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Synthesis and self-assembly of stearic acid-poly (ethylene glycol) block copolymer

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Abstract. Stearic acid-poly(ethylene glycol) (STA-PEG) block copolymers with different hydrophilic segment length were successfully synthesized by the mild esterification. And self-assembly behaviour of the STA-PEGwas followed by fluorescence spectroscopy, dynamic light scattering (DLS) and transmission electron microscopy (TEM). The results show that the sphere micelles are formed with the STA block as the core and PEG block as the shell in aqueous solution. In addition, with the increase of PEG block length, the diameters of micelles increase from 148nm to 228nm, and the critical micelle concentration (CMC) decreased from 0.0013mg/ml to 0.0004mg/ml. The very low CMC value indicated that the STA-b-PEG can self-assemble into micelles easily and the formed micelles were stable in very dilute solution

1. Introduction

Owing to low toxicity, good biocompatibility and biodegradability, the stearic acid-poly(ethylene glycol) (STA-PEG) amphiphilic block copolymer has the valuable potential applications in the fields like drug delivery and biological imaging.[1, 2] However, the traditional methods of preparationof fatty acid-poly(ethylene glycol) block copolymers are ethoxylation and esterification. [3] The high reaction speed of ethoxylation results in high exothermic, so the whole process need to be strictly controlled. In order to achieve high yield, esterification usually proceeds under very high temperature and for long times. Moreover, catalysts such as sulfuric acid or paratoluenesulfonic acid will corrode the equipment. In addition, although fatty acid-poly(ethylene glycol) block copolymers are widely used as the emulsifiers, thickeners in cosmetics and dyes, and as the softeners and antistatic agents in the textile industry,[4-6] little research on the self-assembly of STA-PEG block copolymers in aqueous solution. The particle size, morphology and stability are key factors when be employed as the drug delivery.[7]

In this paper, STA-PEG block copolymers with different hydrophilic segment length were successfully synthesized by the mild esterification. The structure and molecular weight of the STA-PEG was analysed by ^{1}H-NMR and GPC. Self-assembly behavior of these amphiphilic block copolymers in aqueous solution was followed by fluorescence spectroscopy. And the effects of hydrophilic segment length on the morphology and particle size of the micelles were investigated in detail.

2. Experimental

2.1. Reagents

Monomethyl poly(ethylene glycol)(MPEG) was obtained from Aladdin Chemical Reagent Co. Ltd., stearic acid(STA), dicyclohexylcarbodiimide(DCC), 4-dimethylaminopyridine (DMAP), and the solvent like toluene, dichloromethane were all purchased from Shanghai Titan Chemical Co., Ltd.

2.2. Synthesis

Stearic acid, MPEG, DMAP, DCC and dichloromethane were added in a three-neck flask and reacted for 24h at 40°C. After cooling filter, the products were purified with petroleum ether, ether and water. The synthesized block copolymers were named as STA-PEG_{11}, STA-PEG_{17} and STA-PEG_{22}, respectively. And the molecular weights of PEG used are 500g/mol, 750g/mol and 1000g/mol. The reaction equation is shown as follows:

$$CH_3(CH_2)_{16}COOH + CH_3(OCH_2CH_2)_nOH \xrightarrow[DMAP]{DCC} CH_3(CH_2)_{16}COO(CH_2CH_2O)_nCH_3 + H_2O$$

Figure 1. Synthesis of STA-PEG block copolymer

2.3. Self-assembly of STA-PEG Block Copolymer

STA-PEG block copolymers were dissolved into THF with the initial copolymer solution concentration of 0.5mg/ml. The ultra-pure water was added dropwise into the solution until the content of water reached 50%. Then place the copolymer solution in a cellulose membrane bag(MWCO=1000) and dialyzed against ultra-pure water for 48h. The water was replaced every 12h.

2.4. Measurements

^{1}H-NMR spectrum was measured by BUKER400 AVANCE III nuclear magnetic resonance spectrometer by using chloroform-d as the solvent. The measurement of molecular weight as well as its distribution was performed by Waters1515 gel permeation chromatography (GPC). The critical micelle concentration (CMC) of STA-PEG diblock copolymer was determined by a Flurolog-3-P fluorescence spectrophotometer with pyrene as the probe at room temperature. Hydrodynamic diameter and size distribution of polymeric nanomicelles were analysed on a Malvern Zetasizer Nano ZS instrument equipped with a He-Ne laser(663nm) at a scattering angle of 173°. A JEM 2100(HITACHI) transmission electron microscope with an acceleration voltage of 200kV was applied to obtain the morphology and diameter of micelles.

3. Results and Discussion

3.1. Synthesis of STA-PEG Block Copolymer

The structure and molecular weight of the obtained product were analysed by ^{1}H-NMR. As shown in Figure 2, the proton absorption peak of methylene of PEG block appears at δ4.15 ppm(a) and δ3.55ppm(b), and that of end methyl proton at 3.28ppm(c). The chemical shifts at δ2.25ppm(d), δ1.56ppm(e) and δ1.18ppm (f) are related to methylene group of stearic acid, and shifts at δ0.81ppm(g) belong to methyl group of stearic acid. The number average molecular weights of STA-PEG_{11}, STA-PEG_{17} and STA-PEG_{22} calculated according to ^{1}H-NMR spectra were 788g/mol, 1022g/mol and1308g/mol, respectively. The results agreed with the designed structure and molecular weights of STA-PEG block copolymers, implying the successful synthesis of STA-PEG block copolymer.

In addition, the molecular weight as well as molecular weight distribution of STA-PEG block copolymers measured by GPC were 933 (STA-PEG_{11}, PDI=1.05), 1233 (STA-PEG_{17}, PDI=1.04) and 1437 (STA-PEG_{22}, PDI=1.05), which are accorded with that of ^{1}H-NMR.

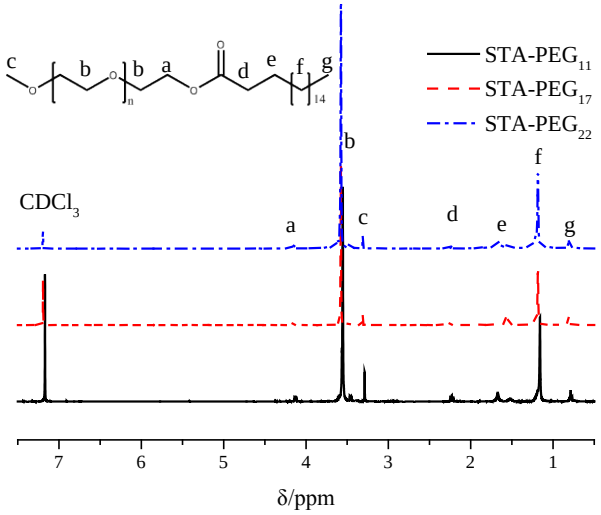

Figure 2. ^{1}H-NMR spectra of STA-PEG

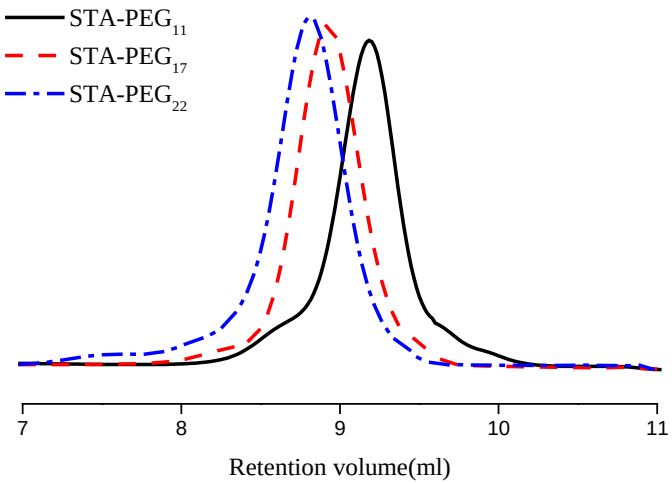

Figure 3. GPC traces of STA-PEG

3.2. Self-assembly of STA-PEG Block Copolymer

With more water was introduced into STA-PEG/THF solution, the STA block aggregates into core gradually due to the hydrophobic force, and the PEG block dissolve in water and cover the surface of the core to maintain the stability of the core. Thus, the amphiphilic block copolymer STA-PEG self-assembled into micelles with STA as the core and PEG as the shell.[8]

Critical micelle concentration(CMC) is an important parameter to characterize the stability of micelles. The lower CMC is, the more stable formed micelles are. The relationship between I_{373}/I_{384} and the logarithm of the diblock copolymer concentrations and the Boltzmann formula fit for each copolymer are displayed in Figure 4. And the CMC values of STA-PEG block copolymers were obtained from the intersection of two straight lines. With the growth of hydrophilic PEG segment length,the CMC of STA-PEG decreased from 0.0013mg/ml to 0.0004mg/ml, which should be attributed to the decrease of solubility of PEG segment and the increase of performance of protecting hydrophobic core from exposure to water.[9, 10] In addition, the very low CMC values indicate that STA-PEG amphiphilic block copolymer can self-assemble into micelle easily. Moreover, the formed micelles also have good stability in very dilution solution.

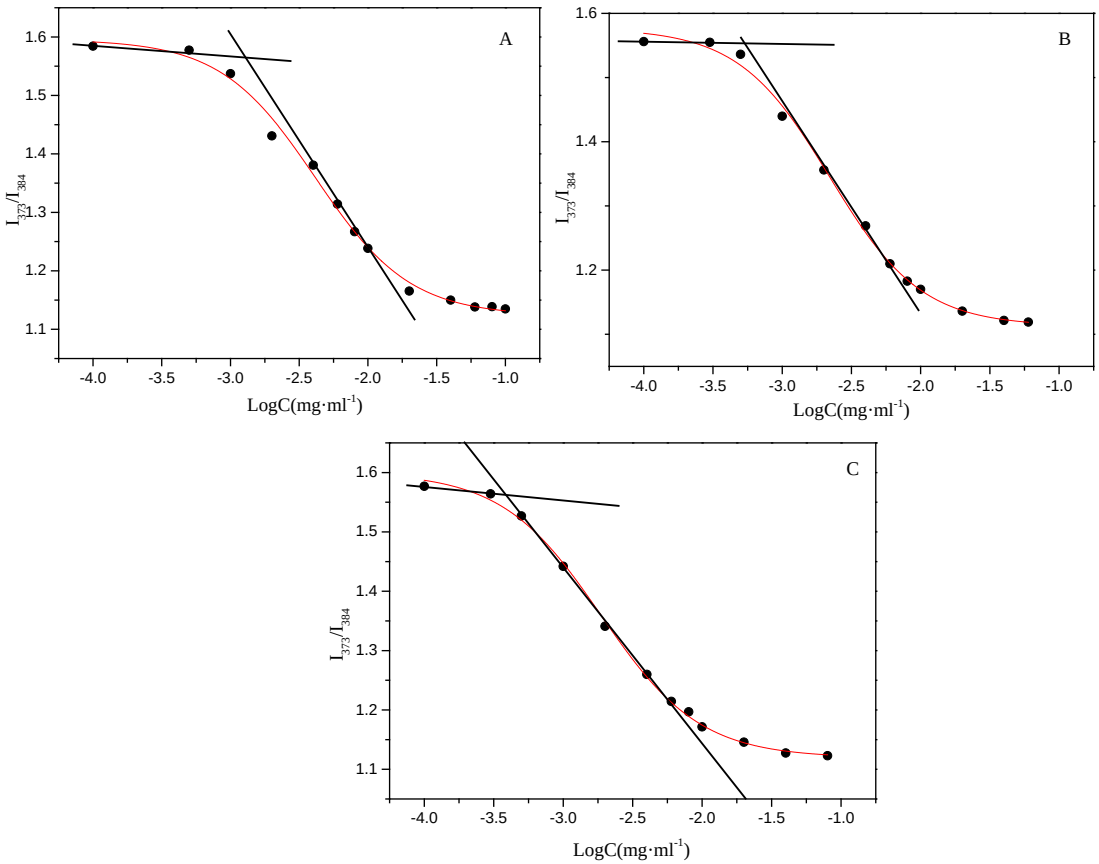

Figure 4. Plot of I_{373}/I_{384} versus logarithm of STA-PEG concentration: A, STA-PEG$_{11}$; B, STA-PEG$_{17}$; C, STA-PEG$_{22}$

The diameters of STA-PEG$_{11}$, STA-PEG$_{17}$ and STA-PEG$_{22}$ micelles measured by dynamic light scattering(DLS) are 148nm, 191nm and 228nm, respectively, as presented in Figure 5. Owing to the growth of PEG segment length, both shell thickness and aggregation number of the micelles increase, arising from the repulsive force among PEG blocks reducing.[11] Therefore, the particle size of STA-PEG micelles increase. According to the Halperin model of polymer micelle with small core and thick shell,[12]the relationship between micelle diameter R and the length of hydrophilic and hydrophobic segments is as follows:

$$R \propto N_B^{4/25} N_A^{3/5} \quad (1)$$

Where N_A, N_B is the degree of polymerization of hydrophilic segments A and hydrophobic segments B, respectively. The $N_B^{4/25} N_A^{3/5}$ values of STA-PEG$_{11}$, STA-PEG$_{17}$ and STA-PEG$_{22}$ are 5.99, 7.78 and 9.08, correspondingly. The diameter ratio of STA-PEG$_{11}$, STA-PEG$_{17}$ and STA-PEG$_{22}$ obtained from DLS measurement well agreed with that calculated according to Halperin model: 148: 191: 228≈5.99: 7.78: 9.08.

In addition, TEM images of the micelles are displayed in Figure 6. The spherical nanoparticles of STA-PEG$_{11}$, STA-PEG$_{17}$ and STA-PEG$_{22}$ dispersed uniformly with the diameter of 70, 110 and 135nm, respectively. The diameter observed by TEM is smaller than that by DLS, because the solid micelles undergone a certain degree of volume shrinkage.

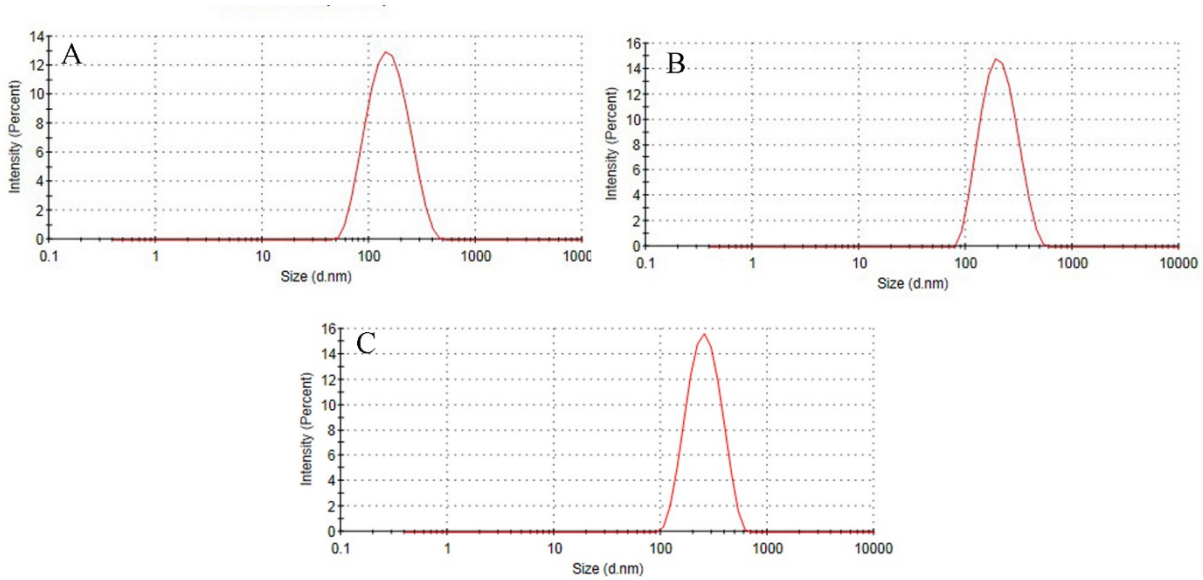

Figure 5. DLS plots of STA-PEG micelles: A, STA-PEG$_{11}$; B, STA-PEG$_{17}$; C, STA-PEG$_{22}$

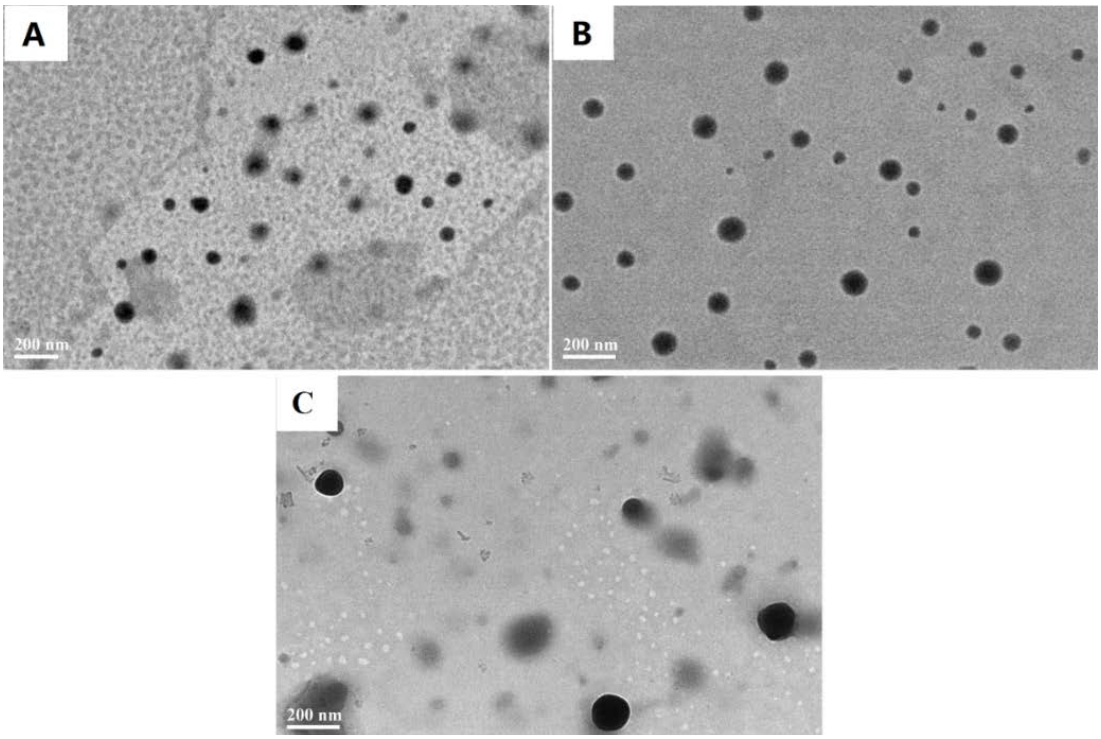

Figure 6. TEM images of STA-PEG micelles: A, STA-PEG$_{11}$; B, STA-PEG$_{17}$; C, STA-PEG$_{22}$

4. Conclusion

The STA-PEG block copolymers with different hydrophilic segments were successfully synthesized by using DMAP as catalyst and DCC as dehydrating agent. In aqueous solution, STA-PEG block copolymer self-assembled into regular sphere micelles with STA as the core and PEG as the shell. As the growth of PEG segments length, the diameter of STA-PEG micelles increased from 148nm to 228nm, while the CMC decreased from 0.0013mg/ml to 0.0004mg/ml. The diameters ratio of STA-PEG micelles obtained from DLS analysis are consistent with the Halperin model. In addition, the low CMC indicated the formed STA-PEG micelles have good stability in very dilution solution

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