrow size distribution. Solution pH value and the micelle concentration strongly influenced the hydrodynamic radius of the spherical micelles (32–90 nm). The obtained polymeric micelles should be useful for biomedical materials such as drug delivery vehicles.

Amphiphilic block copolymers may self-assemble into a wide range of supramolecular structures such as spherical micelles, rods, or vesicles,[1] which are of interest in a number of fields, such as drug delivery,[2] removal of pollutants from water,[3] and stabilization of emulsion polymerization.[4] Among the systems developed, the most interesting ones are stimuli-responsive micelles, which may change their physical parameters (shape, aggregation number, size, etc.) in response to external stimuli, such as pH, ionic strength, and temperature.[5]

Poly(methylacrylic acid) (PMAA) is one of the most commonly used hydrophilic polymers that possess several specific properties such as bioactivity, pH and ionic-strength-responsive properties. A number of polymeric micelles formed from PMAA-based amphiphilic diblock copolymers have been investigated for various applications.[6–8] Macro-monomer FM [$CH_2{=}C(CH_3)OOCH_2CH_2(OCOCH_2CH_2CH_2CH_2CH_2)_5OH$] are novel both in structure and character, which have long biodegradable hydrophobic ε-caprolactone branches.[9] Although hollow nanospheres based on random copolymer of poly(MAA-*co*-FM *co*-MMA) have been reported,[10] there has been no study on the self-assembly behavior of amphiphilic block copolymers of FM and MAA (PMAA-*b*-PFM). Actually, PMAA-*b*-PFM is a kind of graft-like block copolymer, which consists of hydrophilic, pH-sensitive PMAA backbone and a hydrophobic, biodegradable PCL branches. Therefore, it is very interesting to have insight into the self-assembly behavior of this novel stimuli-responsive "graft-like" block copolymer PMAA-*b*-PFM in aqueous solutions.

PMAA-*b*-PFM was synthesized by atom-transfer radical polymerization.[11] To avoid damage to the catalytic system in ATRP by the carboxyl groups in MAA, diblock copolymers of FM and *tert*-butyl methacrylate (*t*-BMA) were prepared via ATRP. After the selective cleavage of the *tert*-butyl esters of the P(*t*-BMA) block, amphiphilic block copolymers of FM and MAA were obtained. PMAA-*b*-PFM was characterized by size exclusion chromatography (SEC) using polystyrene standard and had a M_n of 21 K and a polydispersity of 1.12. The number of structure units of PMMA and PFM blocks is 50 and 25, respectively. A typical procedure of the preparation of PMAA-*b*-PFM micelles in selective solvents is shown as follows: block copolymer PMAA-*b*-PFM (0.05 g) was dissolved in 100 mL of dimethylformamide (DMF), followed by filtration of the solution through a 0.45 µm Teflon membrane filter (Chromatographic Specialties Inc.). The micelles were formed by the addition of the resulting DMF solution into water at a rate of 1 drop per 60 s with continuous stirring. The micelle solution was stirred for 24 h, and then dialyzed in water using a cellulose dialyzer tube. The hydrodynamic radius, R_h, of the micelles was measured by laser light scattering (ALV500E, ALV Co., Germany), and nanosphere morphologies were directly observed using a transmission electron microscope (TEM; Hitachi H-7010A).

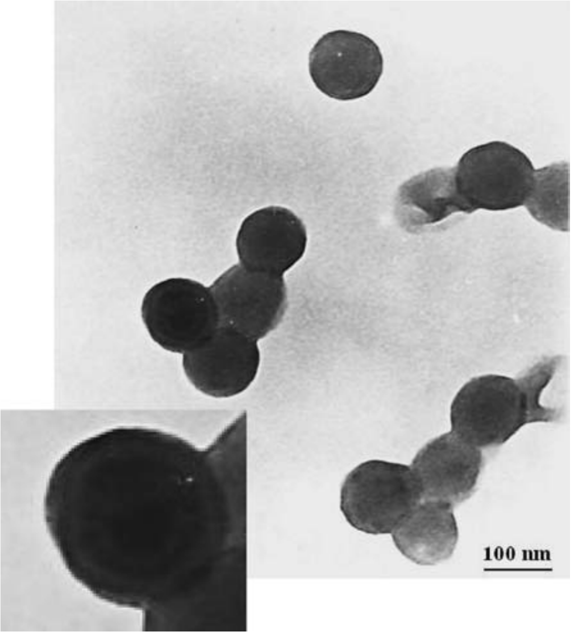

Figure 1. TEM images of PMAA-*b*-PFM polymeric micelles.

A Typical TEM image of micelles is shown in Figure 1. As shown in the Figure, spherical micelles with a narrow size distribution were obtained from PMAA-*b*-PFM. Amplifying the TEM image, obvious core–corona structure of micelles can be clearly observed. In the outer and inner layer of the image, the color is much more black than that of the intermediate space. The number average radius (R_n), weight-average diameter (R_W), and the polydispersity index (PDI) of micelles can be estimated from TEM micrographs using the following equations:

$$R_n = \sum_{i=1}^{N} R_i / N \tag{1}$$

$$R_w = \sum_{i=1}^{N} {R_i}^4 / \sum_{i=1}^{N} {R_i}^3 \tag{2}$$

$$\mathrm{PDI} = R_w / R_n \tag{3}$$

According to the calculation results from TEM, the R_n of the micelles is ca. 49 nm, and the PDI value is 1.007, much lower than 1.05. If the PDI value is less than 1.05, the resulting micelles can be considered to be monodisperse. The average size and size distrubution of micelles could also be determined from DLS measurement. The R_h was 52 nm from DLS method, which was well consistent with the TEM results. The hydrodynamic radius distribution of the micelles was unimodal (Figure 2), also indicating the formation of the expected monodispersed nanosphere micelles.

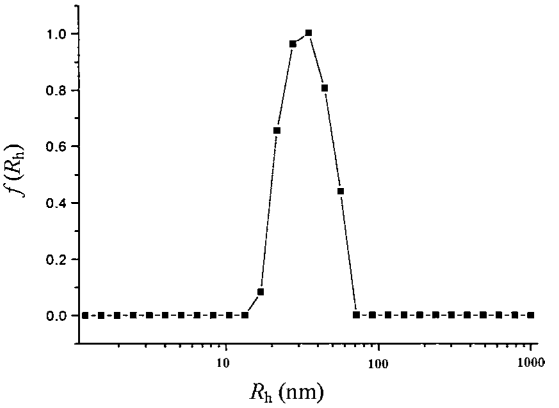

Figure 2. R_h and size distribution of PMAA-*b*-PFM micelles in aqueous solution.

Figure 3 shows the relationship between the hydrodynamic radius (R_h) of the particles measured by DLS and the micelles concentration in aqueous solution. It was found that R_h increased with an increase in micelle concentration from 0.0002 to 0.0013 g/mL. A similar result was obtained in the other amphiphilic block copolymer system, such as PS-*b*-PMAA and PS-*b*-PDMAA (poly(dimethylacrylamide)).[12]

Micelles from block copolymer PMAA-*b*-PFM displayed pH sensitivity in aqueous media since it contained the pH-sensitive PMAA block.[7] Figure 4 shows the dependence of R_h of the micelles on the solution pH value. It was found that the average radius changed drastically between pH 6 and 7. Below pH 6, deprotonation of the carboxyl groups of the PMAA segments was inhibited. So, PMAA-*b*-PFM polymeric micelles can be thought of as more tightly aggregated and integrated under these conditions. Above pH 7, however, electrostatic repulsion between the PMAA segments becomes a crucial factor, directly affecting the average size of the polymeric micelles. The application of these pH-sensitive micelles with their novel structure as a drug carrier will be subsequently reported.

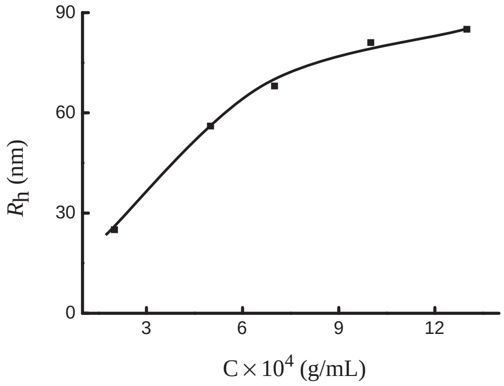

Figure 3. The effects of micelles concentration on the R_h of the PMAA-*b*-PFM micelles in aqueous solution.

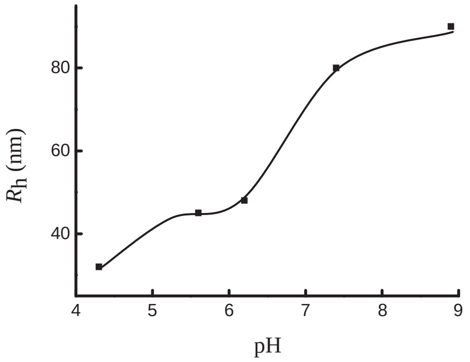

Figure 4. The effects of pH value on the R_h of the spherical micelles.

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