Micelles and Hollow Nanospheres Based on ε-Caprolactone-Containing Polymers in Aqueous Media**

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Motivated by the great range of potential applications, the development of polymeric nanostructures has witnessed great progress in the last decade.[11] Among the target materials, polymeric hollow nanospheres are especially interesting and are in great demand because of their ability to encapsulate large quantities of guest molecules, particularly those with functionalities within the inner cavity.[12] The most studied procedures[4] for preparing polymeric hollow nanospheres from block copolymer precursors involves many steps: preparing micelles in the selective solvents, cross-linking of the micellar core, and removing the core by chemical degradation. However, further development has been limited by the preparation of block copolymers containing both cross-linkable and degradable blocks.

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report here an entirely new approach to the preparation of micelles and hollow spheres through self-assembly of a homopolymer and a random copolymer, both of which are readily attainable. The principle of the procedure is illustrated in Figure 1. The polymer pair of poly(epsilon-caprolactone) (PCL) and the graftlike copolymer MAF (formed from methacrylic acid (MAA), macro-monomer FA [CH2=CHCOOCH2-CH2(OCOCH2CH2CH2CH2CH2)3OH] and methyl methacrylate (MMA), see Experimental Section), which has a hydrophilic backbone and short PCL branches, self-assembles into micelles when a mixture of them in DMF is added to water. The PCL does not precipitate but forms a micellar core that is stabilized by the hydrophilic main chains of MAF, thus forming a shell with the PCL branches anchored to the aggregate. In this new kind of micelle, neither covalent bonds nor hydrogen bonds exist between the core and shell. The affinity between the PCL homopolymer and the short PCL branches is believed to be beneficial to the formation of the micelles. Furthermore, the micelle shell can be cross-linked chemically to form “shell-cross-linked knedel-like nanoparticles” (SCKs),[5] the core of which can be biodegraded by an enzyme to give hollow nanospheres.

The dependence of micelle size on both the composition of MAF and the ratio of [PCL] to [MAF] was investigated by dynamic laser-light scattering (DLS). In all cases, the particles showed relatively narrow size distributions (size polydispersity (\(\sigma_S/\langle D\rangle^2\)) was found to be in the range 0.08 to 0.16. The particle size varies considerably, depending on both the MAF and blend compositions, and ranges from 90 to 190 nm (Figure 2). The three series of particles, composed respectively of MAF-1, 2, and 3 (Table 1, see Experimental Section) show a parallel trend that the particle size increases with increasing PCL content for blends in the range of 10 to 50 wt%. This variation is understandable since the PCL aggregates are stabilized by the hydrophilic main chains in MAF. PCL precipitated out when its content exceeded 50 wt%, when the quantity of PCL branches in the MAF is not sufficient to stabilize the PCL aggregates. In addition, the results also show that for any given PCL concentration, the higher the FA content is, the smaller the respective particles are. This observation is also reasonable as an increase in the FA content implies there is a relative increase in the short PCL branches to the homopolymer, which will certainly favor a finer dispersion of PCL aggregates.

DLS measurements show that after cross-linking, the hydrogel displays less swelling than the un-cross-linked shell. For example, for MAF-2/PCL (1:1, w/w), the average hydrodynamic diameter \(\langle D_h\rangle\) varies from 162 to 128.5 nm as a result of cross-linking.

The enzyme lipolase is a type of lipase that can selectively degrade polymers and fats, hence it was chosen to hydrolyze the polyester core domain without affecting the cross-linked poly(methacrylicamid) structure of the main chains. Changes in the size and morphology of the SCKs upon hydrolysis of the core were studied by using a combination of DLS and transmission electron microscopy (TEM).

DLS was used to trace the process of core degradation as well as the formation of the hollow spheres. For the micelles of MAF-3/PCL (1:1, w/w), the relative intensity and average hydrodynamic diameter of the micelles of MAF-3/PCL (1:1, w/w, Figure 3) apparently follow opposite trends with reaction time, that is, the intensity gradually decreases with increasing size. This trend actually reflects that the size increase was accompanied by a decrease in the mass as the degradation proceeded. During the initial stage of the reaction (0–100 min) the intensity dramatically decreased, which indicates that an immediate and quick degradation occurs, while no distinct change in the particle size was detected. A significant increase in \(\langle D_h\rangle\) from about 110 to 300 nm was observed in the period 400–1200 min, and accompanied by a slow decrease in intensity. In the final stage, neither the intensity nor \(\langle D_h\rangle\) changed, which indicated that degradation of the core was

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**Figure 1.** A schematic illustration of the processes of self-assembly, cross-linking, and degradation.

**Figure 2.** The average hydrodynamic diameter of the micelles of MAF-X/PCL as a function of the weight fraction of PCL. ■: MAF-1, ●: MAF-2, ▲: MAF-3.

**Table 1.** The molecular weight and its distribution and \(T_g\) of MAF.

<table>
<thead>
<tr>
<th>Sample no.</th>
<th>Monomer molar ratio^[a] MMA/FA/MAA</th>
<th>(M_n\times10^3)</th>
<th>(M_n/M_w)^[b]</th>
<th>(T_g) [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAF-1</td>
<td>9.2/11.8/79.0</td>
<td>5.25</td>
<td>1.78</td>
<td>32.6</td>
</tr>
<tr>
<td>MAF-2</td>
<td>6.9/23.8/69.3</td>
<td>3.90</td>
<td>1.60</td>
<td>−27.7</td>
</tr>
<tr>
<td>MAF-3</td>
<td>6.1/34.0/59.9</td>
<td>4.16</td>
<td>1.44</td>
<td>−37.1</td>
</tr>
</tbody>
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\^[a] Measured by \(^1\)H NMR spectroscopy. \^[b] Estimated by size exclusion chromatography in DMF.

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complete. The most remarkable phenomenon, as suggested by DLS data, is the significant increase in micellar diameter from 100 to 350 nm when the mass of the particles was reduced by half. Similar behavior has been previously reported for the micelles of block copolymers on removing species contained within the micellar interior.[3b,4f] This expansion is caused by releasing the restriction imposed by the insoluble blocks on the solvated blocks in the shell. The same phenomenon occurs here, and is indicative of the restriction on the MAF chains caused by the insoluble PCL chains in the core, even though there are no chemical bonds between them. The cross-linked shell, which contains poly(methylacrylamide) segments, can be regarded as a hydrogel that swells more extensively when the core domain fills with water after the removal of the PCL.

The TEM studies gave direct evidence of the morphologies of the micelles and hollow spheres. A typical photograph of the micelles of MAF-2/PCL (1:1, w/w) is shown in Figure 4A in which the micelles clearly display a spherical shape. Figure 4B presents the morphological details of a single micelle at a higher magnification. The micelles have a three-layer structure, with the PCL core being the major constituent of the particle. The gray outer shell is believed to be composed of the hydrophilic main chains of MAF. Interestingly, the inner shell shows much lower chain density, which can be attributed mainly to the short PCL branches. These morphological results illustrate the role of the PCL branches: they act as a “glue” between the outer shell and core by means of the affinity between the PCL homopolymer chains and branches, which are chemically identical. Although the combined thickness of the inner and outer shell is only about 10 nm while the radius of the core is as large as 45 nm, the calculated volume fraction of the shell at 47.7 % is comparable to that of the core, which seems reasonable as the weight ratio of MAF to PCL is about 1:1.

The morphologies of the particles after core degradation are shown in Figure 4C and D, with all of the particles clearly displaying a hollow structure. In comparison with the particles shown in Figure 4A and B, the particles have expanded significantly to about 300 nm in diameter and a shell thickness of up to 100 nm, which is indicative of the swelling of the nanocages after removing the PCL core.

In conclusion, we have succeeded in obtaining micelles and hollow nanospheres by a “block-copolymer-free strategy”. The combination of PCL and MAF led to the formation of micelles possessing a hydrophobic PCL core surrounded by a hydrophilic MAF shell. The central layer, composed of PCL branches in MAF, glues the outer shell to the core. Cross-linking of the micelles gives rise to stable shell-cross-linked nanoparticles. As this route is based on common and inexpensive polymer products and the processing is simple, it may have great potential for further applications in fabricating supramolecular materials for various fields such as medicine, catalysis, and photoelectronics.

**Experimental Section**

A series of the graftlike copolymer MAF was synthesized by free-radical copolymerization of methylacrylic acid (MAA), macro-monomer FA (CH$_2$=CHCOOC$_2$H$_5$, Daicel Chem. Co. Ltd.) and a small amount of methyl methacrylate (MMA) in DMF at 70°C using 2,2'-azo-bisbutyronitrile as initiator. The products were purified by dissolution-precipitation in DMF/water three times. The copolymers are characterized by a hydrophilic main chain and hydrophobic short PCL branches. Table 1 lists the characterization data of the MAF copolymer prepared with different feed compositions. The copolymer compositions were calculated based on $^1$H NMR measurements. The signals at $\delta = 0.93-1.03$ for -CH$_3$ in MAA, $\delta = 1.54$ for COCH$_2$ in FA, and $\delta = 3.52$ ppm for -OCH$_3$ in MMA were used for the calculation. The data show that varying the composition did not significantly affect the molecular weight or the distribution of the copolymers produced under similar reaction conditions. All of the copolymers have a single glass-transition temperature ($T_g$), which decreases as the quantity of macromer FA increases. This observation indicates...
that there are no highly blocked sequences along the copolymer chains. The micellar
nanospheres were prepared by dropwise addition of the various blend
solutions of MAF-PCL in DMP into water, with moderate stirring. The appearance of a bluish hue signals
the formation of micelles. The mixture was stirred for approximately 24 h at room temperature, and then
DMF was removed by dialysis with pure water, which resulted in stable homopolymer/copolymer micelles in water. The micellar structure was locked by cross-linking the hydrophilic shell layer through condensation
reactions between the carboxylic acid groups of poly(methylacrylic acid)
(PMAA) and the amino groups of hexamethylenediamine in the presence
of 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide methiodide, which acti-
vates the carboxylic acid at room temperature.[4][5] The cross-linked product
was then dialyzed with distilled water for 3 days to remove the by-products
of the reaction. The success of the cross-linking was confirmed by the fact
that the resultant nanoparticles maintained their integrity upon switching
the medium from water to a solvent mixture containing a large proportion
of DMF. DLS (Malvern Autosizer-4700) studies on the cross-linked particles
found that no particle aggregation had taken place, which meant that there
had been almost, zero interparticle cross-linking. For conducting biode-
gradation of the core, an appropriate amount of dust-free lipolase solution
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